Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Proposed changes to requirements for listed medicine ingredients: Annual low-negligible risk changes 2023-2024

Final Decisions

Version 1.0, December 2023

Contents

Glossary

ACCM	Advisory Committee on Complementary Medicines
ADI	Acceptable Daily Intake
AE	Adverse Events
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
ARTG	Australian Register of Therapeutic Goods
CMEC	Complementary Medicines Evaluation Committee
COT	(UK Food Standards Agency) Committee on Toxicology
CSFII	Continuing Survey of Food Intakes by Individuals
DILI	Drug-Induced Liver Injury
DILIN	Drug-Induced Liver Injury Network
EC	European Commission
EDI	Estimated Daily Intake
EFSA	European Food Safety Authority
EGCG	Epigallocatechin-3-Gallate
EMA	European Medicines Agency
EU	European Union
F4	Exposure Factor for non-genotoxic effects
FAO	Food and Agriculture Organisation of the United Nations
FDA	US Food and Drug Administration
FSA	UK Food Standards Agency
FSANZ	Food Standards Australia New Zealand
JECFA	Joint FAO/WHO Expert Committee on Food Additives
GLP	Good Laboratory Practice
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GRAS	Generally Recognised as Safe
GRN	Generally Recognised as Safe Notification
HLA	Human Lymphocyte Antigen
HILI	Herb-Induced Liver Injury
IARC	International Agency for Research on Cancer
IC	Information Component
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IUPAC	International Union of Pure and Applied Chemistry
MoS	Margin of Safety
NF	Novel Food
NIH	US National Institutes of Health
NOAEL	No Observed Adverse Effect Level
NSAID	Non-Steroidal Anti-Inflammatory Drug
NTP	National Toxicology Program
OECD	Organisation for Economic Cooperation and Development
PDE	Permitted Daily Exposure
PS	Phosphatidylserine
RUCAM	Roussel Uclaf Causality Assessment Method
SCCS	Scientific Committee on Consumer Safety
SMQ	Standardised MedDRA Query
SPF	Sun Protection Factor
TGA	Therapeutic Goods Administration
TK	Toxicokinetic
USA	United States of America
USP	United States Pharmacopeia
UV	Ultraviolet
WHO	World Health Organisation

Introduction

The Therapeutic Goods (Permissible Ingredients) Determination ('the Determination') is a legislative instrument under section 26BB of the Therapeutic Goods Act 1989. This instrument specifies all of the ingredients that are available for use in listed and assessed listed medicines and their associated requirements. The Determination is continually reviewed by the TGA to ensure that all ingredients and their requirements are appropriate for use in low-risk medicines.

Purpose

The proposed changes to ingredient requirements in the Determination were presented for consultation after they were reviewed and categorised as being of low-negligible risk. The purpose of this consultation was to provide an opportunity for consumers, health professionals, industry, and other interested parties to comment on these changes prior to their implementation.

This document outlines the final decisions made regarding the proposed changes to ingredient requirements specified in the Determination, in consideration of the consultation submissions received.

Public consultation

The consultation opened on **3 August 2023** and closed on **14 September 2023**.

The consultation document can be accessed here.

The TGA thanks all respondents for their participation in this consultation process. A total of 27 submissions were received from health professionals, professional bodies, industry organisations, medicine sponsors/brands/manufacturers and consumers.

All submissions that gave permission to be published are now available on the Consultation Hub. Submissions received with claims of confidentiality or privacy have been redacted or remain unpublished as specified by the submitter.

Transition expectations

All changes described in this Final decisions document will commence on **1 March 2024**, and will include a 12-month transition period until **1 March 2025** (see schedule for low-negligible risk changes for 2023-2024).

Transition periods provide sponsors of existing listed medicines with time to make the necessary arrangements to bring their products into compliance. Sponsors should ensure that no product is **released for supply** after the expiry of the transition period unless that product (including the details in the Australian Register of Therapeutic Goods [ARTG] listing) is compliant with any new requirements. After the expiry of the transition period, any ARTG

listing, or product **released for supply** that does not comply with the new requirements may be targeted for review.

Proposed changes to requirements for listed medicine ingredients

1. *Curcuma* species and curcumin and the risk of liver injury

Background

The consultation document discussed the risk of liver injury associated with modern forms of *Curcuma* species/curcumin extracts in therapeutic goods (e.g. tablets for joint inflammation). Turmeric powder (*Curcuma longa root*) used as a culinary spice in food is not regulated by the TGA and has not been identified as a safety concern.

The TGA invited interested stakeholders to comment on a proposal to require additional label statements and dosage restrictions for oral listed medicines containing *Curcuma* species/curcumin. The proposed amendments were intended to communicate the rare risk of serious liver injury and reduce the potential for severe injury, and to allow consumers to self-select and self-administer these medicines safely. Stakeholders were also invited to submit additional information to support a safe dose for *Curcuma* species/curcumin to mitigate the risk especially from modern high bioavailability products.

Consultation submissions

Ten submissions were received in response to this proposal.

Three submissions from relevant clinical professional organisations (e.g. representing gastroenterologists and toxicologists) fully supported the proposed changes. In contrast, five industry representatives opposed or provided mixed support for the proposals, with another two submissions from an individual health professional and a consumer opposing the proposal.

TGA response

The TGA acknowledges that *Curcuma species* and curcumin have a long history of use as a spice and as a medicine with reported benefits. However, as outlined in the consultation document, recent evidence shows an association between *Curcuma species*/curcumin and liver injury, which can be severe as evidenced by the reporting of at least three deaths. The nature of *Curcuma species* and curcumin associated liver injury appears to be idiosyncratic, therefore, the dose, duration of use, or individual susceptibility for liver injury are unpredictable. Further, the lack of knowledge and awareness of potential Herb Induced Liver Injury (HILI) from widely used supplements may result in a failure to identify a causal association. This can lead to under-reporting and, more concerningly, to more severe outcomes if exposure to *Curcuma species* and curcumin is continued. Such challenges can be overcome by increasing awareness of the

potential risk of liver injury among consumers and healthcare practitioners, with clear identification of symptoms to be aware of and instructions for what to do if they arise.

The TGA acknowledges there are some uncertainties around the safe level of exposure and that there may be increased risk for curcumin containing preparations with a higher bioavailability, but this has not been well characterised. The TGA invited respondents to provide additional information to support a safe dose for *Curcuma* species/curcumin sufficient to mitigate the risk especially from modern high bioavailability products. However, respondents did not provide any conclusive additional data to demonstrate a dose below which the risk of liver injury is sufficiently low as to not require a label warning.

The TGA also acknowledges the apparent rarity of liver injury occurring after consuming *Curcuma species* and curcumin, which are widely available in listed medicines in Australia and in supplements globally. Accordingly, the TGA considers that the proposed label warning, with minor amendments, is proportionate to the available evidence of risk. At this stage, it is not the TGA's intention to remove or restrict access to *Curcuma species* and curcumin containing listed medicines from the Australian market. However, the TGA will continue to monitor this safety concern and consider if further regulatory actions are required to protect consumers.

The TGA thanks stakeholders for their submissions. Key issues raised are discussed below.

International regulation

Current actions taken to address risk:

Several industry respondents commented that other jurisdictions have not implemented warnings or other regulatory requirements in relation to curcumin supplements. However, as stated in the consultation, other jurisdictions have recognised the need for action and have taken measures to address the risk of liver injury. This includes:

- The determination in June 2022 that the daily intake of curcumin from supplements should not exceed 153 mg/60 kg adult, noting this relates to the 'classic form' and not to formulations that increase bioavailability, such as curcumin combined with piperine. (ANSES, 2022)
- Advice against the use of *C. longa*-containing supplements by people with bile duct disease (ANSES, 2022)
- The requirement for the following warnings on all food supplements derived from *C. longa*:
    - *In the case of liver, biliary or calculosis abnormalities in the biliary tract, the use of the product is not recommended.*
    - *Do not use during pregnancy and lactation.*
    - *Do not use for prolonged periods without consulting your doctor. If you are taking medications, it is advisable to discuss with a doctor.*

  Further, labels are not permitted to include indications regarding hepatic function, digestive function, and joint function (Italian Ministry of Health (2022), as reported by Lombardi et al. (2020) and Daniells (2022)).

The following requirements are in place to address negative effects on the liver in certain individuals with pre-existing liver conditions:

- The recommendation that due to possible stimulation on bile secretion *Curcuma longa* is not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones, and any other biliary diseases (EMA, 2018)
- The requirement for a label warning on natural health products to consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if pregnant or breastfeeding, have gallstones, a bile duct obstruction, stomach ulcers, or excess stomach acid. (Health Canada, 2018)

JECFA, EFSA, and EMA:

Many industry respondents referred to the established Acceptable Daily Intake (ADI) for curcumin as evidence of safety up to 3 mg/kg. The ADI was initially established by JECFA in 2004, then further recognised by EFSA in 2010 and the EMA in 2018. However, the evidence used to determine the ADI preceded the more recent evidence of hepatoxicity associated with *C. longa*/curcumin and did not take into consideration the safety of curcumin-containing preparations with enhanced bioavailability. A safe dose for highly bioavailable curcumin has not been subsequently established.

This was further discussed during more recent considerations of this issue by the advisory Committee on Toxicity (COT) for the UK Food Standards Agency (FSA) in 2020 who questioned:

> *"…the relevance of comparing exposures from supplement intake to the ADI for dietary curcumin. It was decided that it would not be appropriate because synthetic forms or adjuvated curcumin, which may be used in supplements, could have altered TK* [toxicokinetic] *profiles and increased bioavailability. Thus, the levels determined as of low safety concern in food may not be relevant for supplements."* (COT, 2022)

Some industry respondents referred to the EFSA approval of tetrahydrocurcuminoids from turmeric (*Curcuma longa* L.) as a novel food (NF) in 2021. The EFSA assessment was specific to tetrahydrocurcuminoids and noted that they have no history of use as food. Tetrahydrocurcuminoids are derivatives of curcuminoids, produced chemically by hydrogenation of curcuminoids extracted from the rhizomes of *C. longa*. Tetrahydrocurcumin was reported as one of the metabolites of curcumin, produced *in vivo* through Phase I metabolism in the liver by hepatic reductases. Non-clinical data provided for the assessment was limited to 6 unpublished proprietary toxicity studies. The EFSA panel considered that acute toxicity studies are, in general, of limited relevance for the safety assessment of NFs. One human study was provided involving 20 subjects who consumed 300 mg (one tablet) per day of the NF for 28 days. The EFSA panel considered this uncontrolled study was of little value for the safety assessment of the NF. The EFSA panel derived a safe level of 2 mg/kg bw per day, based on the 90-day toxicity study provided by the applicant. Broader post market information for curcumin and *C. longa* were not considered as part of the assessment. Therefore, the approval of this novel food by the EFSA does not provide convincing evidence of safety or the absence of liver injury risks for *Curcuma* species or curcumin. Tetrahydrocurcuminoids are not currently permitted for use in listed medicines.

FDA:

Some industry respondents referred to Generally Recognised as Safe (GRAS) notifications by the FDA for various *C. longa* and curcumin substances. However, the data used to support the GRAS notifications was largely based on earlier data, including that used for the JECFA and EFSA

assessments, and predated the emergence of liver injury concerns. One respondent referred to the GRAS designation of a dietary supplement containing curcumin up to 1000 mg per day for a 60 kg person (FDA, 2018). This appears to be referring to GRAS notification No. 686 for curcumin from turmeric (*Curcuma longa* L.) (2017) which was again based on data up to 2015 that predated liver injury concerns, and for which the expert panel concluded that curcumin is generally recognised as safe for its intended use at 180 mg/person/day for the general population and for the use in medical foods at levels of 1000 mg/person/day *for intermittent use under medical supervision* [emphasis added].

The TGA acknowledges that the proposed label warning for listed medicines in Australia is not identical to risk mitigation requirements in other jurisdictions. However, this is not considered reasonable justification to take no risk mitigation action when recent evidence indicates it is warranted to reduce the risk of serious outcomes for Australian consumers. Further, the risk mitigation proposed is consistent with the approach taken by the TGA for other ingredients with a recognised risk of liver injury that are permitted for use in listed medicines in Australia.

Label warning not needed for idiosyncratic drug induced liver injury with rates less than 1 in 10,000

Some industry respondents commented that:

- the low rate of liver injury associated with *Curcuma* species and curcumin does not represent a safety risk proportionally greater than expected for idiosyncratic Drug Induced Liver Injury (DILI) for all substances, and
- the incidence should exceed the background level of expected idiosyncratic DILI for all substances (1 in 10,000 to 1 in 100,000), citing Chalasani et al. (2008), otherwise a liver injury warning would be needed for all substances.

The context of the Chalasani et al. (2008) article is around the use of a prospective network (i.e. the DILI network [DILIN]) to provide early detection of the hepatotoxic potential of newly released medications. The authors' statement of expected rates of idiosyncratic DILI being between 1 in 10,000 to 1 in 100,000 is in the context of any single agent *with a known association with idiosyncratic liver injury*, and is not referring to DILI rates for every medicine. There are many medicines with no association with idiosyncratic DILI, and for which DILI cases have never been reported. Therefore, to apply this figure to all medicines appears to be a misinterpretation of the article.

Further, the Chalasani et al. (2008) article does not suggest that the expected rates of idiosyncratic DILI should be exceeded to warrant risk mitigation, but rather that the rarity of the occurrence in any single agent (with a known association with idiosyncratic liver injury) makes it difficult to define and understand risk factors that contribute to DILI. The quote and the subsequent sentence from the article are as follows:

> *"Idiosyncratic DILI from any single medication is a rare clinical event occurring in less than 1 per 10,000 to 100,000 of subjects who take the drug. The risk factors for this rare occurrence and the pathogenesis are poorly understood*."

The article further states "*Because numerous dietary supplements are consumed by large numbers of US adults on a regular basis, the hepatotoxicity of dietary supplements may be significantly underestimated*".

A recently published article notes that idiosyncratic DILI is an infrequent but important cause of acute and chronic liver disease worldwide, and that newly identified causes include turmeric and green tea extract (Fontana, 2023). The article states that idiosyncratic DILI develops largely independent of the dose or duration of medication used. With regards to rates of (idiosyncratic) DILI the article states: "*Population-based studies from France and Iceland estimate the annual incidence of DILI to be 14–19 cases per 100,000 inhabitants. Lower incidence rates have been reported in the United States and higher rates in China."*

Larrey (2002) also provides comment in the context of medicines with an established risk of hepatotoxicity:

> *"… for the majority of drugs [known to cause DILI], the risk of hepatotoxicity ranges from 1 in 10,000 to 1 in 100,000. Such was the case for troglitazone, for which hepatotoxicity was estimated to be around 1 in 50,000 persons exposed. This explains why liver injury was not clearly detected among the 5000 patients included in clinical trials. For some drugs, such as antihistamines, penicillins, and minocycline, hepatotoxicity is exceedingly low (below 1 in 1,000,000); this makes it impossible to detect at an early stage and also makes the demonstration of a particular susceptibility factor extremely difficult. These difficulties explain why the first cases of hepatotoxicity are generally described within the first 2 years after the beginning of marketing, when a sufficient number of patients have been exposed to the new drug. In older instances, the discovery of hepatotoxicity even occurred several decades after their first use: 40 years for papaverine, 25 years for amiodarone, and perhaps hundreds of years for some herbal medicines such as germander."*

It appears that liver injury associated with *Curcuma* species and curcumin is idiosyncratic. Based on the above, the rate could be estimated to be between 1 in 10,000 and 1 in 100,000, and occurrence cannot be predicted based on dose, duration of use, nor on individual susceptibility. The TGA considers the unpredictable nature of idiosyncratic DILI presents risk to consumers self-administering medicines that contain *Curcuma* species/curcumin and that a warning is needed to reduce the risk of serious outcomes. The submission from clinical professional organisations including clinical toxicologists also considered that the cases observed to date were sufficient to justify the proposed risk mitigation.

International adverse events possibly due to quality issues (contaminants or synthetic curcumin)

Some industry respondents discussed the role of possible contamination or adulteration of curcumin in liver injury cases. They noted that due to the popularity of *Curcuma* species and curcumin, the incidence of adulteration with heavy metals, pesticides, other herbals, and chemical dyes has increased, which may be contributing to liver injury. One respondent noted the risk of this is occurring is greater in overseas jurisdictions that regulate *Curcuma* species and curcumin containing products as foods, where Australian requirements don't apply. The respondent noted raw materials used in Australian listed medicines must be identified, and controlled for adulterants, elemental impurities and contaminants and the potential for adulteration and presence of synthetic curcumin is greater in the overseas context and more likely in unapproved/illegal therapeutic goods in Australia or products purchased online.

Adulteration of the curcumin products being a contributory factor to the Italian reports of hepatotoxicity was thoroughly investigated and subsequently disproven by analyses of suspected products (Menniti-Ippolito et al., 2020). The presence of drugs, NSAIDs, synthetic

dyes and pyrrolizidine alkaloids were excluded, with only trace amounts of heavy metals, aflatoxins, and pesticides detected at levels close to the limit of quantification (Menniti-Ippolito et al., 2020). This together with the absence of high levels of lead, other metals, or azo-dyes on analyses of other supplements and spice samples in the United Kingdom led the COT to comment that the presence of possible contaminants being the reason for the recent incidents of hepatotoxicity is unlikely (COT, 2022).

Some respondents referred to the reported findings of Menniti-Ippolito et al. (2020) which noted that while curcumin was detected in all samples, other curcuminoids normally contained in extracts of *C. longa* were not detected in around 60% of analysed products. The study authors hypothesised that the raw materials consisted of synthetic substances added to enrich the finished product. The authors further commented that although this may reduce turmeric quality, it should not impact on safety. This opinion was disputed by two respondents, who commented that synthetic curcumin and 'other materials by unmonitored residual production chemicals carried with synthetic curcumin', presents a higher risk. One respondent commented that this was considered a mechanism of the liver injury, citing Lombardi et al. (2020).

One respondent commented that while they were not aware of synthetic curcumin being used in listed medicines in Australia, it is nevertheless worthwhile to examine whether this has occurred and whether, like in Italy, there is any increased association of events with synthetic curcumin or purified curcumin in comparison with curcuminoids or other extracts of *Curcuma* species.

The TGA notes that the presence of synthetic curcumin was not conclusively established in 60% samples tested that were involved in the liver injury cases in Italy. Rather, this was hypothesised based on results which found demethoxylated compounds were not detected. Of note was that demethoxylated compounds were detected in 40% of samples involved in liver injury cases.

Further, an increased risk of liver injury for synthetic curcumin has not been conclusively established. Lombardi et al. (2020) stated:

> *"...the impact of substituting (synthetic) curcumin for naturally occurring curcuminoids is not known, both in terms of efficacy and safety."*

The TGA notes that authors further stated that the production of synthetic curcumin may lead to the presence of degradation compounds (i.e. ferulic acid, acetone, and vanillin) and solvent residuals (i.e. isopropanol, ethyl acetate, acetone, methanol, ethanol, and hexane), which may contribute to their final risk profile in humans. However, the presence or causative role of synthetic curcumin and solvent residues have not been confirmed in any liver injury cases.

While curcumin is permitted for use in listed medicines, current requirements do not preclude the use of highly purified and/or synthetic curcumin. The TGA agrees that the use of highly purified or synthetic curcumin in listed medicines in Australia and its possible role in liver injury needs further monitoring, however at this stage, there is insufficient evidence to conclude that there is an increased risk of liver injury for purified or synthetic curcumin over other forms, and that risk mitigation should only apply to these ingredients.

Minimal or no liver-related adverse events in non-clinical studies and clinical trials, some showing hepatoprotective effects

Some respondents referred to multiple non-clinical studies, clinical trials, systematic reviews, and meta-analyses that reported either minimal or no liver-related adverse events (AE), with

some reporting hepatoprotective or beneficial liver effects. However, the reported publications were not sufficiently powered to detect DILI.

According to the 'Rule of three' (Brown, 2017), to detect an adverse reaction with an expected incidence of very rare (<1/10,000), the number of patients needed for an intervention is >30,000. None of the publications cited, individually or collectively comprised this number of subjects. Thus, although liver related AEs were not reported in many of the publications cited, the number of subjects in individual studies was not a sufficient study population to gain an accurate representation of very rare liver related AEs. Furthermore, several studies either did not collect information regarding AEs, or where AEs were mentioned, they did not always report whether liver enzymes were measured.

Some respondents referred to human studies that reported hepatoprotective effects with no reported adverse effects on the liver. While these studies suggest curcumin could have beneficial effects on the liver under some circumstances, studies were underpowered to detect rare AEs and appeared to be of limited value in demonstrating clinically applicable liver benefits. For example, one meta-analysis that examined effect of curcumin on non-alcoholic fatty liver disease only involved studies with a small number of study participants (47-102) and reported moderate to severe heterogeneity in the primary outcome, which included the effect of curcumin on liver enzymes among other measures. The authors commented that the level of evidence that contributed to the review was of low to moderate quality and noted that most of the studies were from Iran which limits the generalisability of results (Ngu et al., 2022).

Some respondents referred to another systematic review and meta-analysis that examined the effects of curcumin/turmeric supplementation on liver function (Dehzad et al., 2023). The study's authors reported that the quality of evidence using the GRADE profile for the effects of curcumin/turmeric supplementation on liver enzymes was low, and that inconsistency presented serious limitations. Again, the small size of individual studies, with intervention group participant numbers ranging from 11 to 71, limits any conclusive findings. The authors commented that due to complexities and the use of various products in the included studies, issues of safety and/or contamination/adulteration with other elements were not studied in this research. The authors also recommended that "*should turmeric/curcumin supplements be administered clinically, specific conditions of the individual must be regarded and utmost caution must be practiced*."

Another article referred to by some industry respondents was a summary of published clinical trials on curcumin formulations with enhanced bioavailability (Hegde et al., 2023). However, once again the authors commented on the small number of patient groups and dissimilarities in the clinical trials reviewed, and commented that more research is needed to examine safety and efficacy in large and diverse patient populations. Notably, while the authors summarised that most of the trials reported no serious AEs, many did not include AE information, nor was it clarified what type of data was collected (e.g. liver enzyme tests) for those that reported no serious side effects.

TGA's analysis of non-clinical data concurred with the premise that only a small number of adverse liver findings have been reported in toxicological studies, and acknowledged there is a significant body of non-clinical data that reported hepatoprotective effects. The TGA's review located two acute and sub-chronic toxicity studies that reported hepatotoxicity in mice and rats, as reported in other toxicological assessments of curcumin (EMA, 2018, COT, 2022).

However, this seemingly low number of studies with adverse findings cannot be equated to reassurance of safety, as idiosyncratic liver injury is difficult to replicate in animal models, which has presented a long-standing challenge in identifying drugs that can cause idiosyncratic liver injury prior to widespread exposure to humans (Roth and Ganey, 2022). Hepatotoxicity findings, even in only two non-clinical studies, supports a plausible association for idiosyncratic liver injury, as does the toxicity prediction model that reported 64 compounds in *C. longa* (including curcumin) could be predicted to cause dose-dependent hepatotoxicity based on the *in silico* models (Balaji and Chempakam, 2010). It should be noted that these studies do not form the basis of the TGA's decision, but rather provide supporting data.

It should also be noted that an efficacy review was not performed by the TGA to evaluate the clinical relevance of reported benefits of the various *Curcuma* species or curcumin as published in animal and human studies, as it is the responsibility of sponsors to hold evidence of efficacy specific to their listed medicine.

Influence of highly bioavailable preparations in liver injury cases

Some respondents commented on the possible increased risk of hepatotoxicity from highly bioavailable formulations, as noted in the consultation document. Similarly, the TGA notes that polypharmacy may increase risk through consumption of multiple curcumin-containing products, or consumption of multiple herbal ingredients associated with liver injury.

Menniti-Ippolito et al. (2020) noted that the majority of products detailed in their reports contained high titre curcumin and piperine to increase bioavailability. The authors commented that the products no longer complied with the conditions examined by the EFSA in determination of the ADI and opined that reassessment of the benefit/risk ratio is needed. However, it should also be noted that liver injury cases have been reported in the literature associated with medicines without *Piper nigrum*/piperine, and that were not reported as highly bioavailable formulations.

Nevertheless, as highly bioavailable formulations of curcumin are used more frequently in medicines, it is possible that reports of hepatotoxicity may further increase, however, the risk profile and characterisation of highly bioavailable curcumin remains to be elucidated. This is further complicated by the increasing variety of bio-enhanced formulations of curcumin available for use in supplements (Hegde et al., 2023). At this stage, there is no established safe dose for highly bioavailable curcumin, nor are these clearly defined.

Therefore, in the absence of a clear risk profile for highly bioavailable formulations that are well defined, together with the idiosyncratic nature of liver injury associated with *Curcuma* species/curcumin (i.e. cannot be predicted based on dose), limiting the risk mitigation measures to certain doses, preparation types, or ingredient combinations is not supported and therefore not considered appropriate.

Comments on literature cases in TGA's consultation document

One industry respondent questioned the numbers from international literature cases reported in the consultation document and suggested that these were overreported and some were duplicate reports. All cases assessed by the TGA and referred to in the consultation document were reviewed for duplicate cases. There was an omission in the consultation document whereby citations were not provided for all literature case reports reviewed by the TGA. Table 1

below has been provided to clarify which cases were referred to, including patient age and sex. All cases reported distinctly different aberrations in liver parameters, supplement/medication use and clinical course, confirming they are unique cases and not duplicates. It should be noted that cases reporting the same patient age and sex are distinctly different cases.

Table 1. Published Australian cases of turmeric-related hepatotoxicity.

Study details	Sex	Age
Chand et al., 2020	F	62
Luber et al., 2019	F	52
	M	55

Table 2. Published overseas cases of turmeric-related hepatotoxicity.

Study details	Sex	Age
Bermejo et al., 2022	F	44
Ayas et al., 2021	F	64
Abdul-Mujeeb et al., 2021	M	36
Sohal et al., 2021	F	57
	F	53*
Koenig et al., 2021	F	53*
Lee et al., 2020	F	55
Abdallah et al., 2019	F	51
Suhail et al., 2019	F	61
Fernández-Aceñero et al., 2019	F	78^
Imam et al., 2019	F	78^
Lukefahr et al., 2018	F	71

*While both cases are reported in 53-year-old women, the pattern of liver injury was different (cholestatic *vs* hepatocellular) as were liver function test results, and the clinical presentation.

^ While both cases are reported in 78-year-old women, the pattern of liver injury was different (acute hepatitis *vs* hepatocellular) as were liver function test results, and the clinical presentation.

The same respondent highlighted an error in the consultation document where the TGA reported that two cases did not report an outcome. The TGA acknowledges this was an oversight and should have stated that two cases did not report a complete return to normal liver enzyme levels after discontinuation, although improvement was noted on cessation of the suspected products (Abdul-Mujeeb et al., 2021, Koenig et al., 2021), noting one of these cases was confounded by the presence of other potentially hepatotoxic ingredients (Koenig et al., 2021).

Comparison to other products that may harm the liver and the impact on consumer expectations

One industry respondent stated that other self-selected products (such as paracetamol) and food (such as alcohol and sugar) can harm the liver yet these products do not require a label warning for liver injury. The respondent called for a whole-of-government approach to liver injury for self-selected products (including food) so that warnings and their effectiveness for consumers

can be considered collectively. The respondent also commented that liver injury warnings are not harmonised across products, and that there should be a condensed harmonised statement.

One respondent asserted that consumers generally only understand that self-selected products are roughly equivalent in terms of availability, and that a warning on one product without an equivalent warning on another could be perceived as a higher level of risk. The respondent commented that this could adversely affect consumer perception and behaviour and create unreasonable fear of very low risk substances while other higher risk substances continue to be used with little to no caution, with several references made to alcoholic beverages.

The TGA notes the same respondent has previously provided similar comments for other consultations. The TGA's position and response are consistent with previous responses. Unlike listed medicines, paracetamol is scheduled and is subject to tighter regulatory control than listed medicines. The risk of liver injury (including idiosyncratic DILI, stated by the respondent to have a latency period of 11-13 days) is mitigated by the requirement for several warning statements, such as: '*Do not use if you are taking other products containing paracetamol unless advised to do so by a doctor or pharmacist*' and '*Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor*'. In addition, clear advice on seeking urgent medical advice is provided to consumers if they suspect an overdose.

The TGA does not regulate foods and is not placed to comment regarding the risk of liver injury from consuming foods such as sugar and alcoholic beverages. Food Standards Australia New Zealand (FSANZ) is a statutory authority in the Australian Government Health portfolio and responsible for setting food standards. A whole-of-government consideration of label warnings on self-selected consumer products as suggested by this respondent is outside the scope of this consultation process and does not appear practical considering the different purpose for consumption and consumer expectations for foods compared to medicines. Unlike sugar or alcoholic beverages, listed medicines are consumed with the expectation of health benefits, as indicated on the medicine labels.

One respondent from a clinical professional organisation commented that patients presenting with liver injury are generally very surprised that over the counter preparations can cause serious liver injury with such severity of jaundice, nausea, fatigue etc. that hospitalisation is required. They noted that while deaths are rare, hospitalisations have been seen in Australia in patients with severe liver injury from compounds containing curcumin/turmeric and it is likely that the association is under-recognised and underreported.

Uncertain causality and frequency

Industry respondents raised concerns about the low number of liver injury reports in Australia with unknown causality being insufficient to confirm a reasonable causal relationship.

One respondent stated that they were opposed to an unreliable style of regulation responding to limited case reports and not examining the genuine level of risk and associated warnings for liver issues across all self-selected product types. The respondent commented that the risk assessment process should be standardised, utilising RUCAM for DILI, and a standardised threshold of cases should be considered, and that such a standardised approach should be applied to all products available for self-selection.

Causality:

The TGA acknowledges the challenges in establishing a diagnosis for idiosyncratic DILI or herb induced liver injury (HILI) because of the need to exclude other causes of liver injury, variable drug latency, and variable formulations and doses. Further challenges of establishing causality can stem from the lack of knowledge and awareness of potential liver injury from herbal supplements which may result in the causative agent (i.e. the herbal medicine) to go unrecognised by both patients and health care professionals (Fontana et al., 2022). Another critical challenge in pharmacovigilance is incomplete information for spontaneous reports of individual cases which was also acknowledged by some respondents.

The TGA agrees that the RUCAM causality assessment method provides a standardised assessment for HILI. However, applying the RUCAM retrospectively can be limited if data is unavailable for analysis. In such cases, causality can be assessed using the available information and clinical expertise. It should be noted that a causality of 'possible' is the highest rating assigned by the TGA for cases in the absence of RUCAM. On this note, several practice guidelines written on idiosyncratic DILI or HILI state that structured expert opinion is frequently used in clinical research studies and is shown to be as useful as RUCAM (Fontana, et al., 2022, Chalasani, et al., 2021).

Consensus expert opinion after a thorough evaluation for competing aetiologies is considered by some to be the current gold standard for establishing causality in individuals with suspected DILI (Chalasani, et al., 2021).

One respondent raised concern that the likelihood score of 'B' (a likely rare cause of clinically apparent liver injury) assigned to turmeric by the NIH LiverTox database was based on reports that lacked a RUCAM assessment. However, the LiverTox entry for turmeric referred to several literature cases that reported probable to highly probable RUCAM ratings (Luber et al., 2019, Lee et al., 2020, Abdallah et al., 2020, Suhail et al., 2019, Lukefahr et al., 2018). It is noted that the LiverTox database content is subject to review by an External Expert Review committee comprised of three experts in DILI, hepatology, pharmacology, and/or herbal supplement safety (LiverTox, 2022).

Noting the challenges of establishing causality, the TGA has determined a causal link between *Curcuma* species/curcumin and liver injury using expert opinion, clinical assessment, and RUCAM analysis. As mentioned in the consultation document, The Advisory Committee on Complementary Medicines (ACCM) also agreed that the strength of the relationship between liver injury and *C. longa*/curcumin is medium to strong, with a higher risk for people with a history of liver problems.

Frequency:

Regarding comments from one respondent who suggested that regulatory action should be based on a threshold number of cases, and that this should be consistently applied to all self-selection products, the TGA provides the following response.

Spontaneous AE reporting systems cannot be relied on to generate frequency data largely due to the absence of usage data but also due to under-reporting. There are several reasons that contribute to under-reporting in spontaneous reporting systems (Palleria et al., 2013), for example:

- the belief that very serious AEs are well documented by the time a medicine is marketed.

- uncertainty around whether a medicine is responsible for a particular adverse reaction.
- the belief that a report should only be made if there is certainty that it is related to the use of a particular drug.
- the belief that a single case could not contribute to medical knowledge.

Uncertainty of the potential causal relationship represents a major limitation for healthcare personnel in reporting events, however, a key principle of pharmacovigilance emphasises that reporting any possible association is beneficial as it supports signal detection which is in the interest of protecting public health (Palleria et al., 2013). Considering any spontaneous AE database does not reflect the true number of reports, other methods of data analysis are utilised to identify signals, such as disproportionality algorithms. While the TGA utilises a disproportionality algorithm for signal detection based on medicine-reaction pairing, it is of limited value for signal detection for multi-ingredient listed medicines, which are too varied in their formulations to generate signals using this algorithm. However, VigiBase, WHO global database of AEs, contains a much larger dataset and can measure disproportionality based on single ingredients using the information component (IC) model. It should be noted that the IC does not imply causality, but a positive IC value that increases over time suggests a connection between the drug and adverse reaction based on reporting to VigiBase. Alternative explanations for the positive IC need to be considered and clinical assessment remains essential (Uppsala Monitoring Centre, 2016). While taking this into account, the IC_{025} figure generated for *Curcuma longa* applying the Standardised MedDRA Query (SMQ) Drug related hepatic disorders - comprehensive search (Broad) reveals a positive value (>0). This indicates a higher-than-expected number of reports, for the reactions jaundice, autoimmune hepatitis, hepatotoxicity, liver injury, hepatic failure, and hepatic cytolysis**Error! Bookmark not defined.**.

The TGA notes that although one industry respondent suggested regulatory action should be based on a threshold number of cases, they did not provide a proposed number of cases above which they considered a consumer warning would be appropriate, apart from referring to idiosyncratic DILI rates for all substances. The TGA has addressed idiosyncratic DILI rates above and considers it has been misinterpreted by industry respondents. Spontaneous AE reporting data cannot be used to establish a frequency of occurrence for AEs as mentioned above. The TGA considers that waiting for more AEs to occur in Australia before implementing a label warning aimed at minimising harm from these potentially life-threatening reactions is not an acceptable approach for listed medicines. There is sufficient evidence and consensus that there is a risk of liver injury from *Curcuma* species and curcumin when consumed as supplements/medicinal dosage forms, and although the risk has not been definitively characterised in terms of the risk profile of various preparation types, preventive action is warranted to reduce the risk of severe outcomes for Australian consumers. This also supports these ingredients remaining suitable for use within the listed medicine framework.

Some respondents referred to the growing association between curcumin-related liver injury and the human lymphocyte antigen (HLA) allele known as HLA-B*35:01 and the suggestion that individuals with this allele may be at greater risk of liver injury. A respondent referred to a study that found 7/10 turmeric patients reported by DILIN were found to carry the HLA-B*35:01 allele, with authors concluding a strong link between liver associated with turmeric and this allele (Halegoua-DeMarzio et al., 2022). While this is an interesting area of research, a requirement for genetic screening to ensure safe use is not consistent with the listed medicines framework, and not all cases have been found to be HLA-B*35:01 positive.

The TGA notes that in the consultation responses, three professional organisations, comprising gastroenterologists, hepatologists and clinical toxicologists, were supportive of the proposed label warning:

- One respondent noted that while deaths are rare, hospitalisations have been seen in Australia in patients with severe liver injury from compounds containing curcumin/turmeric and it is likely that the association is under-recognised and underreported.
- They also note that while it is difficult to mitigate risk, ensuring the public is aware that liver injury may occur allows both an informed choice by the consumer, and also a recognition that the product could be responsible should they be found to have liver derangement, which may assist with early diagnosis and appropriate management.
- Another respondent strongly supported the proposed labelling changes due to the clear risks of hepatotoxicity to consumers. They commented that while relatively rare, the TGA has demonstrated sufficient evidence that warning labels are required to safeguard consumers.
- A third respondent also supported the proposed wording changes by the TGA and recognised the potential risk of liver injury from *Curcuma* species (particularly in concentrated, supplement format).

The TGA consider there is sufficient evidence for this emerging concern and for the need for risk mitigation which is particularly important considering curcumin is included in numerous listed medicines available for self-selection and can be consumed without medical supervision. However, it is recognised that *Curcuma* species/curcumin in supplements/listed medicines are widely consumed relative to reported liver injury cases which at this stage appears to be a very rare risk. Therefore, the proposed warning will be implemented to refer to the risk as being 'very rare' rather than 'rare' as proposed in the consultation document.

Label warning to apply for active ingredients only and at a threshold dose

Use of curcumin as a colour:

One respondent suggested that the label warning should not apply to medicines that contain curcumin as a colour as there have been no liver injury reports for curcumin when used as a colour. The TGA agrees with this proposal and notes that both *C. longa* and curcumin are permitted for use as an excipient ingredient, with curcumin only permitted as a colour when for excipient use. Although *C. aromatica*, *C. zanthorrhiza*, and *C. zedoaria* are not currently permitted for excipient use, having a restriction when used as an active ingredient across all *Curcuma* species and curcumin will allow for a consistent approach to be taken from this public consultation. Therefore, the specific requirements will be amended for all five ingredients accordingly.

Threshold dose:

One respondent from a clinical professional organisation that supported the dose limits for children, commented that while dose limits for children and adolescents will not entirely capture the risk due to formulations with enhanced bioavailability, they will substantially ameliorate the risk.

For listed medicines indicated for use in children under 18 years of age, sponsors will be expected to hold evidence (e.g. batch analysis data, raw material data, scientific literature etc.) that the medicine does not exceed the relevant curcumin limits for each age group once the new requirements come into effect.

The consultation document also invited additional information to support a safe dose. One respondent proposed that the warning statement should only apply to *Curcuma* species when combined with piperine or other bioavailability enhancing substances, for daily doses above 750 mg curcumin, however, specific evidence was not provided to support this as a safe dose.

Considering the nature of liver injury associated with *Curcuma* species/curcumin is idiosyncratic and cannot be predicted based on dose, the TGA considers the label warning is needed for all active ingredients regardless of dose based on the information currently available. This is consistent with advice from ACCM that restrictions on the permitted dose of curcumin were not a practical method of risk mitigation, given that the bioavailability was likely more important than dose.

One respondent noted that curcumin is not a mandatory component of *Curcuma* species, and the proposed dosage limits for curcumin for children and adolescents presents regulatory and analytical challenges for sponsors, particularly for *Curcuma* species containing medicines more closely based on traditional systems of medicine (e.g. Ayurvedic medicine). In addition, industry has had varying interpretation of 'curcumin', some applying it to the single curcuminoid, while others use it to refer to a highly purified mixture of curcuminoids. The respondent suggested that the dosage restriction in children and adolescents should be based on active ingredient input where the active ingredient is the unique *Curcuma* species rather than using curcumin, taking into account the lower amount of curcumin in other *Curcuma* species when applying dosage restriction limits for these ingredients.

The TGA does not intend to make curcumin a mandatory component in listed medicines that contain *Curcuma* species. The TGA is aware that sponsors have used the ingredient name 'curcumin' as it has historically been used; to either refer to the single chemical 1,7-bis(4-Hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione or a highly purified mixture of curcuminoids (according to what was referred to as 'curcumin' by the JECFA monograph available at the time the ingredient was approved for listed medicines).

The Acceptable Daily Intake (ADI) of 0-3 mg/kg bw/day established by JECFA (2004) was based on a multigenerational toxicity study conducted using curcumin comprising of a minimum purity of 95% 1,7-bis(4- hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione, a study later published by Ganiger et al. (2007). Subsequently, the TGA used this ADI to derive the proposed maximum permitted daily dose for the different age brackets for children. Replacing the dosage restrictions using active ingredient input will have unintended consequences on sponsors of current medicines, as this will significantly restrict the amounts of *Curcuma* species, given the curcumin content in *Curcuma* species is relatively low (e.g. *C. longa* rhizome contains 0.5-5% curcumin in dry weight (EMA, 2018); air-dried *C. zedoaria* yields approximately 0.16% curcumin (Lobo et al., 2009)). For clarity, the restrictions relating to safe levels of 'curcumin' in children will be amended to reflect the single chemical as per the substance used to derive the ADI whose IUPAC name is (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Priyadarsini, 2014).

Suggestions for alternative wording in the warning

Two respondents suggested alterations to the wording of the proposed warning statement. One respondent suggested the removal of reference to 'itching' while the other suggested an alternative condensed warning statement with no reference to symptoms or instructions to stop use and see a doctor (*In very rare cases, large doses of Curcuma species may harm the liver in certain individuals*).

It is important to list early signs and symptoms of liver injury so that consumers can identify when to cease the product and seek medical attention.

The pattern of liver injury in cases reported for *Curcuma* species and curcumin has been both cholestatic and acute hepatitis. For cholestatic hepatitis, LiverTox reports the typical presentation of symptoms as nausea, fatigue, and *pruritus* followed by dark urine and jaundice (LiverTox, 2019a). LiverTox reports that symptom onset for acute hepatitis is typically insidious with fatigue and nausea followed by anorexia and abdominal discomfort, and while itching can be absent in the early course, it may arise if jaundice is prolonged (LiverTox, 2019). Considering both cholestatic and acute hepatitis have been reported for *Curcuma* species and curcumin, and that for acute hepatitis, pruritus can suggest that liver injury may be advanced, it is important to list unusual itching as a symptom for consumers to be aware of.

Another key message for consumer protection is the instruction to stop use and see a doctor if symptoms of liver injury arise. Continuation of the offending agent can lead to severe outcomes including the need for liver transplantation or death, while early discontinuation usually leads to reversal of the liver injury, often with only close monitoring required without the need for treatment or hospitalisation. Therefore, the TGA considers the inclusion of the words '*Stop use and see a doctor*' in the label warning is vital to ensure appropriate action is taken to reduce the risk of severe outcomes, particularly for listed medicines that are available for self-selection and often used without healthcare practitioner intervention or supervision.

Concern of further regulatory action for products indicated for liver health

One respondent raised a concern that regulatory action could arise for unacceptable presentation for listed medicines indicated to support liver health due to a perceived contradiction with the proposed warning statement for liver injury. The TGA considers that a warning statement referring to a 'very rare' risk of liver injury is sufficiently distinct from permitted indications for liver health and is essential to inform consumers who may choose to avoid the very rare risk, particularly those with active liver disease or a history of liver disease.

Additional literature cases

Since the TGA's initial review, further case reports involving *Curcuma* species/curcumin products and hepatotoxicity have been published.

One report from the USA involved a 62-year-old female who had consumed a turmeric tea (once daily – no further details) for 3 weeks prior to presentation at hospital, with symptoms present for 5 days prior. The authors reported causality using RUCAM resulted in a score of +9 (highly probable) (Smith et al., 2023). The authors also reported poor recall regarding the quantity consumed or piperine co-supplementation, as well as unclear product labelling which complicated the evaluation of the role of *C. longa* in this case. However, although there is uncertainty around the product formulation, the description of the suspected medicine as 'a

turmeric-containing tea' raises further concerns for the potential risk of liver injury from traditional preparations of *C. longa*.

Four other case reports involved the consumption of piperine-enhanced formulations:

- Ajitkumar et al. (2023) published a report from the USA that involved a 55-year-old female who consumed a turmeric supplement (1500 mg per day) that contained piperine for one month prior to onset of symptoms. The authors reported a RUCAM score of +9 (highly probable).
- Arzallus et al. (2023) published a case report from Spain that involved a 28-year-old male who had consumed the product TURMERIC + (Scientific Nutrition brand) that also contained 'Bioperine black pepper' for 5 months prior to presentation. He was identified as possessing the allele HLA-B*35:01. The authors reported a RUCAM score of +6 (probable).
- Sunagawa et al. (2022) published a case from the USA of a 49-year-old female who consumed 2 capsules daily of a 1000mg turmeric supplement that also contained *Piper nigrum* for approximately 1.5 months prior to hospital admission. The authors reported a RUCAM score of +7 (probable). The supplement was analysed and found to contain curcumin, demethoxycurcumin, and bisdemethoxycurcumin, but at less than the labelled amount.
- Liu and Chang (2022) reported a case from the USA of a 49-year-old female who had consumed a 1000 mg daily dose of turmeric in a formulation with *Piper nigrum* for 3 months prior to hospital admission. Re-exposure resulted in another hospital admission one month later. No RUCAM score was reported by the authors, but a TGA assessment resulted in a RUCAM score of +6 (probable).

The case described by Sunagawa et al. (2022) also reported that the analysis confirmed the absence of other hepatotoxic ingredients, although details were not provided. As the amount of curcumin determined to be present in the product was less than that stated on the label, the authors speculated that lower doses of curcumin in combination with piperine may still have the potential to cause liver injury, and that there may be a synergistic effect, although further studies are needed.

As the number of case reports of hepatotoxicity associated with curcumin continues to increase, the TGA considers that adopting a 'wait and see' approach is not appropriate in this situation. To mitigate the risk of a more severe, or fatal reaction occurring, consumers should be provided with sufficient information to identify if they are experiencing symptoms of liver injury, in order to know when to cease the medicine and to seek medical advice promptly.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions. In consideration of the responses received, the TGA will implement new requirements for *Curcuma* species/curcumin as presented for consultation with minor amendments to provide clarity around exclusion of the label warning requirements for *Curcuma* species/curcumin when used as an excipient ingredient, to replace 'rare' with 'very rare' in the warning statement, and clarify the dosage restrictions for children are based on the chemical (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione.

The TGA will continue to monitor this safety signal and adverse events related to this issue. The current requirements may be revised in the future if new evidence becomes available to the TGA to support the change.

Affected ingredients

- CURCUMA AROMATICA
- CURCUMA LONGA
- CURCUMA ZANTHORRHIZA
- CURCUMA ZEDOARIA
- CURCUMIN

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New specific requirements
CURCUMA AROMATICA	-	When used in oral medicines as an active ingredient, the following warning statement is required on the medicine label: 'In very rare cases, Curcuma species may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' When used in oral medicines the maximum daily dose of (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione in the medicine must not provide more than: (a) 36 mg for children from 2-3 years (inclusive) (b) 48 mg for children from 4-11 years (inclusive) (c) 123 mg for children from 12-17 years (inclusive) Not permitted for use in children aged below 2 years.

Ingredient name	Existing specific requirements	New specific requirements
CURCUMA LONGA	-	When used in oral medicines as an active ingredient, the following warning statement is required on the medicine label: 'In very rare cases, Curcuma species may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' When used in oral medicines the maximum daily dose of (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione in the medicine must not provide more than: (a) 36 mg for children from 2-3 years (inclusive) (b) 48 mg for children from 4-11 years (inclusive) (c) 123 mg for children from 12-17 years (inclusive) Not permitted for use in children aged below 2 years.
CURCUMA ZANTHORRHIZA	-	When used in oral medicines as an active ingredient, the following warning statement is required on the medicine label: 'In very rare cases, Curcuma species may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' When used in oral medicines the maximum daily dose of (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione in the medicine must not provide more than: (a) 36 mg for children from 2-3 years (inclusive) (b) 48 mg for children from 4-11 years (inclusive) (c) 123 mg for children from 12-17 years (inclusive) Not permitted for use in children aged below 2 years.

Ingredient name	Existing specific requirements	New specific requirements
CURCUMA ZEDOARIA	-	When used in oral medicines as an active ingredient, the following warning statement is required on the medicine label: 'In very rare cases, Curcuma species may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' When used in oral medicines the maximum daily dose of (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione in the medicine must not provide more than: (a) 36 mg for children from 2-3 years (inclusive) (b) 48 mg for children from 4-11 years (inclusive) (c) 123 mg for children from 12-17 years (inclusive) Not permitted for use in children aged below 2 years.
CURCUMIN	When for excipient use, only permitted for use as a colour in topical and oral medicines.	When for excipient use, only permitted for use as a colour in topical and oral medicines. When used in oral medicines as an active ingredient, the following warning statement is required on the medicine label: 'In very rare cases, Curcumin may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' When used in oral medicines the maximum daily dose of (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione in the medicine must not provide more than: (a) 36 mg for children from 2-3 years (inclusive) (b) 48 mg for children from 4-11 years (inclusive) (c) 123 mg for children from 12-17 years (inclusive) Not permitted for use in children aged below 2 years.

2. Green tea extract and the risk of liver injury

Background

This consultation discussed the risk of liver injury associated with concentrated *Camellia sinensis* (green tea) extracts in therapeutic goods (e.g. weight loss tablets). Green tea in food (e.g. brewed beverages) is not regulated by the TGA and has not been identified as a safety concern.

The consultation document presented information that demonstrated an association between use of products containing *C. sinensis* extracts and liver injury. The TGA invited stakeholders to comment on a proposal to require additional label statement for oral listed medicines containing *C. sinensis.* The proposed statements were intended to communicate the rare risk of serious liver injury and reduce the potential for severe injury. For consistency, the term *C. sinensis* will be used to refer to green tea.

Consultation submissions

Seven submissions were received for this proposal. There was clear support for the proposed changes from relevant clinical professional organisations (e.g. representing gastroenterologists and clinical toxicologists) while complementary medicines industry stakeholders provided mixed support and an individual health professional opposed the proposal.

TGA response

The TGA acknowledges that *C. sinensis* has a long history of use as a food and medicine with some reported benefits. However, the currently available evidence shows that there is a rare risk that *C. sinensis* can cause liver injury. The nature of *C. sinensis* associated liver injury has both an intrinsic dose dependent aspect, as well as a dose independent idiosyncratic aspect for certain individuals. Further, the lack of knowledge and awareness of potential Herb Induced Liver Injury (HILI) from widely used supplements may result in a failure to identify a causal association which can lead to under-reporting, and more concerningly can lead to more severe outcomes if exposure to *C. sinensis* is continued. Such challenges can be overcome by increasing awareness of the risk of HILI among consumers and healthcare practitioners, with clear identification of symptoms to be aware of and instructions for what to do if they arise.

The TGA acknowledges there are some uncertainties around the safe level of exposure and the rarity of liver injury occurring after consuming *C. sinensis*. Accordingly, the TGA considers that a label warning is commensurate with the available evidence. The TGA will continue to monitor this safety concern and consider if further regulatory actions are required.

The TGA thanks stakeholders for their submissions. Key issues raised are discussed below.

Safety of aqueous extracts vs other preparations

Three respondents suggested widening the scope of *C. sinensis* preparations that are excluded from the proposed label warning (i.e. containing ≤300 mg epigallocatechin-3-gallate [EGCG] per maximum recommended daily dose from only aqueous extracts of *C. sinensis*) to include other preparations such as non-aqueous extracts, leaf dry, and leaf powder.

EGCG is the suspected component linked to the observed liver injury, however it is unclear if there are other chemical components that may be associated. *C. sinensis* preparations may have different chemical compositions making it difficult to anticipate the safety implications of non-aqueous extracts. The composition of aqueous extracts is expected to be largely consistent with infusions consumed as a beverage for which the risk of liver injury is considered low. This is consistent with Europe where labelling statements are not required for foods (including food supplements) that contain aqueous green tea (*C. sinensis*) extracts containing EGCG which after reconstitution in beverages have a composition comparable to traditional green tea infusions (90 to 300 mg/day EGCG)[1]. The EFSA scientific opinion concluded that catechins from green tea infusion, prepared in a traditional way, and reconstituted drinks with an equivalent composition to traditional green tea infusions, are in general considered to be safe (EFSA, 2018).

As discussed in the consultation, the EFSA scientific opinion concluded that doses of >800 mg EGCG/day taken as food supplements significantly increase serum liver injury markers in treated subjects compared to controls, based on clinical trials. The above-mentioned European Commission regulation does not permit food or food supplements (excluding aqueous green tea extracts containing EGCG which after reconstitution in beverages have a composition comparable to traditional green tea infusions) to contain more than 800 mg EGCG per daily portion. Foods that contain less than 800 mg have additional labelling requirements to address risks of liver injury:

- The label shall provide the maximum number of portions of the food for daily consumption and a warning not to consume a daily amount of 800 mg of EGCG or more.
- The label shall indicate the content of EGCG per portion of the food.
- The label shall include the following warnings:
    - "*Should not be consumed if you are consuming other products containing green tea on the same day*".
    - "*Should not be consumed by pregnant or lactating women and children below 18 years old*".
    - "*Should not be consumed on an empty stomach*".

One respondent referred to the UK Committee on Toxicity (COT 2022) which assessed if new evidence has emerged since the adoption of the EFSA opinion on green tea catechins in 2018. The respondent refers to the papers conclusion that there is no additional data suggesting that EFSA's conclusion, that 800 mg/day EGCG was probably safe, is no longer appropriate. The TGA notes that the COT's final conclusions were that based on both the previous and additional data, it has still not been possible to identify a no observed adverse effect level (NOAEL) for *C. sinensis* extract or for EGCG.

Respondents referred to proposed restrictions for foods by Health Canada, to allow up to 300 mg/day EGCG (that includes other preparation types that are non-aqueous extracts) as a supplemental ingredient in foods based on Health Canada's Food Directorate's safety assessment. The conditions proposed by Health Canada are noted to be based on the available evidence that supports that standardized green tea extract can be safely consumed as a supplemental ingredient on a daily basis at levels consistent with a cup of brewed green tea.

[1] Commission regulation (EU) 2022/2340 of 30 November 2022 amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards green tea extracts containing (-)-epigallocatechin-3-gallate https://eur-lex.europa.eu/eli/reg/2022/2340

The TGA agrees that products containing a maximum daily dose of an aqueous extract consistent with a brewed cup of green tea can be expected to be low risk, and notes that in Australia listed medicines are permitted to utilise extraction methods that would result in medicines with components, and at concentrations, that are not consistent with a cup of brewed green tea. As discussed in the consultation paper, a cup of brewed green tea is estimated to contain up to 300mg EGCG (and this is also consistent with the mean daily intakes reported by the European Commission that ranges from 90-300mg/day).

Health Canada's proposal and the European Commission require a range of conditions such as label warning statements, restrictions on use in adults, pregnant, and breastfeeding women, restrictions on the content of EGCG and total catechins per serving and per day, and restrictions on not consuming other foods with the same ingredients in the same day. The Health Canada proposal has not been finalised as at time of publication of this Final Decisions document. However as mentioned in the consultation document, Health Canada has existing requirements in place for Natural Health Products that restrict EGCG and total catechin content, and for label warnings to address liver injury, to take with food, for certain population groups, and for use beyond 12 weeks. These measures are not considered the most effective option for listed medicines in Australia as they are lengthy and more complicated than what has been proposed, noting the lack of product label space concerns consistently raised by the complementary medicines industry.

Respondents noted concerns about requiring EGCG content to be declared as this would present challenges for more traditional forms of *C. sinensis* that are used at lower doses and would not have this information typically available.

The TGA considers that 300 mg/day of EGCG from *C. sinensis* as green tea aqueous infusions can be expected to be low risk and unlikely to cause liver injury. The TGA considers that insufficient information is available for the safety of other *C. sinensis* preparations used in listed medicines including non-aqueous extracts, leaf dry, and leaf powder, to support exclusion from the label warning requirement. The TGA is not requiring that manufacturers will need to declare EGCG content for their listed medicines as a result of this consultation.

Alternative warning statements

Three respondents suggested alterations to the proposed warning statement. This included removal of reference to "itching", and shorter alternatives.

Two of the possible liver injury AE reports received by the TGA associated with *C. sinensis* reported itching (pruritus), one of which reported this as an initial symptom along with jaundice. Although most liver injury cases present with an acute hepatitis-like syndrome and a markedly hepatocellular pattern of enzyme elevations (LiverTox, 2020), cholestasis can occur, as reported in one of the TGA cases mentioned above. LiverTox reports that symptom onset for acute hepatitis is typically insidious with fatigue and nausea followed by anorexia and abdominal discomfort, and while itching can be absent in the early course, it may arise if jaundice is prolonged (LiverTox, 2019). For cholestatic hepatitis, LiverTox reports the typical presentation of symptoms as nausea, fatigue and pruritus followed by dark urine and jaundice (LiverTox, 2019a). Considering some cases have reported pruritus, including as an initial symptom, and that for acute hepatitis pruritus can suggest that liver injury may be advanced, it is important to list unusual itching as a symptom for consumers to be aware of and to stop use immediately and seek medical advice.

One respondent note that itching has not been included as a symptom for previously consulted liver injury warnings. The TGA notes this is not correct as itching has been included in similar liver warnings for products containing *Valeriana officinalis.*[2]

The unusual symptoms: nausea, appetite loss, abdominal pain may also be the first symptoms of liver injury. The TGA has taken into consideration feedback from previous consultations to differentiate between mild/transient symptoms experienced by consumers from time to time that may be unrelated to liver injury, by including the qualifier 'unusual' to inform consumers to act if symptoms arise that are not typical for them.

The inclusion of the words '*Stop use and see a doctor*' in the label warning is vital and succinct to ensure appropriate action is taken to reduce the risk of severe outcomes, particularly for listed medicines that are available for self-selection and often used without healthcare practitioner intervention. Continuation of the offending agent can lead to the need for liver transplantation or death, while early discontinuation usually leads to reversal of the liver injury, often with only close monitoring required without the need for treatment or hospitalisation.

The TGA notes submissions that were in favour of the proposed wording of the warnings, noting the importance that consumers presenting with liver failure or injury are not aware and have not been warned that ingredients they were taking were associated with liver injury.

On reviewing the responses, the TGA has re-restructured the requirement to improve clarity of the exemptions and for when the warning statements are required.

Management of EGCG in *Camellia sinensis*

One respondent was not clear on the approach that the TGA will be taking to manage EGCG in *C. sinensis* containing products. The TGA is not proposing to require EGCG as a mandatory component of *C. sinensis* or apply a specific condition of listing for this ingredient. Sponsors may choose to apply the label warning even if the EGCG in their *Camellia sinensis* aqueous extract is below 300 mg per daily dose. Sponsors who apply the label warning, irrespective of the amount of EGCG in an aqueous extract per daily dose would not be expected to hold evidence of EGCG content in their medicine unless the EGCG content is claimed on the label. However, sponsors that do not apply the label warning would be expected to hold information to demonstrate that the maximum amount of EGCG in their *C. sinensis* aqueous extract does not exceed 300 mg EGCG per daily dose once the new requirements come into effect.

Removal of *Camellia sinensis* extracts in weight loss supplements

One respondent proposed removal of *C. sinensis* extracts from herbal and dietary supplements advertised for weight loss that are currently regarded as food additives. In Australia, food and medicines are regulated under separate legislative frameworks, commensurate with the intended use and potential risks that those products pose to public health and safety. The TGA is responsible for regulating therapeutic goods, whereas the regulation of food is a joint responsibility of Food Standards Australia & New Zealand and the state and territory government food authorities and local councils. The TGA considers the proposed requirements for *C. sinensis* mitigate the risk of serious liver injury for consumers wishing to use therapeutic goods regulated as listed medicines. From 30 November 2023, sports supplements making therapeutic claims (including those containing *C. sinensis* promoted for weight loss) that are

[2] Annual low-negligible risk changes 2022-2023

presented in the form of tablets, capsules or pills, will be regulated as therapeutic goods and must meet legislated requirements, including the requirement to be included in the Australian Register of Therapeutic Goods (ARTG) to be supplied in Australia. Sports supplements that are included in the ARTG as listed medicines will be required to comply with the requirements for *C. sinensis* when they come into effect.

Camellia sinensis for use in flavour proprietary excipient formulations

One respondent did not support the proposal that *C. sinensis* can only be used as an excipient in a flavour proprietary excipient formulation and suggested the rationale behind the additional restriction was not included in the consultation paper. The respondent proposed exempting the requirement for a warning statement when *C. sinensis was used as an excipient, at any concentration and any preparation*.

The consultation document proposed that the warning statement would not apply to *C. sinensis* used as part of a proprietary ingredient formulation for flavouring (limited to 5% of the total medicine in line with acceptable flavour proprietary ingredient limits in listed medicines). *C. sinensis* used as a component in a proprietary ingredient is not expected to be extracted to contain concentrated catechins, and only be present in minor amounts in a medicine and therefore unlikely to raise concerns of liver injury. Sponsors are still permitted to use *C. sinensis* as an excipient in oral listed medicines other than in flavour proprietary ingredients and will be exempt from requiring a warning statement where the preparation of *C. sinensis* is derived from an aqueous extract and contains 300 mg or less epigallocatechin-3-gallate per maximum recommended daily dose. The TGA notes that there are numerous listed medicines for topical use (such as sunscreens) that contain *C. sinensis* as an excipient and a safety concern has not been identified when *C. sinensis* is used topically. The warning statement would not apply to excipients for topical use. Minor changes to the wording of the requirements have been made to better clarify when the warning statement is not required, such as for flavour proprietary ingredient formulations.

Quality of *Camellia sinensis* containing products

One respondent suggested the number of excipients should be reduced and the quality of herbal raw materials should be improved instead of imposing restrictions on the ingredient, *C. sinensis*, suggesting this would mitigate the risk of liver injury.

The TGA acknowledges that the quality of *C. sinensis* containing products on the international market is highly diverse, and variable product quality may impact the incidence of adverse events (AEs). Listed medicines in Australia must be manufactured under Good Manufacturing Practice and comply with other quality requirements such as the Therapeutic Goods Order No. 101 - Standard for tablets, capsules and pills. However, the TGA has received reports of serious liver injury for single ingredient *C. sinensis* products included in the ARTG. It is further noted that issues of quality contamination would be associated with a clear cluster of AEs, which is not evident in the reports received by the TGA or internationally.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue. In consideration of the responses received, the changes to requirements for *Camellia sinensis* which were presented for consultation will be implemented as described below, with minor amendments to the wording for consistency

throughout the Determination and to improve clarity regarding exceptions when a warning statement is not required.

The TGA will continue to monitor this safety signal and adverse events related to this issue. The current requirements may be revised in the future if new evidence becomes available to the TGA to support the change.

Affected ingredient

- CAMELLIA SINENSIS

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New additional specific requirements
CAMELLIA SINENSIS	Caffeine is a mandatory component of Camellia sinensis. When the medicine is packaged for supply as a divided preparation and is for internal use or oral application, the medicine must not contain a concentration of total caffeine greater than 33%. When for internal use or oral application, the maximum recommended daily dose of the medicine must provide no more than 400 mg of total caffeine. When the medicine is packaged for supply as an undivided preparation and is for internal use or oral application, the medicine must not contain a concentration of total caffeine greater than 1%. When the medicine is for internal use or oral application, a maximum recommended dose of the medicine must not provide more than 100 mg of total caffeine within a 3 hour period. When the maximum recommended daily dose of the medicine provides greater than 10 mg of total caffeine and the medicine is for internal use or oral application, the following warning statements are required on the label: - (ADULT) 'Adults only' (or words to that effect). - (CAFF) 'Contains [state quantity per dosage unit or per mL or per gram of product] total caffeine [per dosage unit or per mL or per gram]. A cup of instant coffee contains approximately 80mg of caffeine.' - (CAFFPREG) 'Caffeine intake more than 200 mg per day is not recommended during pregnancy or breastfeeding.' When the maximum recommended daily dose of the medicine provides greater than 80 mg of total caffeine and the medicines is for internal use or oral application, the following warning statements are required on the label: - (CAFFLMT) 'Limit the use of caffeine-containing products (including tea and coffee) when taking this product.' - (CAFFCYP) 'Caffeine interacts with enzyme CYP1A2 in the liver. Consult your health professional before taking with other medicines' (or words to that effect).	When used in oral medicines, the following warning statements are required on the medicine label: - 'In rare cases, Camellia sinensis may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes, or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.' - (FOOD) 'To be taken with food.' unless when: (a) the preparation of Camellia sinensis is derived from an aqueous extract and contains 300 mg or less epigallocatechin-3-gallate per maximum recommended daily dose; or (b) Camellia sinensis is used in combination with other permitted ingredients as a flavour proprietary excipient formulation. The total concentration of flavour proprietary excipient formulations containing Camellia sinensis must not be more than 5% of the total medicine.

3. Safe levels of benzophenone

Background

The consultation document proposed an amendment to the requirements for use of benzophenone and octocrylene in listed medicines. As benzophenone is an established potential degradant of sunscreens that contain octocrylene, it was proposed to be declared as a mandatory component of octocrylene to ensure it is not present above an acceptable trace level. The TGA invited stakeholders to provide information regarding acceptable safe levels of benzophenone that could be considered low risk.

Consultation submissions

Sixteen submissions were received regarding this issue from clinical professional organisations including dermatologists and toxicologists, sponsors/manufacturers/importers and industry organisations within the sunscreen and cosmetic industry.

Half of the responses did not support the proposed changes, while the other half supported certain aspects of the changes. Overall, however there was clear support for establishing an appropriate safety limit. Further information was also provided by respondents to assist in recalculation of a safe limit which demonstrates significantly less benzophenone absorption when applied topically.

TGA response

The TGA acknowledges that at the time of publication of this Final Decisions document, no international authority has established limits on benzophenone levels as proposed in the consultation. Based on the current information available to the TGA, there is no imminent safety concern with compliant listed sunscreens that contain octocrylene in the Australian market at this time. The TGA will defer introducing a specific regulatory limit until further consideration and consultation is undertaken as discussed below.

TGA thanks stakeholders for their submissions. Key issues raised are discussed below.

Sunscreen exposure estimation

The majority of respondents commented that the daily sunscreen exposure amount of 140 mL used by the TGA in the consultation document is unrealistic. In addition, Cancer Council Australia indicated that the use of 35 mL of sunscreen applied to the skin 4 times a day (i.e. 140 mL/day) is not an accurate reflection on the full breadth of their recommended sunscreen application and sun protection measures. They also commented that the model used by the TGA assumes that application of sunscreens is the only form of skin protection and implies that 140 mL of sunscreen would be used every day throughout the year.

The TGA notes that several respondents suggested that the TGA adopt the 18 g/day sunscreen exposure estimation used by the European Commission's Scientific Committee on Consumer Safety (SCCS) in their Margin of Safety (MoS) calculation, with one respondent proposing an alternate exposure rate of 45 ml/day. Some respondents provided sunscreen sales data to support that the actual daily sunscreen usage may be substantially lower than what was proposed in the consultation document.

The 18 g/day sunscreen usage is based on European 'habits and practice' data, that may not be relevant to the Australian climate and context. The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation (12th revision) states that '[18 g/day] *is a standard exposure value, used in the safety evaluation by the SCCS, is not meant as a recommended amount to be applied by the consumer*' (pp. 102). For a sunscreen product to reach a comparable sun protection factor (SPF) as indicated on the product label, it must be applied in quantities similar to those used in SPF testing (i.e. 2 mg/cm^2; approx. 36 g if applied to the whole body surface of an average adult). The TGA acknowledges that consumers may be applying less than 2 mg/cm^2 sunscreen (Diaz et al., 2012), which is also suggested by the sunscreen sales data provided by some industry respondents. However, this practice of applying less sunscreen does not reflect the intended directions for use, or amount of sunscreen required to achieve the labelled SPF.

The TGA acknowledges that the sunscreen exposure amount used in the consultation paper (140 mL/day) is an overestimate of the daily sunscreen usage by Australians. A sunscreen exposure model that reflects the appropriate sunscreen usage by the Australian population will be considered by the TGA and consulted on through targeted consultation with relevant industry and professional stakeholders in the future.

Dermal absorption of benzophenone

Several respondents were concerned that acetone was used as the vehicle in the study by Bronaugh et al. (1990), which was the dermal absorption study available to the TGA and cited in the consultation to derive the 44% dermal absorption value for benzophenone. Acetone is a likely penetration enhancing agent in certain situations, which may disrupt the stratum corneum, enhancing skin penetration of ingredients (Tsai et al., 2001).

One respondent provided an unpublished *in vitro* percutaneous benzophenone absorption study (in confidence), which was performed in accordance with Good Laboratory Practice (GLP) and other internationally recognised study standards (such as OECD 428, OECD Guidance 28). The dermal absorption value for benzophenone is concluded to be 12.42% in this study. The TGA has evaluated this new study and concludes this study may be of higher quality compared to the study by Bronaugh et al. and should be considered in determining the dermal absorption value for benzophenone.

Two respondents mentioned a dermal absorption study for Benzophenone-3 (Oxybenzone), however this is a different ingredient to benzophenone and absorption data for oxybenzone is unable to be used for benzophenone.

Based on the new absorption data provided to the TGA, the dermal absorption value for benzophenone is considered to be 12.42% instead of 44%.

Factors used to derive the Permitted Daily Exposure

Some respondents suggested that since the TGA used the no observed adverse effect levels (NOAEL) from an oral study to ascertain risks from dermal application, a conservative approach is already being applied to derive the Permitted Daily Exposure (PDE) of benzophenone, and that dermal studies to date have not shown the possibility of severe toxicity. Hence, the F4 factor used in the safety calculation to account for the possibility of non-genotoxic carcinogenic effects should be 1 instead of 2.5.

As per ICH Q3C(R8) guideline on impurities: for residual solvents, the TGA considers that an F4 factor value of >1 should be used as there are severe toxicity concerns arising from the non-genotoxic carcinogenic effects seen in chronic oral studies on benzophenone. The only available chronic dermal carcinogenicity studies conducted by Stenbäck and Shubik (1974; in mice) and Stenbäck (1977; in rabbits) provide insufficient information on administered doses, application conditions, histological examinations as well as study results, thereby making them unsuitable for regulatory purposes. Based on the available animal studies documented by IARC and NTP as discussed in the consultation paper, benzophenone is possibly carcinogenic to humans. It can be exposed to systemic circulation by penetrating the skin when applied topically. Given that similar toxic effects observed in oral studies may occur even when the ingredient is applied topically and benzophenone is considered a Group 2B carcinogen by IARC, applying a F4 value of 2.5 is necessary and is considered appropriate for the safety evaluation of topical benzophenone. The TGA maintains that the PDE for benzophenone remains at 1.6 mg/day, unless new information becomes available to the contrary.

Benzophenone limit for topical use

One respondent strongly supported the establishment of safe levels of benzophenone in sunscreens through a detailed risk assessment approach and agreed with the proposed limit of 26 ppm. However, most respondents commented that the proposed 26 ppm benzophenone limit is too restrictive and was calculated based on overly conservative parameters. Some respondents proposed concentration limits for benzophenone, based on a permutation/combination of the parameters discussed above (i.e. Daily exposure rate = 18g or 45g; Dermal absorption = 10, 12 or 44%; F4 factor = 1 or 2.5). These re-calculations provided a permitted concentration in sunscreens ranging from 202 ppm to 1852 ppm**:**

- Two respondents recommended a concentration limit of 202 ppm based on an 18 g/day sunscreen exposure.
- Another respondent recommended that, based on a revised dermal absorption coefficient of 12.42% and a daily sunscreen exposure of 18 g, the concentration limit can be updated to 400 ppm.
- Two respondents recommended that, based on an F4 value of 1, a dermal absorption coefficient of 10%, and a daily sunscreen exposure of 50 mL, the concentration limit can be updated to 800 ppm.
- Another respondent recommended that, based on an F4 value of 1, a dermal absorption coefficient of 12%, and a varying daily sunscreen exposure, the benzophenone concentration limit can be updated to 741 ppm (at 45 mL/day sunscreen exposure) or 1852 ppm (at 18 g/day sunscreen exposure).

Based on the new data made available to the TGA, the dermal absorption for benzophenone is considered to be 12.42% instead of 44% and an Australian sunscreen exposure model that defines an appropriate use of sunscreen by Australians will be considered in consultation with relevant industry and professional bodies. This will be used to ascertain a regulatory concentration limit for benzophenone. The TGA notes that if the European SCCS daily exposure approach is used (noting this is based on European 'habits and practice' data) a concentration limit of 717 ppm benzophenone would be derived as per the calculation below.

$$Benzophenone\ concentration = \frac{PDE\ (mg/day)}{Applied\ volume\ (mL/day) \times Dermal\ absorption\ (\%)}$$

$$Benzophenone\ concentration = \frac{1.6\ mg/day}{18\ g/day \times 0.124}$$

$$Benzophenone\ concentration = 0.71684\ mg/mL = 716.84\ \mu g/mL \approx 717\ ppm$$

The TGA recognises that Australia has one of the highest rates of skin cancer in the world and most melanoma and keratinocyte cancer cases are attributed to excessive exposure to UV (which is classified as a Group 1 carcinogen compared with benzophenone that is considered a Group 2B carcinogen by IARC). As such, it is critical that safe and efficacious sunscreens continue to be available to reduce skin cancer in Australia and products are considered based on their risks and benefits. Based on the current information available to the TGA, there is no imminent safety concern with compliant listed sunscreens that contain octocrylene in the Australian market. As such, the TGA will defer introducing a specific regulatory limit until further consideration and consultation is undertaken as discussed above.

USP monograph for octocrylene allows for 0.5% individual impurities

Some respondents commented that the USP monograph for octocrylene (that does not specifically mention Benzophenone as an impurity) allows higher levels of impurities in the raw material, than proposed for benzophenone in the consultation and suggested this would theoretically allow up to 500ppm benzophenone impurity in a sunscreen containing 10% octocrylene.

The TGA notes the USP monograph for octocrylene only provides a limit for individual impurities at 0.5% (with not more than 2.0% of total impurities) in octocrylene. However, benzophenone is not a specific impurity mentioned or considered in the monograph. The TGA notes impurity limits for octocrylene are based on data submitted before the monograph became official. The USP monograph can potentially be revised if new information becomes available subject to consideration by USP's Expert Volunteers, noting that the monograph only applies to quality limits on the raw material and not to safety limits when octocrylene is used in sunscreen products.

As such, the impurity quality limits for the raw material would also not apply to products at the end of shelf life, and the degradation of octocrylene has been identified to be formulation dependant which was discussed in the consultation document.

Benzophenone used as fragrance or flavour

One respondent recommended that as the benzophenone in the fragrance does not contribute to sunscreen efficacy, it would be reasonable to exclude the use of benzophenones in fragrances used in sunscreens. The TGA acknowledges this recommendation, however, exclusion of benzophenone as part of fragrances in sunscreens would not be required provided that the total concentration of benzophenone in the listed medicine is maintained below a safe limit. There is currently no safety concern for benzophenone being used as part of a fragrance formulation in sunscreens given that the total fragrance concentration in a medicine is restricted to 1% and the additional information provided by respondents demonstrating significantly less potential absorption of benzophenone when topically applied. At that percentage, the amounts of

benzophenone in such products, and potential absorption are expected to be minimal. As such the new specific requirements for benzophenone have been amended to clarify this.

No responses were received regarding removal of the use of benzophenone as a flavour. The TGA will therefore remove the use of benzophenone as a flavour.

Transition period

Some respondents expressed concerns that the proposed one-year transition period is insufficient to reformulate and retest the replacement sunscreen products. Hence, this may cause a sunscreen shortage in the Australian market. Some respondents also recommended the implementation of a safe limit of benzophenone to happen concurrently with the transition to the new 2021 Australia/New Zealand Sunscreen Standard.

The TGA will consider the impact and transition for any future limit to the availability of sunscreen products in the Australian market.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue for their submissions.

The TGA maintains that the PDE for benzophenone is 1.6 mg/day. However, the decision to amend the requirement for octocrylene in the Determination to introduce a regulatory limit for benzophenone has been deferred pending further consultation with relevant industry and professional bodies via future targeted consultation. Based on the new dermal absorption study provided as part of the consultation, there is no imminent safety concern with compliant listed sunscreens that contain octocrylene in the Australian market. Although a specific regulatory limit has not been established for benzophenone in listed sunscreens as part of this consultation, sponsors must comply with existing legal requirements and must continue to:

- consider the stability of their individual formulations to ensure there is minimal degradation and formulations are stable throughout their shelf-life
- ensure sunscreens formulations are efficacious and comply with the Australian/New Zealand Sunscreen Standard
- ensure they hold evidence to justify the safety of the sunscreen for its intended use e.g. in children whose surface area/body weight ratio and toxicokinetic parameters differ from adults
- monitor impurities and hold evidence that ensures any impurity does not exceed unsafe levels throughout the shelf-life
- consider emerging evidence in relation to the safety of their products and notify the TGA as part of ongoing pharmacovigilance responsibilities

The TGA will consider whether a sunscreen exposure model can be developed for the Australian context and review any emerging literature to inform a safe regulatory limit for benzophenone in sunscreens.

The use of benzophenone as a flavour will be removed from the Determination. As there are currently no products that contain benzophenone as a flavour formulation on the ARTG, there is no impact on sponsors. Therefore, a transition period for this change is not required.

Affected ingredients

- BENZOPHENONE

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New specific requirements
BENZOPHENONE	Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance. If used in a flavour the total flavour concentration in a medicine must be no more than 5%. If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.	Permitted for topical use only in combination with other permitted ingredients as a ~~flavour or a~~ fragrance. ~~If used in a flavour the total flavour concentration in a medicine must be no more than 5%.~~ The total concentration of fragrance proprietary formulations containing benzophenone must not be ~~in a medicine must be no~~ more than 1% of the total medicine.
OCTOCRYLENE	Only for use as an active ingredient in sunscreens for dermal application and not to be included in medicines intended for use in the eye. The concentration in the medicine must not be more than 10%. When used in primary sunscreen products, the following warning statements are required on the label: - (AVOID) 'Avoid prolonged exposure in the sun' (or words to this effect); and - (SUNPRO) 'Wear protective clothing - hats and eyewear when exposed to the sun' (or words to this effect).	No Change

4. Clarification of the requirements for soy phosphatidylserine-enriched ingredients

Background

The consultation document proposed to amend the restrictions for soy phosphatidylserine (PS)-enriched soy lecithin liquid and soy PS-enriched soy lecithin powder to allow a concentration of soy PS in the medicine of at least 15% to align with the original recommendation in 2000. A restriction to ensure that listed medicines provide no more than 300 mg soy PS per day to align with the available evidence and the Health Canada assessment was also proposed.

Consultation submissions

Four submissions were received regarding this issue. One respondent agreed with the proposed changes and three respondents did not agree with certain aspects of the proposed changes.

TGA response

The TGA thanks stakeholders for their submissions. Key issues raised are discussed below.

Maximum daily dose of soy phosphatidylserine

Two respondents did not agree with the proposed restriction of the maximum daily dose of 300 mg soy PS based on the estimated dietary intake of PS and published studies demonstrating the safety of higher doses.

The TGA notes the additional studies provided by the respondents to support the safe use of soy PS above the proposed maximum limit of 300 mg/day. All the studies, except Heiss et al. (1994), were of short duration (between 10 days and 3 weeks). The clinical dataset undertaken using more than 300 mg/day PS does not meet ICH E1 guidelines to support the safe ongoing use at dosages exceeding 300 mg/day PS (Jorissen et al., 2002, Hellhammer et al., 2004, Kingsley et al., 2005 and 2006, Starks et al., 2008, Fahey, 1998). The study from Heiss et al. (1994) was conducted using 400 mg/day of non-soy PS for 6 months. However, due to the small number of subjects, the lack of assessment of haematological/biological parameters and reporting of adverse events, the information is considered supporting evidence only.

The TGA considers that the safe long-term and ongoing use of 300 mg soy-PS can be established based on the double-blind, randomised controlled study by Kato-Kataoka et al. (2010) which was undertaken for a longer duration of 6 months. A Generally Recognized As Safe Notification (GRN 637) referenced by the two respondents also emphasised that the safety of soy PS has been confirmed at up to 300 mg/day for up to 6 months.

Dietary intakes and margin of safety of phosphatidylserine

Two respondents raised concerns that the dietary intake of PS cited by the Health Canada safety assessment was higher than that cited GRN 637. The TGA notes that the respondents cited GRN 637 for the lower dietary intake of PS based on United States Department of Agriculture's consumption data from the 1994-96, 1998 Continuing Survey of Food Intakes by Individuals (CSFII). This is the same database referred to by Health Canada in their safety assessment. The estimation of 44.8 mg/day [mean intake] and 98.7 mg/day [90th percentile] is for dietary intakes

of PS that are intentionally added to food. The data from GRN 637 also states that the estimated dietary intake of PS from its natural presence in the diet is 75-184 mg/day. Therefore, the total Estimated Dietary Intake (EDI) of PS (regardless of source) is 228.8 mg/day, considering the mean intake from food additives and maximum intake from natural presence in diet. This value is similar to the EDI cited by Health Canada, i.e. 228 mg/day. Therefore, the comment about the disparity in dietary intakes considered by both the GRN and Health Canada is unsupported.

The TGA acknowledges the absence of an estimation of the total dietary intake of soy PS in the Australian population. Recognising that soy PS can be derived from food source in a daily diet (e.g. fish, soy bean, eggs) and that soy PS-enriched ingredients are also used in foods in Australia[3], the EDI cited by Health Canada may also be applicable for the Australian population in the absence of further data. GRN 637 and the safety assessment by Health Canada have cited two 26-week sub-chronic toxicity studies in rodents and dogs and a 13-week sub-chronic developmental toxicity study in rats. These studies reported NOAELs of 960-1000 mg/kg bw/day. Applying an uncertainly factor of 100 (10 for interspecies variation and 10 for intrapopulation variation) arrives at an Acceptable Daily Intake of 9.6-10 mg/kg bw/day. A maximum recommended daily dose of 300 mg soy PS in listed medicines, in addition to an EDI of 228 mg, will amount to a total daily intake of 528 mg/day of soy PS. This results in a Margin of Safety of approximately 1 which is acceptable from a safety perspective. A maximum recommended daily dose more than 300 mg/day of soy PS will increase the Margin of Safety to >1.

The combined pre-clinical and clinical dataset supports a maximum recommended daily dose of 300 mg/day soy PS, which is a pragmatic approach without having to impose an additional warning statement against consuming other sources of soy PS on the same day or restricting the duration of use.

Restriction on phosphatidylserine concentration

The TGA notes the suggestion from one respondent to not apply a restriction for a minimum 15% soy PS concentration. The TGA acknowledges that the proposed change would be an unnecessary regulatory burden for sponsors who had been proactive in their compliance when the 'not less than 15%' was inadvertently changed to 'not more than 15%'. The requirement of setting a minimum 15% of soy PS was related to efficacy rather than safety of the ingredient. As efficacy is not pre-market evaluated for ingredients for use in listed medicines, the new requirements will not include this restriction.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue. In consideration of the responses received, the changes to requirements for soy phosphatidylserine-enriched ingredients which were presented for consultation will be implemented with the restriction for a minimum of 15% soy PS removed.

If there is new evidence to suggest the safe ongoing use of soy PS at daily dosage exceeding 300 mg/day become available, applicants can accordingly apply to extend the use of soy PS-enriched ingredients with this evidence.

[3] Australia New Zealand Food Standards Code – Schedule 15 – Substances that may be used as food additives

Affected ingredients

- SOY PHOSPHATIDYLSERINE-ENRICHED SOY LECITHIN LIQUID
- SOY PHOSPHATIDYLSERINE-ENRICHED SOY LECITHIN POWDER

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New specific requirements
SOY PHOSPHATIDYLSERINE-ENRICHED SOY LECITHIN LIQUID	Soy phosphatidylserine is a mandatory component of soy phosphatidylserine-enriched soy lecithin liquid. The concentration of soy phosphatidylserine in the medicine must be no more than 15%.	Soy phosphatidylserine is a mandatory component of soy phosphatidylserine-enriched soy lecithin liquid. ~~The concentration of soy phosphatidylserine in the medicine must be no more than 15%.~~ The maximum daily dose of the medicine must not provide more than 300 mg of soy phosphatidylserine.
SOY PHOSPHATIDYLSERINE-ENRICHED SOY LECITHIN POWDER	Soy phosphatidylserine is a mandatory component of soy phosphatidylserine-enriched soy lecithin powder. The concentration of soy phosphatidylserine in the medicine must be no more than 15%.	Soy phosphatidylserine is a mandatory component of soy phosphatidylserine-enriched soy lecithin powder. ~~The concentration of soy phosphatidylserine in the medicine must be no more than 15%.~~ The maximum daily dose of the medicine must not provide more than 300 mg of soy phosphatidylserine.

5. Clarification of the requirements for *Terminalia ferdinandiana*

Background

The consultation document proposed to amend the requirements for *T. ferdinandiana* to align with the CMEC recommendation and original listing notice. The TGA also invited sponsors using *T. ferdinandiana,* particularly other preparation types including fruit flesh oil fixed and fruit flesh oil infused, to submit information they hold that is relevant to the safety of their ingredients. If insufficient information were received to establish the safety of other preparations, the TGA proposed to clarify the requirements to align with the CMEC recommendation and original listing notice.

Consultation submissions

Three submissions were received from industry peak bodies that did not support the proposed changes. Respondents provided reasoning for why other preparations of *T. ferdinandiana* are low risk or not identified as being of safety concern, especially at low concentrations for excipient use.

TGA response

The TGA thanks stakeholders for their submissions. Key issues raised are discussed below.

Plant parts and preparations of *T. ferdinandiana*

One respondent noted that the fruit of *T. ferdinandiana* has a history of use as a food and that no toxicity associated with the use of the fresh fruits or seeds has been identified to date. They acknowledged that an oil extract of *T. ferdinandiana* may have different composition to an aqueous extract, however, noted that the TGA has not identified any risks from the use of oil extracts, therefore the proposed changes are unnecessary, especially at the low concentrations for excipient use.

The TGA acknowledges that the fresh fruit, seeds, and beverages prepared from *T. ferdinandiana* fruit have had a history of use in traditional foods, as evident in the diets from Aboriginal peoples in Northwestern Australia. Fresh or dried fruits can also be soaked in water to make a beverage. Members of the Wurrkikandjarr clan are not known to have used the seeds of *T. ferdinandiana* as food, however kernels of other *Terminalia* species (by means of breaking the seed coat open with stones) have been eaten as food (Hegarty et al., 2001). The gum from *T. ferdinandiana* is also eaten, by means of cooking in sand, chewing directly or pounding into a powder to form an edible jelly following soaking (Kenneally et al., 1996, Specht, 1958). The TGA acknowledges there is no evidence to suggest there is any toxicity associated with oral consumption of the *T. ferdinandiana* fruit. The information available suggests that use of fresh, dried and aqueous preparations of the fruit flesh, and seeds appear to align with what the indigenous members of the Australian community have traditionally consumed.

Although the publication provided by a respondent investigated the constituents (e.g. ascorbic acid, phenolic content) of 8 commercial products containing Kakadu plum powder (either on its own or with other ingredients) and found that they exhibited high antioxidant activity, total

phenolic content, ascorbic acid and ellagic acid content, the authors had not defined the preparation of the Kakadu plum powder in the study other than mention that the seeds were not included during the manufacturing process (Zhou et al., 2023). The composition of other preparations of *T. ferdinandiana* fruit flesh, other than the fresh, dried and aqueous preparation is unknown.

Respondents contended that no safety issues were identified for use of the ingredient in infused and fixed oil preparations. As per the Code Tables[4], the following plant preparation are defined:

> Oil fixed – An oil that is non-volatile and is usually prepared from herbal material, such as seeds, by pressing or by extraction with a non-polar solvent such as hexane. Fixed oils are composed of lipids or lipid-soluble carbohydrates and are prone to becoming rancid on oxidation.
>
> Oil infused – An oil that is initially absorbed from the herbal material, such as petals, into an oil or fat base, then recovered through successive extractions in alcohol to obtain a complex mixture, including oils, resins and oleoresins. Several methods may be used, including infusion into thin layers of oil to obtain a pomade (enfleurage), infusion into volatile oil carried in a current of warm air (pneumatic) and digestion in melted fat.

These preparations are highly unlikely to align with use in traditional food.

A respondent noted that infusions and fixed oil preparations were grandfathered[5] for numerous complementary medicine substances at the inception of the listed medicine scheme. The TGA notes *T. ferdinandiana* was originally approved for use in listed medicines in Australia in 2003 following evaluation by the TGA and was not grandfathered. The premise of the listed medicine framework assumes there is adequate pre-market safety and quality evaluation of new ingredients, as this underpins these medicines being considered low risk. *T. ferdinandiana* fruit flesh dry and aqueous extracts of the fruit flesh were deemed suitable for use as an ingredient in listed medicines and written into legislation in 2003 to reflect the plant part and preparation evaluated based on the evidence presented.

Another new study provided to the TGA by a respondent showed that seed kernels of *T. ferdinandiana* comprise of up to 35% fat delivered as fatty acids (linoleic acid, oleic acid, palmitic acid, stearic acid), 32% protein, 3.2% carbohydrate, 21.2% fibre, minerals and trace elements known to be of low risk (Akter et al., 2008). Given the composition of the *T. ferdinandiana* seeds are characterised of low-risk constituents, and there has not been any reported toxicity associated with the oral consumption of *T. ferdinandiana*, and it appears to have been used traditionally, the TGA considers that the permitted plant part can include the seed. If further information emerges the TGA will review the requirements to ensure they continue to allow the ingredient to be used safely in listed medicines.

Ascorbic acid content of *T. ferdinandiana*

One respondent suggested it is not appropriate to consider the high ascorbic acid content of *T. ferdinandiana* to be a reason to restrict the use of oil extractions, as ascorbic acid is currently

[4] The Code Tables provide terminology for use in product applications. This information is publicly available in the TGA eBusiness Service portal under 'Public TGA information'.
[5] 'Grandfathered products' are those products that were available in Australia prior to the *Therapeutic Goods Act* coming into effect in 1990. These products were included in the ARTG without undergoing evaluation or assessment of their quality and safety.

permitted for use in listed medicines. The TGA wishes to clarify that the restriction for *T. ferdinandiana* was not proposed based on ascorbic acid content.

Risks associated with the use of *T. ferdinandiana*

A respondent noted that given the very low levels of use of *T. ferdinandiana* as an excipient in topical products (0.3%), it is likely the alternative preparations should be acceptable as they represent a very low risk to consumers and this material is likely to be consistent with materials that are safely used in cosmetic products.

The TGA evaluation in 2016 for extending the use of the ingredient as an excipient for dermal use had considered safety of *T. ferdinandiana* extract used for cosmetic purposes. It is also considered that Akter et al., (2018) reported the compositional analysis of seed kernels of *T. ferdinandiana*, highlighting that kernels comprise up to 35% fat delivered as fatty acids (linoleic acid, oleic acid, palmitic acid, stearic acid, minerals and trace elements which are deemed to have good safety profiles. The TGA agrees that 0.3% *T. ferdinandiana*, when derived from various preparations and plant parts, used as an excipient in topical products is low risk. As such, the requirement for use of the specific plant part and preparations will only be applicable when *T. ferdinandiana* is used as an active ingredient. The requirements for excipient use have also been amended for clarity and consistency throughout the Determination.

Final decision to amend the Permissible Ingredients Determination

The TGA thanks all respondents to this issue. In consideration of the responses received, the changes to requirements of *T. ferdinandiana* which were presented for consultation will be implemented as described below, with amendments to permit the seed as a plant part and restrict the use of plant part and preparations when the ingredient is used as an active. The requirements for excipient use have also been amended for clarity and consistency throughout the Determination.

Affected ingredient

- TERMINALIA FERDINANDIANA

Final changes to specific ingredient requirements in the Determination

Ingredient name	Existing specific requirements	New specific requirements
TERMINALIA FERDINANDIANA	Only for use when the plant part is fruit flesh, fruit flesh dry or the preparation is as an aqueous extract of the fruit flesh. When used as an excipient, the ingredient is only for use in topical medicines for dermal application and not to be included in medicines intended for use on damaged skin or in the eye. When used as an excipient, the concentration in the medicine must be no more than 0.3%.	When used as an active ingredient, ~~Only for use when~~ the plant part must be limited to ~~is~~ fruit flesh and seed, and the plant preparation must be limited to fresh, ~~fruit flesh~~ dry, or ~~the preparation is as~~ an aqueous extract ~~of the fruit flesh~~. When used as an excipient ingredient: (a) ~~, the ingredient is only for use in~~ the route of administration for medicines that contain Terminalia ferdinandiana must be limited to topical ~~medicines~~ for dermal ~~application~~use; (b) ~~and~~ is not to be included in medicines intended for use on damaged skin or in the eye~~.~~; (c) ~~When used as an excipient,~~ the concentration of Terminalia ferdinandiana in the medicine must not be more than 0.3%.

Timetable

The confirmed changes to the Determination will commence on **Friday 1 March 2024**.

The transition period of 12 months will end on **Saturday 1 March 2025** unless otherwise specified.

Enquiries

Please contact us if you have any questions relating to this consultation at the following email address: complementary.medicines@health.gov.au.

References

1. Curcuma species/curcumin and the risk of liver injury

Abdallah M.A., Abdalla A., Ellithi M., Abdalla A.O., Cunningham A.G., Yeddi A. et al., 2019. Turmeric-Associated Liver Injury. Am. J. Ther. [ePub ahead of print]. D20-3129610

Abdul-Mujeeb S., Quraishi E., Qazi R., 2021. Turmeric-induced fulminant hepatitis. Am J Gastroenterol. Conference: Annual Scientific Meeting of the American College of Gastroenterology, ACG 2021. Las Vegas, NV United States. 116 (SUPPL): S1119 (conference abstract). D22-5892925

Ajitkumar A, Mohan G, Ghose M, Yarrarapu S, Afiniwala S., 2023. Drug-Induced Liver Injury Secondary to Turmeric Use. Eur J Case Rep Intern Med. Apr 21;10(5) D23-3689613

ANSES (French Agency for Food, Environmental and Occupational Health and Safety), 2022. Adverse effects associated with the consumption of food supplements containing turmeric. [Accessed 19 October 2023] 22-5791782

Arzallus T, Izagirre A, Castiella A, Torrente S, Garmendia M, Zapata EM., 2023. Drug induced autoimmune hepatitis after turmeric intake. Gastroenterologia y hepatologia. Jan 9:S0210-5705. D23-3688491

Ayas M.F., Nashed B., Elazzamy H., Barawi M., 2021. Turmeric-induced hepatitis. J Gastroenterol. Conference: Annual Scientific Meeting of the American College of Gastroenterology, ACG 2021. Las Vegas, NV United States. 116 (SUPPL); S1189 (conference abstract). D22-5892925

Balaji S. and Chempakam B., 2010. Toxicity prediction of compounds from turmeric (Curcuma longa L). Food Chem Toxicol. 48: 2951-2959. D20-295570

Bermejo, M. F., et al., 2022. Curcumin and curcumoids: hepatoprotection or hepatotoxicity? Revista espanola de enfermedades digestivas: organo oficial de la Sociedad Espanola de Patologia Digestiva, 114(5), pp. 304-305. D22-5582882

Brown, J. P., 2017. Rare adverse events in clinical trials: understanding the rule of three. [Online] Available at: Rare adverse events in clinical trials: understanding the rule of three - BMJ EBM Spotlight. [Accessed 23 October 2023].

Chalasani, N., Fontana, R. J., Bonkovsky, H. L., Watkins, P. B., Davern, T., Serrano, J., Yang, H., Rochon, J. & Drug Induced Liver Injury Network (DILIN), 2008. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology, 135(6), 1924–1934. e19344. doi. 10.1053/j.gastro.2008.09.011

Chalasani, N. et al., 2021. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. American Journal of Gastroenterology, Volume 116, pp. 878-898.

Chand S., Hair C. and Beswick L., 2020. A rare case of turmeric-induced hepatotoxicity. Intern. Med. J. 50: 258–259. D20-3129595

Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), 2022. First draft statement on the potential risk to human health of turmeric and curcumin [Accessed 19 October 2023]. Available from: https://cot.food.gov.uk/First%20draft%20statement%20on%20the%20potential%20risk%20to%20human%20health%20of%20turmeric%20and%20curcumin D23-3794126

Daniells S., 2022. Italy Prohibits all health claims linked to turmeric, issues warning for labels. Nutra-Ingredients. D22-5798489.

Dehzad, M. J., Ghalandari, H., Amini, M. R., & Askarpour, M., 2023. Effects of curcumin/turmeric supplementation on liver function in adults: A GRADE-assessed systematic review and dose-response meta-analysis of randomized controlled trials. Complementary therapies in medicine, 74, 102952. doi.10.1016/j.ctim.2023.102952 D23-3725727

European Food Standards Agency (EFSA), 2010. Scientific opinion on the re-evaluation of curcumin (E 100) as a food additive. EFSA Journal, 8(9), pp. 1679.

EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Turck, D., Bohn, T., Castenmiller, J., De Henauw, S., Hirsch-Ernst, K.I., Maciuk, A., Mangelsdorf, I., McArdle, H.J., Naska, A. and Pelaez, C., 2021. Safety of tetrahydrocurcuminoids from turmeric (Curcuma longa L.) as a novel food pursuant to Regulation (EU) 2015/2283. EFSA Journal, 19(12), p.e06936.

European Medicines Agency (EMA),2018. Assessment report on *Curcuma longa* L., rhizoma [Accessed 19 October 2023] Available from: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-curcuma-longa-l-rhizoma-revision-1_en.pdf D19-6181326

Fernández-Aceñero M.J., Ortega Medina L. and Maroto M., 2019. Herbal Drugs: Friend or Foe? J. Clin. Exp. Hepatol. 9: 409–411. D20-3129639

Fontana RJ, Bjornsson ES, Reddy R, Andrade RJ., 2023. The Evolving Profile of Idiosyncratic Drug-Induced Liver Injury. Clin Gastroenterol Hepatol. Jul;21(8):2088-2099. D23-3658315

Fontana, R. et al., 2022. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. Hepatology, Volume 00, pp. 1-29.

Ganiger S, Malleshappa HN, Krishnappa H, Rajashekhar G, Ramakrishna Rao V, Sullivan F. A two generation reproductive toxicity study with curcumin, turmeric yellow, in Wistar rats. Food Chem Toxicol. 2007 Jan;45(1):64-9. doi: 10.1016/j.fct.2006.07.016.Halegoua-DeMarzio et al., 2022.

Health Canada (2018). *Green tea extract monograph* [Online]. Available: https://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=curcumin.curcumine&lang=eng [Accessed 24 November 2023].

Hegde, M., Girisa, S., BharathwajChetty, B., Vishwa, R., & Kunnumakkara, A. B., 2023. Curcumin Formulations for Better Bioavailability: What We Learned from Clinical Trials Thus Far?. ACS omega, 8(12), 10713–10746. doi.10.1021/acsomega.2c07326 D23-3808843

Imam Z., Khasawneh M., Jomaa D., Iftikhar H. and Sayedahmad Z., 2019. Drug Induced Liver Injury Attributed to a Curcumin Supplement. Case Rep Gastrointest Med. 2019: 6029403. D20-295835

JECFA, 2004. Safety evaluation of certain food additives and contaminants: Sixty-first report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), World Health Organisation.

Koenig G., Callipari, C. and Smereck JA., 2021. Acute liver injury after long-term herbal ''liver cleansing'' and ''sleep aid'' supplement use. J Emerg Med. 60 (5): 610-614. D22-5850048

Larrey D., 2002. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin Liver Dis. 2002;22(2):145-55. Doi: 10.1055/s-2002-30105. PMID: 12016546. D23-3757575

Lee B.S., Bhatia T., Chaya C.T., Wen R., Taira M.T. and Lim B.S., 2020. Autoimmune Hepatitis Associated With Turmeric Consumption. ACG Case Rep. J. 7: e00320. D20-3129620

Liu, Angeline MD1; Chang, Paul MD2., 2022. S2904 A Superfood With a Dark Side: A Case of Severe Liver Injury Due to Turmeric. The American Journal of Gastroenterology 117(10S):p e1891, October 2022. D23-3690535

Lobo, R., Prabhu, K.S., Shirwaikar, A. and Shirwaikar, A. (2009), Curcuma zedoaria Rosc. (white turmeric): a review of its chemical, pharmacological and ethnomedicinal properties. Journal of Pharmacy and Pharmacology, 61: 13-21. https://doi.org/10.1211/jpp.61.01.0003

Lombardi N., Crescioli G., Maggini V., Ippoliti I., Menniti-Ippolito F., Gallo E. et al., 2020. Acute liver injury following turmeric use in Tuscany: An analysis of the Italian Phytovigilance database and systematic review of case reports. Br J Clin Pharmacol. 1–13. D21-2190100

Luber R.P., Rentsch C., Lontos S., Pope J.D., Aung A.K., Schneider H.G. et al., 2019. Turmeric Induced Liver Injury: A Report of Two Cases. Case Reports Hepatol. 2019: 6741213. D20-295888

Lukefahr A.L., McEvoy S., Alfafara C. and Funk J.L., 2018. Drug-induced autoimmune hepatitis associated with turmeric dietary supplement use. BMJ Case Rep. bcr-2018. D20-295901

Menniti-Ippolito, F., et al. (2020). Turmeric (*Curcuma longa L.*) food supplements and hepatotoxicity: An integrated evaluation approach. Annali dell'Istituto Superiore di Sanità, 56(4), pp. 462-469.

Ngu, M. H., Norhayati, M. N., Rosnani, Z., & Zulkifli, M. M. (2022). Curcumin as adjuvant treatment in patients with non-alcoholic fatty liver (NAFLD) disease: A systematic review and meta-analysis. Complementary therapies in medicine, 68, 102843. doi.10.1016/j.ctim.2022.102843 D23-3805448

NIH LiverTox, 2019. Clinical and Research Information on Drug Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Acute Hepatitis [Updated 2019, May 4] Available from: https://www.ncbi.nlm.nih.gov/books/NBK548606/ [Accessed 23 October 2023]

NIH LiverTox, 2019a. Clinical and Research Information on Drug Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Cholestatic Hepatitis [Updated 2019, May 4] Available from: https://www.ncbi.nlm.nih.gov/books/NBK548914/ [Accessed 23 October 2023]

NIH LiverTox, B., 2022. Clinical and Research Information on Drug-Induced Liver Injury [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. LiverTox – Editors and External Expert Review Committee. [Updated 18 April 2023] Available at: https://www.ncbi.nlm.nih.gov/books/NBK548242/ [Accessed 23 October 2023].

Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Bruno L, Lista RM, Staltari O, Scuteri A, Scicchitano F, Russo E., 2013. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two "challenging" case reports. J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1):S66-72. Doi: 10.4103/0976-500X.120955. PMID: 24347986; PMCID: PMC3853673. [Accessed 23 October 2023]

Priyadarsini KI. The chemistry of curcumin: from extraction to therapeutic agent. Molecules. 2014 Dec 1;19(12):20091-112. doi: 10.3390/molecules191220091.

Roth R.A. and Ganey P.E., 2020. What have we learned from animal models of idiosyncratic, drug-induced Liver Injury? Expert Opin Drug Metab Toxicol. 2020 Jun; 16(6): 475–491.

Smith DN, Pungwe P, Comer LL, Ajayi TA, Suarez MG., 2023. Turmeric-associated liver injury: a rare case of drug-induced liver injury. Cureus. 2023 Mar 31;15(3). D23-3690133

Sohal A., Alhankawi D., Sandhu S. and Chintanaboina JK., 2021. Turmeric-Induced Hepatotoxicity: Report of 2 Cases. International Medical Case Reports Journal. D22-5802082

Suhail F.K., Masood U., Sharma A., John S. and Dhamoon A., 2019. Turmeric supplement induced hepatotoxicity: a rare complication of a poorly regulated substance. Clin. Toxicol. (Phila). 58: 216–217. D20-3129628

Sunagawa SW, Houlihan C, Reynolds B, Kjerengtroen S, Murry DJ, Khoury N., 2022. Turmeric-Associated Drug-Induced Liver Injury. ACG Case Rep J. 2022 Dec 26;9(12):e00941 D23-3688395

Uppsala Monitoring Centre (UMC), 2016. The UMC Measures of Disproportionate Reporting. A brief guide to their interpretation. Available from https://who-umc.org/media/164041/measures-of-disproportionate-reporting_2016.pdf [accessed 23 October 2023]

US Food and Drug Administration (FDA) GRAS Notices. GRN No. 686 Curcumin from turmeric (Curcuma longa L.), 2017. [Accessed 19 October 2023]. Assessment available from GRAS Notice 000686, Curcumin from turmeric (*Curcuma longa* L.) (fda.gov)

2. *Camellia sinensis* (Green tea) extract and the risk of liver injury

Committee on Toxicity (2022). The safety of green tea catechins- first draft statement. [Accessed 9 October 2023). Available from: https://cot.food.gov.uk/The%20safety%20of%20green%20tea%20catechins-%20first%20draft%20statement#cot-conclusions

EFSA (2018). Scientific opinion on the safety of green tea catechins. EFSA Journal, 16(4), pp. e05239.

NIH LiverTox (2020): Clinical and Research Information on Drug Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Green Tea [Updated 2020, November 20]

NIH LiverTox (2019): Clinical and Research Information on Drug Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Acute Hepatitis [Updated 2019, May 4]

NIH LiverTox (2019a): Clinical and Research Information on Drug Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Cholestatic Hepatitis [Updated 2019, May 4]

3. Safe levels of Benzophenone

Bronaugh R. et al. (1990). *In vivo* percutaneous absorption of fragrance ingredients in rhesus monkeys and humans. *Food and Chemical Toxicology.* 28(5), pp. 369-373.

Diaz A. et al. (2012). The Children and Sunscreen Study: A Crossover Trial Investigating Children's Sunscreen Application Thickness and the Influence of Age and Dispenser Type. *Archives of Dermatological Research.* 148(5), pp. 606–612.

Stenbäck F, Shubik P. (1974). Lack of toxicity and carcinogenicity of some commonly used cutaneous agents. *Toxicology and Applied Pharmacology.* 30, pp. 7-13.

Stenbäck F. (1977). Local and Systemic Effects of Commonly Used Cutaneous Agents: Lifetime Studies of 16 Compounds in Mice and Rabbits. *Basic & Clinical Pharmacology & Toxicology*. 41(5), pp. 417-431

Tsai J., et al. (2001). Effect of barrier disruption by acetone treatment on the permeability of compounds with various lipophilicities: implications for the permeability of compromised skin. *Journal of Pharmaceutical Sciences*. 90(9), pp. 1242-1254.

4. Clarification of the requirements for soy phosphatidylserine-enriched ingredients

Fahey T, Pearl MS (1998) The hormonal and perceptive effects of phosphatidylserine administration during two weeks of resistive exercise-induced overtraining. *Biology of Sport*, 15(3) 135-144.

FDA (2016). GRAS Notice 637: Phosphatidylserine derived from Soy Lecithin. Available from: https://www.fda.gov/media/98569/download

Heiss, W. D., Kessler, J., Mielke, R., Szelies, B., & Herholz, K. (1994). Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease. A neuropsychological, EEG, and PET investigation. *Dementia (Basel, Switzerland)*, *5*(2), 88–98.

Hellhammer, J., et al. (2004). Effects of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) on the endocrine and psychological responses to mental stress. *Stress (Amsterdam, Netherlands)*, 7(2), 119–126.

Heywood, R., et al. (1987). Toxicology of a phosphatidylserine preparation from bovine brain(BC-PS). *Clinical Trials Journal,* 24(1), pp. 25-32.

Jorissen, B., et al. (2002). Safety of soy-derived phosphatidylserine in elderly people. *Nutritional Neuroscience,* 5(5), pp. 337-343.

Kato-Kataoka, A., et al. (2010). Soybean-derived phosphatidylserine improves memory function of the elderly Japanese subjects with memory complaints. *Journal of Clinical Biochemistry and Nutrition,* 47(3), pp. 246-255.

Kingsley, M. I., et al. (2005). Effects of phosphatidylserine on oxidative stress following intermittent running. *Medicine and science in sports and exercise*, *37*(8), 1300–1306.

Kingsley, M. I., et al. (2006). Effects of phosphatidylserine on exercise capacity during cycling in active males. *Medicine and science in sports and exercise*, *38*(1), 64–71.

Klinkhammer, P., et al. (1991). Effect of Phosphatidylserine on Cerebral Glucose Metabolism in Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders, 1(4), 197–201.*

Lifshitz, Y., et al. (2015). Sub-chronic (13-week) oral toxicity study, preceded by an in utero exposure phase and genotoxicity studies with fish source phosphatidylserine in rats. *Food and Chemical Toxicology,* 86, pp. 234-244.

Monteleone, P., et al. (1992). Blunting by chronic phosphatidylserine administration of the stress-induced activation of the hypothalamo-pituitary-adrenal axis in healthy men. *European journal of clinical pharmacology*, *42*(4), 385–388.

Starks, M. A., et al. (2008). The effects of phosphatidylserine on endocrine response to moderate intensity exercise. *Journal of the International Society of Sports Nutrition*, *5*, 11.

5. Clarification of requirements for *T. ferdinandiana*

Akter, S., et al. (2018). Chemical and Nutritional Composition of Terminalia ferdinandiana (Kakadu Plum) Kernels: A Novel Nutrition Source. *Foods*, 7(4), pp.60.

Hegarty, MP, Hegarty, EE & Wills, RBH 2001, Food safety of Australian plant bush foods, Rural Industry Research & Development Corporation, Canberra (Publication 01/28).

Kenneally KF, Edinger DC, Willing T et al. (1996). Broome and Beyond: Plants of the Dampier Peninsula, Kimberley, Western Australia. CALM, WA.

Specht, R. L. & Mountford, C. P. Botany and plant ecology. American-Australian Scientific Expedition to Arnhem Land (1948). 1958. Melbourne University Press.

Specht, RL (1958). Records of the American-Australian Scientific Expedition to Arnhem Land. 3: 479-503. Melbourne University Press, Carlton Vic.

Zhou, Y., et al. (2023). Bioactive Properties of Kakadu Plum-Blended Products. *Molecules,* [online] 28(6), pp. 2828.

Version history

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V1.0	Original publication	Complementary Medicines Evaluation Section	1 December 2023

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

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