



**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

## Consultation paper

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## 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 the ingredients that are available for use in [listed and assessed listed medicines](#) and their associated requirements. Listed medicines are low-risk products that are not pre-market assessed by the TGA for their quality, safety, and efficacy. To ensure listed medicines can be safely used by consumers, they may only contain pre-approved low-risk ingredients that are specified in the Determination, which have been evaluated for their quality and safety to determine their suitability for use in listed medicines. 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 ingredient changes in this consultation have been reviewed and categorised as being of [low-negligible risk](#). The purpose of this consultation is to provide an opportunity for consumers, health professionals, industry, and other interested parties to comment on these changes, which are proposed to commence on 1 March 2024 (see [schedule for low-negligible risk changes for 2023-2024](#)). Sponsors of listed medicines will be provided with a 12-month transition period from the commencement of the Determination to align their products with these changes.



### Proprietary ingredients

Sponsors and proprietary ingredients (PI) suppliers should consider whether the ingredients covered under the current consultation are included in PIs used in listed medicines. The TGA is not intending to contact individual manufacturers or suppliers of PIs that contain ingredients discussed in the consultation.

Sponsors who choose to use PIs in their medicines are responsible for verifying with PI suppliers whether the ingredients within the PIs comply with the current or future listing requirements. Sponsors should have appropriate arrangements with PI suppliers to ensure compliance with all legal obligations.

## Transition expectations

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 applicable requirements.

After the expiry of the transition period, any ARTG listings or products **released for supply** that do 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 *Curcuma* species comprises of 70 perennial rhizomatous species distributed widely throughout tropical and subtropical regions of the world (Xia et al., 2005). The rhizomes of *Curcuma*, including *Curcuma longa* (*C. longa*, also known as turmeric), have been traditionally used as spices, food preservatives, and flavouring agents (Xiang et al., 2011, Al-Reza et al., 2010). *Curcuma* has also been used in traditional medicines for the treatment of a variety of illnesses, including gastrointestinal disorders, diabetes, hepatic disorders, thoracic disorders, skin diseases, and rheumatism (Rajkumari and Sanatombi, 2017, Nelson et al., 2017). *C. longa* contains curcuminoids (1-6%), of which 60-70% is curcumin. The average daily dietary intake of *C. longa* from an Indian diet is approximately 2.0-2.5 g, which equates to approximately 60-100 mg of curcumin (Amalraj et al., 2017).

Extracts of the *curcuma* species are used in listed medicines containing varying levels of curcuminoids. The principal curcuminoid is a single chemical, 1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione (often referred to as 'curcumin'), however, its desmethoxy- and bisdesmethoxy-derivatives are also present in varying proportions. The TGA is aware that the ingredient name 'curcumin', has historically been used in listed medicines to either refer to the single curcuminoid, 1,7-bis(4-Hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione, or to a highly purified mixture of curcuminoids. For consistency, the term 'curcumin' is used in this consultation to refer to the single chemical compound.

Although curcumin absorption via the oral route is poor (<10%) (Dei Cas and Ghidoni, 2019), its bioavailability can be dramatically enhanced up to 20-fold when administered with piperine, the major active component of black pepper (*Piper nigrum*) (Shoba et al., 1998). *C. longa* preparations that contain *Piper nigrum* appear to be designed for enhanced bioavailability of curcumin (Asai and Miyazawa, 2000, Garcea et al., 2004). The TGA is aware of other enhanced bioavailability preparations with nanoparticle delivery methods including complexes of curcumin with phospholipids, polymeric micellar formulations, and curcumin-loaded solid lipid nanoparticles (Menniti-Ippolito et al., 2020). These formulations are designed to increase absorption of curcumin to improve its oral bioavailability.

*C. longa* and 3 related *Curcuma* species (*C. aromatica*, *C. zanthorrhiza*, and *C. zedoaria*) are currently permitted for use in listed medicines with no restrictions on dose, concentration, or type of preparation. These *Curcuma* species are all reported to contain curcumin (Burapan et al., 2020, EMA, 2013). Curcumin is also currently permitted as an active ingredient in listed medicines without restrictions. A safe dose for *C. longa*/curcumin in medicines and supplements has not been established in the available literature, particularly in the case of formulations with enhanced bioavailability, due to the wide variations in formulation, dose, and duration of use. Notwithstanding, the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) published [a safety alert](#) on 29 June 2022 warning consumers that 'ANSES's *Nutrivigilance* scheme has received over 100 reports of adverse effects, including 15 reports of hepatitis, potentially related to the consumption of food supplements containing turmeric or curcumin.' ANSES determined that curcumin from supplements should not exceed 153 mg/60 kg adult, however, this relates to the 'classic form' that is the rhizome powder or extracts and not to formulations that increase bioavailability, such as curcumin combined with piperine. ANSES is yet to determine a safe

limit for this type of preparation but advises against the use of *C. longa*-containing supplements by people with bile duct disease and on certain medications (anticoagulants, cancer drugs, and immunosuppressants) due to interactions.

A 2018 European Medicines Agency (EMA) assessment report on *Curcuma longa* L. rhizoma assessed the non-clinical and clinical data pertaining to the oral administration of dry extract and/or herbal preparations of *C. longa* (EMA, 2018). The report referred to a subchronic toxicity study where rodents given large dietary doses of *C. longa* (5.0% of their diet for 90 days) exhibited liver toxicity. An Acceptable Daily Intake (ADI) for curcumin of 0-3 mg/kg body weight (bw) has been established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2004, based on a multigeneration toxicity studies in rodents conducted on curcumin (80% pure) with a no observed adverse effect levels (NOAEL) of 250-320 mg/kg bw/day (JECFA, 2004) which later became the basis for a 3 mg/kg bw ADI (i.e. 180 mg per day for a 60 kg adult) established by the European Food Safety Authority (EFSA) (EFSA, 2010). The EFSA Panel also concluded that, at the maximum levels of use, intake estimates for children 1 to 10 years of age at the mean and the high percentile (95<sup>th</sup>) are above the ADI in some European countries. The Panel noted that intake of curcumin from the normal diet amounts to less than 7% of the 3 mg/kg bw/day ADI.

The EMA assessment report (2018) concluded that the estimated maximum daily intake of curcumin recommended in the [European Union herbal monograph for \*Curcuma longa\* L., rhizoma \(2018\)](#) of 126 mg (which corresponds to 2.1 mg/kg bw for a 60 kg adult) can be considered safe as it was within the earlier established ADI by EFSA (EMA, 2018).

Some studies have shown that low-dose curcumin exhibits hepatoprotective effects through its anti-oxidative stress properties (Farzaei et al., 2018). However, these are relevant to dietary amounts of *Curcuma* species. While 'third-generation' formulation delivering high doses of bioavailable curcumin in clinical trials have been conducted, these are of small sample sizes and have limited value in demonstrating absence of liver injury or adverse events (AE) (Pancholi et al., 2021, Cox et al., 2020). These trials on recently developed formulations may not apply to other concentrated *C. longa*/curcumin formulations available in listed medicines.

### Adverse event reports

In July 2019, the TGA became aware of a cluster of 28 hepatotoxicity cases in Italy following consumption of *C. longa*/curcumin supplements. 61% (17/28) received a WHO causality assessment of probable, 36% (10/28) were assessed as possible, while one case did not provide complete data. Of the 28 cases, 19 (67%) involved a suspected medicine that also contained various doses of piperine (Menniti-Ippolito et al., 2020). Of note, 33% (9/28) of cases did not involve piperine-containing medicines.

Further investigation identified an additional 64 international AE reports of drug related hepatic disorders (reported in [VigiBase](#)<sup>1</sup> as of 02 July 2023) of which 15 reported *C. longa*/curcumin as the only suspected ingredient. Only 2 cases also involved piperine or black pepper, which were reported as 'suspect' along with multiple other suspected ingredients. Of the 15 cases that reported *C. longa*/curcumin as the only suspected ingredient, 9 were reported as 'serious'. There was limited information in this dataset for further analysis.

Between 2002 and June 2023, the TGA received 18 liver-related AE reports associated with *C. longa*/curcumin containing products. The TGA has investigated these AE reports and

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<sup>1</sup> VigiBase, the WHO global database of reported potential side effects of medicinal products, is developed and maintained by Uppsala Monitoring Centre (UMC). The information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information does not represent the opinion of the UMC or the World Health Organization.



found that 4 cases involved *C. longa*/curcumin in multi-ingredient products that contained no other known hepatotoxic ingredients. One case was fatal, while another case, that reported biomarkers of severe liver injury, listed curcumin and *Piper nigrum* as the only active ingredients. A further 5 cases involved products that contained other ingredients that may have contributed to liver injury, while 9 cases were either not clear liver injury cases or did not include enough information for assessment. In addition, there have been three Australian literature reports of acute hepatitis which are summarised below (Chand et al., 2020, Lubber et al., 2019).

### Published case reports

The TGA is aware of 3 case reports in the literature published between 2019-2020 that describe Australian cases of hepatotoxicity associated with *C. longa* supplements. The cases involved patients between 52 and 62 years of age, two of whom presented with liver injury symptoms or acute hepatitis, evident from elevated liver function tests and/or serum bilirubin levels. The other case was asymptomatic but diagnosed with acute hepatitis, based on elevated liver enzyme levels, and diffuse steatosis revealed by ultrasonography. The cases had all commenced supplementation with *C. longa* for durations between 3 weeks and 10 months, with only one case reporting dosage information (i.e. 375 mg curcuminoids and 4 mg black pepper per tablet, 1 tablet per day). All oral medications were ceased on admission, and liver enzyme levels normalised thereafter. One patient occasionally used diclofenac for arthritic pain, and was given a presumptive diagnosis of diclofenac-induced liver injury. However, acute hepatitis reoccurred three weeks after re-administration of *C. longa* supplement (1125 mg curcuminoids per day) as sole therapy for her arthritis. Two cases were assigned [Roussel Uclaf Causality Assessment Method \(RUCAM\)](#) scores of 6 (probable) and 9 (highly probable) for the *C. longa* supplements (Lubber et al., 2019).

Between 2018 and 2022, 12 international cases were reported in the literature. Patients (males and females, 36-78 years of age) presented with symptoms consistent with liver injury (e.g. fatigue, abdominal pain, nausea, bloating, jaundice, dark urine, and elevated liver enzyme levels). All patients were taking *C. longa* or curcumin (various daily dosages with one also containing black pepper) for 3 to 33 weeks prior to presentation. For 10 cases, liver function tests returned to normal after discontinuation of the *C. longa* or curcumin, albeit with prolonged recovery ( $\geq 6$  months) in 3 cases (Fernández-Aceñero et al., 2019, Bermejo et al., 2022, Lukefahr et al., 2018), while 2 cases did not report an outcome (Koenig et al., 2021, AbdulMujeeb et al., 2021). RUCAM scores were reported in 7 cases and ranged from 6-9 ('probable' to 'highly probable') (Lee et al., 2020, Suhail et al., 2020, Sohal et al., 2021). In another 4 cases, a RUCAM score was not reported but the available information suggested a link to *C. longa* or curcumin (Abdallah et al., 2020). Confounding ingredients were noted in 2 cases (Koenig et al., 2021, Fernández-Aceñero et al., 2019).

### International regulation

In response to the reported adverse events, the Italian Ministry of Health introduced mandatory label warnings for food supplements containing *Curcuma* species to recommend that the supplement not be used by individuals with liver problems and to seek medical advice if using other medicines. Labels in Italy are no longer permitted to include indications regarding hepatic function, digestive function and digestive health (Lombardi et al., 2021). These requirements were strengthened in August 2022 to include a contraindication during pregnancy and lactation and advice not to use for prolonged periods without medical advice, with health claims relating to joint function no longer permitted (Daniells, 2022).

The TGA is aware that a number of other international agencies have issued advice against the use of *C. longa* and curcumin by individuals with hepatic disease or dysfunction:



- The [Health Canada monograph](#) for 'Turmeric – Oral' includes the warning statement: '*Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are pregnant or breastfeeding, have gallstones, a bile duct obstruction, stomach ulcers, or excess stomach acid.*'
- The [European Union herbal monograph for \*Curcuma longa\* L., rhizoma \(2018\)](#) includes the warning statement: '*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.*' The use in children and adolescents under 18 years of age is not recommended.
- [LiverTox](#) have assigned a likelihood score of 'B' (i.e. likely rare cause of clinically apparent liver injury) for *C. longa* and curcumin from medical supplements. This is based on the available case reports, particularly those linked to high bioavailability forms of *C. longa*. LiverTox found that, liver injury typically presents 1-3 months following commencement of *C. longa* with symptoms including fatigue, nausea, poor appetite, dark urine, and jaundice. Further investigations typically reveal elevated liver enzyme levels and histological changes. According to the LiverTox assessment, severe and/or fatal cases may occur if the product is not promptly discontinued.

### ACCM advice

The TGA sought advice on this issue from the Advisory Committee on Complementary Medicines (ACCM) at their 30<sup>th</sup> meeting in November 2022. The committee acknowledged that there have been rare reports of serious liver injury in association with curcumin. The Committee 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. They also noted the potentially increased risk from highly bioavailable forms, such as when combined with piperine/*Piper nigrum*. The Committee advised 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.

The Committee advised that, given the strength of evidence, the reported adverse events, and the serious nature of liver injury, risk mitigation was warranted. One of the risk mitigation strategies the Committee recommended was to introduce a label warning to inform consumers that *C. longa*/curcumin may cause liver injury and provide sufficient information for consumers to determine when to stop the medicine and seek medical advice. It was further recommended that the label warning should apply to listed medicines containing curcumin as well as any species of *Curcuma* available for use in listed medicines, due to the potential for products with highly bioavailable curcumin to be developed from these ingredients.

### Consultation

The TGA notes that many of the medicinal products currently on the Australian market produced by modern extraction methods, tend to contain highly concentrated curcuminoids, with recommended daily doses of curcumin of 1000 mg or greater. Given the potential risk of liver injury and after consideration of available data, the TGA is proposing a new warning statement for oral listed medicines containing curcumin and *Curcuma* species. Listed medicines formulations are not pre-market assessed by the TGA for safety, quality, or efficacy. As discussed above, the bioavailability of these medicines can vary greatly depending on the formulation (e.g. combination with *P. nigrum*, and or micellar complexes) and setting a maximum daily dose would not practically address the risk of harm from these products.

The proposed warning statement is intended to communicate the rare risk of liver injury to consumers and reduce the potential for severe injury by recommending cessation of the product and consultation with a doctor when specific symptoms are observed.

The TGA believes that the proposed warning statement will provide consumers with information to make an informed decision at the point of purchase, as well as minimise harm if symptoms of liver injury occur.

The TGA understands that curcumin extracts are mainly used in listed medicines for adults over 18 and notes the European Union herbal monograph for *Curcuma longa* L., rhizoma recommends against use in under 18 years of age. However, the TGA is aware that *Curcuma longa* is also used in smaller doses in a limited number of children's multivitamin formulations. As an additional layer of risk mitigation in children, the TGA is proposing that curcumin is not permitted for use in children below 2 years; and to limit the maximum permitted daily dose of curcumin to not exceed the 3 mg/kg bw/day ADI established by EFSA using the Centers for Disease Control (CDC) [clinical growth charts](#) (rounded to nearest whole number):

- 36 mg for children from 2-3 years
- 48 mg for children from 4-11 years
- 123 mg for children from 12-17 years

This proposed risk mitigation is critical to ensure that listed medicines containing *Curcuma* species/curcumin remain low-risk to allow consumers to self-select and self-administer these medicines.

**The TGA is inviting interested stakeholders to comment on the TGA proposal and submit additional information to support a safe dose for *Curcuma* species/curcumin to mitigate the risk especially from modern high bioavailability products.**

Following consideration of comments received for this consultation, and subject to any revisions of the proposals and consideration by the Delegate of the Minister, sponsors of existing listed and assessed listed medicines containing the affected ingredients will have until the end of the transition period to amend their products in line with any new requirements.

### **Affected ingredients**

1. CURCUMA AROMATICA
2. CURCUMA LONGA
3. CURCUMA ZANTHORRIZA
4. CURCUMA ZEDOARIA
5. CURCUMIN

As of 22 June 2023, there were 536 oral listed medicines included in the ARTG that contained at least one *Curcuma* species (the majority being *C. longa*), 56 of which included *C. longa* as part of a proprietary ingredient (PI). There were 136 oral listed medicines that contained curcumin as an ingredient, 33 of which included curcumin as part of a PI.

## Proposed specific requirements

Ingredient name	Existing specific requirements	Proposed specific requirements
CURCUMA AROMATICA	-	<p>When used in oral medicines, the following warning statement is required on the medicine label:</p> <p>'In 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.'</p> <p>When used in oral medicines the maximum daily dose of curcumin in the medicine must not provide more than:</p> <ul style="list-style-type: none"> <li>(a) 36 mg for children from 2-3 years (inclusive)</li> <li>(b) 48 mg for children from 4-11 years (inclusive)</li> <li>(c) 123 mg for children from 12-17 years (inclusive)</li> </ul> <p>Not permitted for use in children aged below 2 years.</p>
CURCUMA LONGA	-	<p>When used in oral medicines, the following warning statement is required on the medicine label:</p> <p>'In 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.'</p> <p>When used in oral medicines the maximum daily dose of curcumin in the medicine must not provide more than:</p> <ul style="list-style-type: none"> <li>(a) 36 mg for children from 2-3 years (inclusive)</li> <li>(b) 48 mg for children from 4-11 years (inclusive)</li> <li>(c) 123 mg for children from 12-17 years (inclusive)</li> </ul> <p>Not permitted for use in children aged below 2 years.</p>

Ingredient name	Existing specific requirements	Proposed specific requirements
CURCUMA ZANTHORRIZA	-	<p>When used in oral medicines, the following warning statement is required on the medicine label:</p> <p>'In 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.'</p> <p>When used in oral medicines the maximum daily dose of curcumin in the medicine must not provide more than:</p> <ul style="list-style-type: none"> <li>(a) 36 mg for children from 2-3 years (inclusive)</li> <li>(b) 48 mg for children from 4-11 years (inclusive)</li> <li>(c) 123 mg for children from 12-17 years (inclusive)</li> </ul> <p>Not permitted for use in children aged below 2 years.</p>
CURCUMA ZEDOARIA	-	<p>When used in oral medicines, the following warning statement is required on the medicine label:</p> <p>'In 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.'</p> <p>When used in oral medicines the maximum daily dose of curcumin in the medicine must not provide more than:</p> <ul style="list-style-type: none"> <li>(a) 36 mg for children from 2-3 years (inclusive)</li> <li>(b) 48 mg for children from 4-11 years (inclusive)</li> <li>(c) 123 mg for children from 12-17 years (inclusive)</li> </ul> <p>Not permitted for use in children aged below 2 years.</p>

Ingredient name	Existing specific requirements	Proposed specific requirements
CURCUMIN	When for excipient use, only permitted for use as a colour in topical and oral medicines.	<p>When used in oral medicines, the following warning statement is required on the medicine label:</p> <p>'In 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.'</p> <p>When used in oral medicines the maximum daily dose of curcumin in the medicine must not provide more than:</p> <ul style="list-style-type: none"> <li>(a) 36 mg for children from 2-3 years (inclusive)</li> <li>(b) 48 mg for children from 4-11 years (inclusive)</li> <li>(c) 123 mg for children from 12-17 years (inclusive)</li> </ul> <p>Not permitted for use in children aged below 2 years.</p> <p>When for excipient use, only permitted for use as a colour in topical and oral medicines.</p>

## 2. Green tea extract and the risk of liver injury

### Background

Green tea (*Camellia sinensis*) is an evergreen plant that grows primarily in tropical and temperate regions of Asia, and is cultivated in several African and South-American countries (Senanayake, 2013). Green tea is rich in polyphenolic compounds known as flavonols or catechins (Song and Chun, 2008). The main catechins in green tea are epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG), with EGCG being the most abundant in green tea. Green tea generally has the highest EGCG content (50-80%) compared to other teas (Muhamud and Amran, 2018) with a single cup of brewed green tea (250 mL) containing approximately 100-300 mg of EGCG (Park et al., 2021). In 2018, the EFSA Panel estimated the mean daily intake of EGCG resulting from the consumption of green tea infusions to be 90-300 mg/day while exposure via food supplements containing concentrated green tea extracts (GTE) is estimated to be up to 866 mg EGCG/day, in the adult population in the European Union (EFSA, 2018, Chacko et al., 2010, Nagle et al., 2006). Green tea consumed as part of the diet, is reported to have protective properties such as antioxidative, anti-inflammatory, antiarthritic, and cholesterol-lowering effects which are usually attributed to low-dose EGCG (Chacko et al., 2010, Nagle et al., 2006).

*Camellia sinensis* is permitted for use in listed medicines, with no restrictions on the type of preparation, dose, or concentration other than the restrictions pertaining to the caffeine content of the medicine. However, medicines containing green tea, and more specifically GTE, have been implicated in numerous cases of liver injury worldwide, with accumulative safety concerns arising from many published case reports in the literature, cases reported in Australia to the TGA, as well as cases reported to regulators in overseas jurisdictions.

The available evidence suggests that liver injury associated with GTE has both an intrinsic dose dependent aspect, as well as a dose independent idiosyncratic aspect for susceptible consumers (EFSA, 2018, Navarro et al., 2017). Although no specific at-risk population has been identified, there may be an increased risk for consumers with pre-existing liver conditions. The exact mechanism of hepatotoxicity has not been confirmed (Navarro et al., 2017), but there is evidence that EGCG is largely responsible (Mazzanti et al., 2015). In medicinal products available in the Australian market, concentrations of EGCG in GTE have been reported to range from 50% to 98%.

An application was made to amend the Poisons Standard in July 2022 to include GTE in Schedule 2 and Schedule 5 (depending on use) except when labelled with warnings to take with food and advising consumers to be aware of symptoms of liver damage. The proposal was to provide a mechanism for ensuring consumers were adequately informed of the risks of GTE and how to identify potential symptoms, as well as to capture products containing GTE such as sports supplements which are not currently included in the ARTG.

The scheduling Delegate released their [interim decision](#) in February 2023 to not amend the current Poisons Standard in relation to GTE. The reasons can be read in the interim decision (pp 41-45). Interested persons were invited to make submissions in relation to the interim decision. After the closing date, the Delegate's [final decision was deferred](#) pending further consultation and consideration by the Delegate. The TGA is aware that new information has emerged in relation to GTE that was not available to the scheduling committee in July 2022. The new information is discussed in 'Adverse event reports', 'Literature review', and 'International regulation' sections below. In light of this new information and considering the proposed changes to the Poisons Standard have arisen from safety concerns that also relate to listed medicines, the TGA is proceeding with the present consultation to address the safety concerns around the use of GTE in listed medicines. A range of options are currently being separately considered by the scheduling Delegate.



## Adverse event reports

GTE is a frequently reported causative agent in several international drug-induced liver injury registries (Latin America, Spain, USA, and Korea). According to [LiverTox](#), discontinuation of the GTE product along with medical attention resulted in the resolution of the liver injury in most reported cases of liver damage in humans. However, in some cases, the consequences of the liver injury can be severe. LiverTox has assigned green tea a likelihood score of 'A' (i.e. a well-established cause of clinically apparent liver injury). Literature reports include at least 9 international cases of liver injury necessitating liver transplant associated with green tea, and more than 100 instances of clinically apparent liver injury attributed to GTE (Gloro et al., 2005, Hoofnagle et al., 2021, Mazzanti et al., 2015, Percevault et al., 2022).

As of 30 June 2023, there have been 30 cases of liver-related adverse events associated with products containing *Camellia sinensis* or green tea in Australia reported to the TGA with slightly more than half (18/30) associated with products on the ARTG, while in 5 cases there was insufficient information to establish whether the suspected medicine was on the ARTG. The TGA undertook investigation and found that most of the adverse events involved multi-ingredient formulations, while 3 were associated with medicines that contained GTE as the sole active ingredient. No trends were observed in relation to dosage or duration of use of the medicines. The reported symptoms include hepatitis, abnormal hepatic function, abnormal liver enzyme levels, jaundice, abdominal pain, lethargy, and nausea. One known Australian case resulted in severe hepatotoxicity requiring liver transplantation. However, this case involved 2 suspected medicines, neither of which were included on the ARTG. While TGA analysis confirmed the presence of *Camellia sinensis* in one of the suspected medicines, the other suspected medicine was also reported to contain an ingredient associated with liver injury.

Of the 30 cases reported, the TGA's [RUCAM](#) causality assessment assigned a rating of 'probable' for 2 cases and 'possible' for a further 3 cases that liver injury was due to the *Camellia sinensis*-containing medicine. In 3 of these cases the suspected medicine contained no other potentially hepatotoxic ingredients, including one probable case where *Camellia sinensis* was the only active ingredient in the suspected medicine. For 77% (23/30) of the other cases, there was either insufficient information to apply a RUCAM assessment (20/30) or the *Camellia sinensis* containing medicine could not be conclusively identified (3/30) so no further assessment was undertaken. While a causal association could not be confirmed for these cases using formal assessment, it could not be ruled out. Of note was that in 15 of the 20 cases with insufficient data for a RUCAM assessment, the *Camellia sinensis* containing medicine was the only suspected medicine, and in 11 of these reports the suspected medicine contained no other potentially hepatotoxic ingredients.

In addition, 66 adverse event reports of drug related hepatic disorders associated with *Camellia sinensis* have been reported internationally, excluding Australian cases (reported in [VigiBase](#)<sup>2</sup> as of 28 June 2023). Of these, 27 reported *Camellia sinensis* as the only suspected ingredient, with 15 of these 27 cases reported as serious. There was limited information in this dataset for further analysis.

## Literature review

A TGA review of the literature revealed a consistent association between use of products containing *Camellia sinensis* and adverse hepatic events, although these events appear to be rare and unpredictable when consumed at normal doses. Although a dose-response relationship has been observed in the literature, hepatic adverse effects have also been reported after lower doses, and also after consumption of large amounts of a green tea

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<sup>2</sup> The information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information does not represent the opinion of the UMC or the World Health Organization.



beverage over a long period (i.e. 1.5 litres of green tea per day over 5 years) (Mazzanti et al., 2015). At the time of publication, there is insufficient data for the TGA to establish a threshold dose below which the potential for liver-related adverse events does not occur.

In 2017, Health Canada reviewed GTE and its potential risk of liver injury, evaluating available evidence including literature reports, clinical trials, toxicological data, as well as adverse event reports (Health Canada, 2017). Health Canada's review concluded that there may be a link between the use of GTE and a risk of rare and unpredictable liver injury.

In 2018, EFSA also published a review on the safety of green tea catechins which concluded that doses of 800 mg and above EGCG/day taken as a food supplement significantly increase serum liver injury markers in treated subjects compared to controls, based on clinical trials. The Panel concluded that it was not possible to identify an EGCG dose from GTE that could be considered safe (EFSA, 2018).

In 2022, the United States Pharmacopeia (USP) Green Tea Extract Hepatotoxicity Expert Panel conducted a comprehensive literature review of pharmacokinetics, clinical data, animal pharmacology and toxicology data for GTE from 2008 to 2017. A total of 12 non-clinical studies, 28 clinical studies and 35 published case reports associated with single ingredient GTE were analysed. The review found a clear occurrence of severe hepatotoxicity from ingestion of GTE in humans, suggesting that green tea constituents, particularly EGCG and other catechins, are likely to be associated with the observed hepatotoxicity. Further, while dosing data and NOAELs from animal studies exist, the human evidence regarding dose-response is less robust, with hepatotoxicity occurring at doses below those observed in animal studies. The setting of a dose below which toxicity will not occur was deemed impractical due to a possible role of genetic factors and the idiosyncratic nature of hepatotoxicity in humans (Oketch-Rabah et al., 2020). Some of the major findings of the review included:

- The Minnesota Green Tea Trial (MGTT) in postmenopausal women (daily GTE dose containing 800 mg EGCG for 12 months) found moderate or severe abnormalities in liver function tests in 5.1% of subjects given GTE compared to baseline levels, with an odds ratio of 7.0 for developing liver function abnormalities compared to the placebo arm. A rise-fall pattern in liver enzyme levels was observed following challenge-dechallenge-rechallenge cycles of GTE consumption which was considered compelling evidence implicating the effect of high-dose GTE on potential liver injury.
- Case reports of liver injury associated with GTE as the sole suspected ingredient (35 out of the 75 cases found) were analysed. Causality assessments were undertaken by experts from the Drug-Induced Liver Injury Network using the RUCAM method. In total 29 cases were considered positive for liver injury (RUCAM score of 6 or above), 4 of which were considered as 'definite,' 11 were 'highly likely,' and 14 were 'probable.' Twenty-six of these cases involved concentrated GTE, and 19 specifically excluded other drugs. One case resulted in fulminant liver failure.

A systematic review conducted by Hu et al. (2018) reported that toxicological studies confirmed GTE hepatotoxicity. Liver injury was strongly associated with dosing conditions and positively correlated with total catechin and EGCG content. Data from 48 human intervention studies that monitored hepatic adverse events further confirmed the non-clinical evidence. Authors reported the overall incidence rate of hepatic AEs to be 4.9% based on the number of events of elevated liver function biomarkers (111 events out of 2269 subjects consuming a green tea preparation). The majority were considered mild to moderate in severity (98/111), while 13 were more severe (liver enzyme levels elevated >5 times the upper limit of normal (ULN) and/or bilirubin >3 times ULN). Hepatic adverse events were reported after consumption of concentrated, catechin-rich green tea preparations

administered in bolus dose in a dose-dependent manner, but not after consumption as brewed tea or extracts in beverages or as part of food (Hu et al., 2018).

Overall, green tea has a history of safe use in foods/beverages except for isolated cases that involved consumption at a high dose for a prolonged period (Percevault et al., 2022). Many of the safety concerns stem from published case reports linking consumption of concentrated GTE (i.e. in supplements) with liver injury. Hu et al. (2018) concluded that for adults with normal liver function, a safe intake limit of 338 mg EGCG/day (fed or fasted) or a conservative limit of 300 mg EGCG/day could be considered for GTE ingested in solid dosage forms. An Observed Safe Level of 704 mg EGCG/day (fed or fasted) may be considered for a green tea preparation consumed in beverage form (Hu et al., 2018).

### International regulation

In 2017, Health Canada recommended a standardised upper permissible daily limit of 300 mg for EGCG for all GTE-containing products in Canada, regardless of the type of claim (Health Canada's Marketed Health Products Directorate, 2017). The Health Canada Natural Health Product monograph for GTE (Health Canada, 2018) restricts health products supplied in Canada with health claims for antioxidants to not exceed 690 mg/day total catechins, and 150 mg/day of caffeine. GTE-containing products with health claims for weight management can only provide daily doses of 136-300 mg EGCG and 75-150 mg caffeine, with an EGCG:Caffeine ratio of 1.8:1 to 4:1, and must not exceed 690 mg/day of total catechins (including EGCG). The monograph also requires label statements to take GTE with food, and to stop use and consult a healthcare professional if symptoms of liver injury develop such as yellowing of the skin/eyes (jaundice), stomach pain, dark urine, sweating, nausea, unusual tiredness and/or loss of appetite. Label statements are also required for those who are pregnant/breastfeeding, have pre-existing liver disorder or iron deficiency to consult a healthcare professional prior to use, and to consult a healthcare professional for use beyond 12 weeks.

The USP Dietary Supplements monograph for 'Powdered Decaffeinated Green Tea Extract' requires the following label statements:

- *'Do not take on an empty stomach'*
- *'Take with food'*
- *'Do not use if you have a liver problem'*
- *'Discontinue use and consult a healthcare practitioner if you develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice (yellowing of the skin or eyes)'*

In November 2022, the European Commission enacted a [new regulation](#) on the permitted concentrations of EGCG in GTE in foods, which requires:

- the daily portion of food must contain less than 800 mg/day of EGCG; and
- that food labels provide:
  - the maximum number of portions of the food for daily consumption,
  - the content of EGCG per portion, and
  - warnings *'not to consume 800 mg/day or more of EGCG'*, and that it should not be consumed:
    - *'if consuming other products containing green tea on the same day'*
    - *'by pregnant or lactating women and children below 18 years old'*
    - *'on an empty stomach'*

This excludes aqueous GTE containing EGCG which after reconstitution in beverages have a composition comparable to traditional green tea infusions.

There are separate European Commission requirements for [EGCG as a purified extract from the leaves of \*Camellia sinensis\*](#) (composed of a minimum of 90% EGCG) when used in food

supplements or fortified foods, with a maximum permitted level of 150 mg of extract in one portion of food or food supplement, and with labelling that more than 300 mg extract per day should not be consumed.

As of July 2022, the Health Sciences Authority (HSA) of Singapore lists *Camellia sinensis* in the [list of health supplements with specific concerns](#) because of rare and unpredictable cases of liver injury. HSA has noted that risk mitigation includes providing information to users to highlight potential liver injury risks.

### ACCM advice

The TGA sought advice on this issue from the ACCM at their 19<sup>th</sup> meeting in March 2018. The Committee agreed that the available information (adverse events reported to the TGA, safety review, and regulatory status of GTE) suggested there may be a link between *Camellia sinensis* and liver injuries. However, it was noted that the reactions appear to be idiosyncratic and have occurred at low doses, therefore, it would be difficult to set a maximum permitted dose to address risk of liver injury. The Committee advised that continued monitoring of adverse reactions was warranted and advised that it would be appropriate for the TGA to give further consideration to risk mitigation strategies such as suitable risk communication, including publication of a web advisory statement and label warning statements.

In June 2018, the TGA published a [safety advisory](#) on GTE and its potential risk of harm to the liver. [Health Canada](#) and [EFSA](#) have also published information on the risk of harm to the liver by *Camellia sinensis* extracts. Since the ACCM advice, the TGA has received additional liver-related adverse reaction reports, and more information has become available including international regulatory actions as described above.

### Consultation

GTE are used in listed medicines using the ingredient name *Camellia sinensis*. The composition of these preparations is not always clear from the ARTG entries and there are different extraction methods utilised and the amount of catechins delivered from products containing these preparations might vary widely.

**In light of the current information that demonstrates an association between use of products containing GTE and adverse hepatic events, the TGA is inviting interested stakeholders to comment on the proposal to make an amendment to the Permissible Ingredients Determination to require a warning statement for oral listed medicines that contain GTE.**

The proposed warning statement is intended to communicate the rare risk of serious liver damage and reduce the potential for severe injury by recommending cessation of the product and consultation with a doctor when specific symptoms are observed. Discontinuing use of the toxic agent as early as possible is important to reduce the risk of severe outcomes for drug induced liver injury.

This approach is consistent with previous warnings applied to herbal products associated with liver injury as well as with similar warnings applied by international regulatory agencies for GTE. The proposed warning statement would only be applicable to medicines for oral use and would not apply to *Camellia sinensis* used as part of a proprietary ingredient formulation for flavouring (limited to 5% of the total medicine in line with flavour PI requirements) or to medicines containing aqueous *Camellia sinensis* extracts that provide up to 300 mg EGCG per maximum recommended daily dose (comparable to the estimated maximum amount provided by one cup of brewed green tea infusions). To be exempt from the warning, sponsors would be expected to demonstrate with batch data, that the maximum amount of EGCG in the aqueous extract does not result in the medicine exceeding 300mg per daily dose.

Additionally, medicines containing *Camellia sinensis* are proposed to require a statement to 'Take with food' on the medicine label as the evidence suggests the risk of liver injury can be reduced when taken with food rather than when taken on an empty stomach.

Following consideration of comments received for this consultation, and subject to any revisions of the proposals and consideration by the Delegate of the Minister, sponsors of existing listed and assessed listed medicines containing the affected ingredients below will have until the end of the transition period to amend their products in line with any new specific requirements.

### **Affected ingredients**

#### **1. CAMELLIA SINENSIS**

As of 2 August 2023, there are 339 oral listed medicines included in the ARTG that contain *Camellia sinensis*. Most of these (323) included the ingredient as an extract. There were 19 products that contained *Camellia sinensis* as part of a proprietary ingredient formulation for oral use.

## Proposed specific requirements

Ingredient name	Existing specific requirements	Proposed additional specific requirements
CAMELLIA SINENSIS	<p>Caffeine is a mandatory component of <i>Camellia sinensis</i>.</p> <p>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%.</p> <p>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.</p> <p>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%.</p> <p>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.</p> <p>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:</p> <ul style="list-style-type: none"> <li>- (ADULT) 'Adults only' (or words to that effect).</li> <li>- (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.'</li> <li>- (CAFFPREG) 'Caffeine intake more than 200 mg per day is not recommended during pregnancy or breastfeeding.'</li> </ul> <p>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:</p> <ul style="list-style-type: none"> <li>- (CAFFLMT) 'Limit the use of caffeine-containing products (including tea and coffee) when taking this product.'</li> <li>- (CAFFCYP) 'Caffeine interacts with enzyme CYP1A2 in the liver. Consult your health professional before taking with other medicines' (or words to that effect).</li> </ul>	<p>The following warning statement is required on the medicine label when the medicine is for oral use (excluding when in combination with other permitted ingredients as a flavour, or when the preparation of <i>Camellia sinensis</i> is derived from an aqueous extract and contains 300 mg or less epigallocatechin-3-gallate per maximum recommended daily dose):</p> <ul style="list-style-type: none"> <li>- 'In rare cases, <i>Camellia sinensis</i> 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.'</li> <li>- (FOOD) 'To be taken with food.'</li> </ul> <p>If used in a flavour the total flavour proprietary excipient formulation in a medicine must not be more than 5%.</p>



### 3. Safe levels of benzophenone

#### Background

Benzophenone is an aryl ketone naturally occurring in food. Concentrations of benzophenone in food products can range from 0.57 ppm in non-alcoholic beverages to 3.27 ppm in frozen dairy products. It can also be present as a contaminant in drinking water and is known for its migration from food packaging. Benzophenone is used as a flavour, a fragrance enhancer, and a perfume fixative (IARC, 2012).

Benzophenone is currently permitted for use in listed medicines only in combination with other permitted ingredients as a flavour or a fragrance, where the total flavour or fragrance concentration in a medicine must be no more than 5% and 1%, respectively.

In 2012, the [International Agency for Research on Cancer \(IARC\) Working Group](#) concluded that benzophenone is “possibly carcinogenic to humans (Group 2B)”, based on animal oral carcinogenicity studies, noting that no data was available for the working group to assess the risk of carcinogenicity in humans. The data presented in the report showed significant increased occurrence of tumours/adenomas/lesions from high doses of benzophenone administered orally as employed by carcinogenicity studies. The working group noted that although the mechanisms of tumourigenesis are not fully known, the effects may include generation of reactive oxygen species, endocrine disruption, or alteration of endogenous steroid hormones. The working group indicated that “dermal application of benzophenone did not induce tumours in mice” (IARC, 2012).

A study investigating 17 commercial sunscreen products found that products containing octocrylene (a common active ingredient used in sunscreens), when subjected to accelerated aging and stability testing, resulted in increasing amounts of benzophenone concentrations over time. In contrast, benzophenone was not detectable in the product that did not contain octocrylene. The results demonstrated that the rate of increase of benzophenone concentration is dependent on the product formulation rather than how much octocrylene was initially present in the product (Downs et al., 2021).

In December 2021, the TGA published a news page ([ensuring the effective and safe use of sunscreens](#)) regarding the safety and testing of benzophenone in sunscreens. As there is currently no restriction in the Permissible Ingredients Determination in relation to the benzophenone content in sunscreens that contain octocrylene, listed medicines sponsors must establish an appropriate quality control specification and stability protocol to monitor relevant impurities to ensure the safety of each batch of the product throughout its shelf life.

Recent TGA laboratory testing has confirmed the presence of benzophenone at various concentrations in sunscreens on the ARTG that contain octocrylene as an active ingredient. Although most of the tested products complied with the USP monograph for octocrylene as a raw material and its identified quality limits, the monograph does not specify a safe limit for benzophenone as a degradant in finished products. Based on the expected use of the products tested, the detected levels did not indicate an imminent safety concern however did identify the need for restrictions to be put in place to ensure benzophenone remains within acceptable safe limits and sunscreens remain within the low-risk listed medicines framework. The TGA has reviewed available information to establish a safe permitted daily exposure and a limit for benzophenone as a degradant in sunscreens.

#### Literature review

A literature review has found that at certain doses benzophenone is associated with a wide range of toxicities in experimental animals, including genotoxicity, carcinogenicity, and endocrine disruption. In sub-chronic oral studies, the liver is the primary target organ of

benzophenone toxicity in rats and mice. The kidney was also identified as a target organ of benzophenone toxicity in rats only (EFSA, 2017).

In 14-week oral studies evaluated by JECFA, the NOAELs for benzophenone in mice were 200 mg/kg bw/day in males and 270 mg/kg bw/day in females, based on increased kidney weights. A 14-week oral study in rats found marked changes in haematological parameters, and significant liver and kidney toxicity, resulting in NOAELs of 75 mg/kg bw/day in males and 80 mg/kg bw/day in females (JECFA, 2011).

Benzophenone and its common metabolites, benzhydrol and *p*-hydroxybenzophenone, were positive in Ames tests and SOS/Umu assay (Robinson, 1958, Takemoto et al., 2002, Wang et al., 2018, Zhao et al., 2013). Benzophenone was found to induce mutations in *Salmonella Typhimurium* (TA102) at low doses (without metabolic activation) (Wang et al. 2018). Benzophenone also induced thymine dimerization and double-stranded DNA break formation in the presence of UV light, similar to effects produced by x- or  $\gamma$ -ray irradiation (Charlier et al., 1972).

Oral carcinogenicity studies using benzophenone resulted in significant increased incidence of hepatocellular adenoma in male mice ( $\geq 80$  mg/kg bw/day), histiocytic sarcoma in female mice (35 mg/kg bw/day), and mononuclear cell leukemia in male rats ( $\geq 15$  mg/kg bw/day) (NTP, 2006). As various lesions were identified at all doses, respective NOAELs could not be obtained from these data. Therefore, lowest observed adverse effect levels of 40 mg/kg bw/day in mice and 15 mg/kg bw/day in rats were derived. These data were considered by the IARC in their classification of benzophenone as a possible human carcinogen.

A range of evidence indicate that benzophenone and its metabolites are potential endocrine disruptors (Kawamura et al., 2005, Nakagawa and Tayama, 2001, Suzuki et al., 2005). Studies have found that benzophenone and its derivatives have estrogenic and anti-androgenic activity in human estrogen and androgen receptors *in vitro* (Kawamura et al., 2005) and in rats *in vivo* (Suzuki et al., 2005). The benzophenone metabolite, *p*-hydroxybenzophenone, was also found to have intrinsic xeno-estrogenic effects in female rats at doses of 100 mg/kg bw and above (Nakagawa and Tayama, 2001). A 2018 study by Lee et al. showed that benzophenone could alter thyroid-hormone balances in a zebrafish embryo model by influencing the central regulation and metabolism of these hormones (Lee et al., 2018).

### Local and international regulation

Most of the local and international regulation has been focused on the presence of benzophenone in food in low concentrations. In 2009, EFSA assessed benzophenone as a food contact material (EFSA, 2009). The report indicated that the margin of exposure was low and recommended that more data on the occurrence of the substance in foods should be provided as well as appropriate toxicity data corresponding to the level of exposure to enable a full risk assessment. The EFSA Panel also concluded that benzophenone was not genotoxic but caused kidney adenoma, including hyperplasia and nephropathy in rats at the lowest dose level tested of 15 mg/kg bw/day in a carcinogenicity study, and established a Tolerable Daily Intake (TDI) of 0.03 mg/kg bw/day, equating to 1.5 mg/day for a 50 kg person). The TDI is in the same order of magnitude as the chronic dietary exposure of adults and children to benzophenone in Europe (i.e. 10-20  $\mu$ g/kg bw/day) for added flavouring substances. The toxicity of benzophenone was re-evaluated by EFSA in 2017 (EFSA, 2017) and the TDI established by EFSA in 2009 was re-confirmed.

The Australian Industrial Chemicals Introduction Scheme (AICIS) completed a [Human Health Tier II assessment for benzophenone](#) on 1 September 2015. While showing low acute toxicity in rabbits following dermal exposure (LD<sub>50</sub> of >2000 mg/kg bw), AICIS concluded that



benzophenone was a potential oral carcinogen (based on the available animal studies by IARC and NTP discussed above).

In 2018, the [US FDA](#) amended its food additive regulations to no longer allow the use of benzophenone (and other substances) in food. However, the FDA stated that this removal was only a matter of law, and concluded that these substances do not pose a risk to public health under the conditions of their intended use. As of late 2020, its use in food products or food packaging was banned in the US. Under [California Proposition 65](#), there are no legal provisions for safe levels of benzophenone in any personal care products, including sunscreens, anti-aging creams, and moisturisers.

The Health Canada [Natural Health Product Ingredients Database](#) has a TDI for benzophenone of 0.03 mg/kg bw/day when the route of administration is oral for medical use, or up to 3.27 ppm for oral non-medicinal use as a flavour enhancer. In January 2021, Health Canada undertook a [Screening Assessment](#) for benzophenone to determine whether it presents a risk to the environment or to human health. Although benzophenone was found to be non-genotoxic, chronic oral exposure to benzophenone induced kidney adenoma and leukemia in male rats, liver tumours in male and possibly female mice, and histiocytic sarcomas in female mice. The assessment also indicated that dermal studies on the carcinogenicity of benzophenone performed on mice and small groups of rabbits showed no carcinogenic potential. However, the assessment could not verify the quality of the studies given the limited information provided in the published reports, and the extent of the histological examinations appears to have been limited. The Health Canada assessment concluded that benzophenone meets the human health criterion for a toxic substance and, subsequently, [proposed to make an Order](#) to add benzophenone as a toxic substance to Schedule 1 of the Canadian Environmental Protection Act (the List of Toxic Substances) in April 2022.

### TGA assessment

The TGA has reviewed the available published data for benzophenone in relation to carcinogenicity risk taking into consideration the assessments undertaken by other international agencies. Based on available data, the TGA concluded that there is evidence of carcinogenic potential from benzophenone primarily via the oral route and should remain at trace levels in listed medicines that are for oral use. Noting that benzophenone is not currently present in any oral listed medicines on the ARTG, the TGA proposes to remove the use of benzophenone as a flavour. The TGA has also concluded that there is limited safety concern from low concentrations of topical exposure to benzophenone for most topical listed medicines when present at a concentration of 26 ppm (0.0026%). This concentration is based on the safe Permitted Daily Exposure (PDE) of 1.6 mg/day for benzophenone derived below.

A PDE is derived using the method described in Appendix 3 of the TGA adopted [ICH guideline Q3C \(R6\) on impurities: guideline for residual solvents \(CHMP/ICH/82260/2006\)](#), by applying safety factors for interspecies variability, for variability between individuals, for the short-term study and 2.5 (F4) for the possibility of non-genotoxic carcinogenic effects. The NOAEL of 20 mg/kg bw/day in rats was obtained from a 13-week oral study in rats (Burdock et al., 1991, ECHA, 2018). The calculated concentration (1.6 mg/day) approximately aligns with the TDI established by EFSA for the oral route of administration (1500 µg/day for a 50 kg person). It should be also noted that, this limit is calculated based on adult data as no data are available for other populations and is, thus a conservative approach warranted to ensure listed medicines remain low risk in other age groups.

$$PDE = \frac{NOAEL \times \text{weight adjustment}}{F1 \times F2 \times F3 \times F4}$$

$$PDE = \frac{20 \times 50}{5 \times 10 \times 5 \times 2.5}$$

$$PDE = 1.6 \text{ mg/day}$$

- F1: safety factor to account for interspecies variability  
 F2: safety factor to account for variability between individuals  
 F3: safety factor to account for short-term study (~3 months)  
 F4: to account for the possibility of non-genotoxic effects

Using a PDE of 1.6 mg/day, a safe and conservative concentration for benzophenone for topical use was established based on a maximum recommended use of 35 mL of sunscreen applied to the skin 4 times (140 mL) a day (using [Cancer Council of Australia](#) recommendations for application) and assuming 44% of the benzophenone is absorbed as found in the literature (Bronaugh et al., 1990). The calculation shown in the equation below reveals that 26 ppm (or 0.0026%) of benzophenone is regarded as safe for therapeutic sunscreens that are listed on the ARTG.

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

$$\text{Benzophenone concentration} = \frac{1.6 \text{ mg/day}}{140 \text{ mL/day} \times 0.44}$$

$$\text{Benzophenone concentration} = 0.02597 \text{ mg/mL} = 25.97 \text{ } \mu\text{g/mL} \approx 26 \text{ ppm}$$

The TGA recognises that actual sunscreen usage in Australia can be different from recommendations from government and public health organisations and the directions for use on Australian products. The latter specify liberal and frequent application of sunscreen, although not all consumers may apply it that way and may use other sun protection measures such as seeking shade, or wearing a hat, sunglasses, and protective clothing. It is important to note that the TGA regulates therapeutic goods based on their intended usage and potential usage as per the directions for use so they remain low-risk for consumers. As indicated above, benzophenone can be present in sunscreens formulations as an impurity, fragrance, and/or can be a degradant from the active ingredient octocrylene. The TGA is also aware of listed sunscreens that contain both octocrylene as an active ingredient, and benzophenone as a component in a fragrance proprietary ingredient (PI).

Products with a high rate of octocrylene degradation to benzophenone are likely to raise quality, safety, and efficacy concerns for these products. The TGA does not premarket assess the formulations for listed sunscreens. As such, it is the responsibility of sponsors to ensure the ongoing stability of their developed formulations during the product shelf life. The current USP monograph for the octocrylene raw material does not impose a safe dose limit for benzophenone in finished products, and there is currently no specific safety or quality requirement for benzophenone levels in finished products, nor a requirement when benzophenone is present in a fragrance or as an impurity or degradant. Based on the PDE derived above, the TGA proposes that benzophenone in octocrylene containing sunscreens should remain at trace amounts that do not exceed 26 ppm during the product shelf life.

Further, sunscreens are not the only listed medicine that may contain benzophenone as it is currently present as a component of a fragrance PI in other listed medicines including baby creams. In that respect, the proposed concentration limit was also considered relevant to benzophenone present in baby cream formulations for application in the nappy area. Considering the PDE calculated above for benzophenone (i.e. 1.6 mg/day for a 50 kg individual), this can be extrapolated to younger populations weighing less than 50 kg. Assuming dermal application several times a day using a product containing benzophenone as a component of a fragrance PI and a dermal absorption of 69% for benzophenone in the

occluded area of the nappy (Bronaugh et al., 1990), the amount of benzophenone absorbed was estimated to be below the identified PDE.

### Consultation

The TGA is seeking consultation on an amendment to the requirements for use of benzophenone and octocrylene in listed medicines.

**The TGA is inviting interested stakeholders to comment on the proposal to make an amendment to the Permissible Ingredients Determination to address the potential carcinogenicity risk from benzophenone in listed medicines, and ensure that benzophenone remains at trace levels that are considered to be low-risk to consumers in line with the calculated 26 ppm concentration. As benzophenone is an established potential degradant of sunscreens that contain octocrylene, it is also proposed to be declared as a mandatory component of octocrylene to ensure it is accounted for by sponsors in a sunscreen product that contains octocrylene.**

Following consideration of comments received for this consultation, and subject to any revisions of the proposals and consideration by the Delegate of the Minister, sponsors of existing listed and assessed listed medicines containing the affected ingredients below will have until the end of the transition period to amend their products in line with any new specific requirements.

### Affected ingredients

1. BENZOPHENONE
2. OCTOCRYLENE

As of 27 June 2023, octocrylene is present in 551 listed medicines as an active ingredient in sunscreens. As of 27 June 2023, benzophenone is only present in 4 listed medicines as part of fragrance PIs in topical formulations. Three of these are sunscreens that also contain octocrylene as an active ingredient. Benzophenone is not currently used as a flavour for oral use in listed medicines.

## Proposed specific requirements

Ingredient name	Existing specific requirements	Proposed specific requirements
BENZOPHENONE	<p>Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.</p> <p>If used in a flavour the total flavour concentration in a medicine must be no more than 5%.</p> <p>If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.</p>	<p>Permitted for <b>topical</b> use only in combination with other permitted ingredients as a <del>flavour or a</del> fragrance.</p> <p><del>If used in a flavour the total flavour concentration in a medicine must be no more than 5%.</del></p> <p>If used in a fragrance the total <del>fragrance</del> concentration of <b>fragrance formulations containing benzophenone</b> must not be <del>in a medicine must be no</del> more than 1% of the total medicine.</p> <p>The total concentration of benzophenone in the medicine must not be more than 26 ppm (0.0026%).</p>

Ingredient name	Existing specific requirements	Proposed specific requirements
OCTOCRYLENE	<p>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.</p> <p>The concentration in the medicine must not be more than 10%.</p> <p>When used in primary sunscreen products, the following warning statements are required on the label:</p> <ul style="list-style-type: none"> <li>- (AVOID) 'Avoid prolonged exposure in the sun' (or words to this effect); and</li> <li>- (SUNPRO) 'Wear protective clothing - hats and eyewear when exposed to the sun' (or words to this effect).</li> </ul>	<p>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.</p> <p>The concentration in the medicine must not be more than 10%.</p> <p><b>Benzophenone is a mandatory component of octocrylene.</b></p> <p><b>The total concentration of benzophenone in the medicine must not be more than 26 ppm (0.0026%).</b></p> <p>When used in primary sunscreen products, the following warning statements are required on the label:</p> <ul style="list-style-type: none"> <li>- (AVOID) 'Avoid prolonged exposure in the sun' (or words to this effect); and</li> <li>- (SUNPRO) 'Wear protective clothing - hats and eyewear when exposed to the sun' (or words to this effect).</li> </ul>

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

### Background

Phosphatidylserine (PS) is a phospholipid that is claimed to enhance neurological membrane functions and improve memory performance (Jorissen et al., 2002). It can be derived from several sources, including recently developed sources, soybean and egg. Soy phosphatidylserine-enriched soy lecithin powder and soy phosphatidylserine-enriched soy lecithin liquid are commonly used in listed medicines in Australia. As per the Determination, these ingredients are currently permitted for use in listed medicines with a restriction on the maximum amount of soy PS of 'no more than 15%'.

The soy PS ingredients were [made available for use in listed medicines](#) in March 2000, following an application to use the substances. The ingredients were presented to [Complementary Medicines Evaluation Committee \(CMEC\) at the 18<sup>th</sup> meeting](#) in February 2000. CMEC noted that the available non-clinical and clinical data have found to have no safety concerns for PS or soy lecithin PS. CMEC recommended that "soy phosphatidylserine-enriched soy lecithin is suitable for use as an active ingredient in listable therapeutic goods, and that no substance-specific conditions of use were required at the time". Thus, at the time of listing in March 2000, there were no restrictions on the amount of soy PS in medicines containing these ingredients.

The Electronic Listing Facility (ELF)<sup>3</sup> validation rules applied as of May 2003 and provided sponsors with the message: "*Concentration of soy phosphatidylserine in soy phosphatidylserine powder/liquid must be 15% or **higher***". The minimum amount of soy PS was established based on the compositional guideline of the substance that was evaluated in 2000. However, the current restriction for the soy PS ingredients in the Determination does not reflect a minimum amount of soy PS of 15%.

In September 2022, Health Canada completed a [safety assessment](#) for soy based on information related to chemistry, nutrition, microbiology, toxicology, and allergenicity. It was concluded that "[PS] (soy) is well tolerated in clinical studies, is not associated with reports of allergic reactions, and does not pose any toxicological or nutritional concerns when used as a supplemental ingredient in accordance with the conditions of use outlined in the [\[Notice of Proposal\]](#)". Health Canada, therefore, recommended that a maximum daily intake of 300 mg soy PS was established safe for use as a supplement.

### TGA assessment

The TGA has reviewed the available published data relating to the safety of soy PS. Animal toxicity studies were not identified for phosphatidylserine derived from soy, however, studies have been conducted using bovine- and fish-derived PS. A study by Heywood et al. (Heywood et al., 1987) found no adverse events in animals given to 1000 mg/kg bw/day of bovine PS (rats for 6 months and dogs for 12 months), and no significant reproductive or developmental impacts in rats (up to 200 mg/kg bw/day) or rabbits (up to 450 mg/kg bw/day) given bovine PS during gestation. A more recent study found that fish PS was not mutagenic (according to an Ames test and a human lymphocyte micronucleus assay) and did not have any notable reproductive or developmental effects in rats given up to 1480 mg/kg bw/day prior to and during mating, gestation and lactation (Lifshitz et al., 2015).

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<sup>3</sup> The TGA's ELF System sets out the ELF validation rules based on the legislative requirements for the different low risk ingredients as set out in the Determination to ensure that listed products are compliant with the current legislation.

A clinical study in elderly patients with memory impairment given soy PS for 12 weeks found no significant differences in adverse events or other safety parameters compared to placebo at doses of 300 and 600 mg/day (Jorissen et al., 2002). A longer study also found no significant difference in adverse events, vital signs, haematological, or biochemical safety parameters in 78 elderly patients given soy PS at up to 300 mg/day for 6 months, compared to placebo (Kato-Kataoka et al., 2010).

Overall, the available evidence supports the safety of soy PS for ongoing use at up to 300 mg per day. The TGA proposes to amend the current restrictions for soy 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 provided by CMEC for the soy PS ingredients. The TGA is also proposing to introduce 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.

### **Consultation**

The TGA has not identified a safety concern with raising the amount of soy PS to be at least 15% and at a maximum daily dose of 300 mg.

**As such, the TGA is seeking consultation on an amendment to the requirements of the ingredients below which are included in the Permissible Ingredients Determination to align to the amount of enriched soy PS which was originally recommended in 2000 and the evaluation conducted by Health Canada.**

Following consideration of comments received for this consultation, and subject to any revisions of the proposals and consideration by the Delegate of the Minister, sponsors of existing listed and assessed listed medicines containing the affected ingredients below will have until the end of the transition period to amend their products in line with any new specific requirements.

### **Affected Ingredients**

1. SOY PHOSPHATIDYLSERINE-ENRICHED SOY LECITHIN LIQUID
2. SOY PHOSPHATIDYLSERINE-ENRICHED SOY LECITHIN POWDER

As of 9 June 2023, there were 36 listed medicines included in the ARTG containing at least one of these ingredients.



## Proposed Specific Requirements

Ingredient name	Current specific requirements	Proposed specific requirements
SOY PHOSPHATIDYLSERINE-ENRICHED SOY LECITHIN LIQUID	<p>Soy phosphatidylserine is a mandatory component of soy phosphatidylserine-enriched soy lecithin liquid.</p> <p>The concentration of soy phosphatidylserine in the medicine must be no more than 15%.</p>	<p>Soy phosphatidylserine is a mandatory component of soy phosphatidylserine-enriched soy lecithin liquid.</p> <p>The concentration of soy phosphatidylserine in the medicine must be <del>no more than 15%</del> <b>at least 15%</b>.</p> <p><b>The maximum daily dose of the medicine must not provide more than 300 mg of soy phosphatidylserine.</b></p>
SOY PHOSPHATIDYLSERINE-ENRICHED SOY LECITHIN POWDER	<p>Soy phosphatidylserine is a mandatory component of soy phosphatidylserine-enriched soy lecithin powder.</p> <p>The concentration of soy phosphatidylserine in the medicine must be no more than 15%.</p>	<p>Soy phosphatidylserine is a mandatory component of soy phosphatidylserine-enriched soy lecithin powder.</p> <p>The concentration of soy phosphatidylserine in the medicine must be <del>no more than 15%</del> <b>at least 15%</b>.</p> <p><b>The maximum daily dose of the medicine must not provide more than 300 mg of soy phosphatidylserine.</b></p>

## 5. Clarification of the requirements for *Terminalia ferdinandiana*

### Background

*Terminalia ferdinandiana* (*T. ferdinandiana*, also known as Kakadu plum) is a native Australian plant, with a very limited natural distribution, localised in the northern regions of the Northern Territory, Queensland, and Western Australia (Dunlop et al., 1995). The fresh fruit, seeds, and a drink prepared from the Kakadu plum fruit are traditional foods of some Aboriginal peoples in Northwestern Australia (Specht and Mountford, 1958, Das et al., 2020, Konczak et al., 2014). It is also used in gourmet jams and sauces. *T. ferdinandiana* has higher amounts of vitamin C content compared to other fruit (Brand et al., 1982).

*T. ferdinandiana* is currently included in the Determination for use as both active and excipient ingredient in listed medicines, when the plant part is fruit flesh, fruit flesh dry or the preparation is an aqueous extract of the fruit flesh. When used as an excipient, it is only for use in topical medicines for dermal application and the concentration of *T. ferdinandiana* must not exceed 0.3%. However, over time there have been discrepancies regarding the plant preparations permitted for use in listed medicines.

*T. ferdinandiana* was originally approved for use in listed medicines in Australia in 2003, following a quality and safety evaluation by the TGA. The ingredient, Kakadu plum concentrate containing 25% vitamin C as the active ingredient, was considered by the CMEC at its [42<sup>nd</sup> meeting](#). The committee indicated that *T. ferdinandiana* fruit has been analysed for possible toxic compounds. This supported the TGA evaluation which found that traditional evidence has shown that the flesh or kernels of *T. ferdinandiana* fruit are not toxic to humans when consumed orally, although there are few adverse reactions associated with the consumption of high doses of vitamin C. Also, there was no evidence at the time of evaluation that there is any toxicity associated with the use of *T. ferdinandiana* in food products.

The original [Listing Notice](#) published in December 2003, as a recommendation following the TGA evaluation, permitted preparations of *T. ferdinandiana* (Kakadu plum) fruit flesh dry, or aqueous extracts of the fruit flesh as an active ingredient in listed goods. As per item 49A of Division 2 of Part 4 of Schedule 4 of the [Therapeutic Goods Regulations 1990 \(No. 394 as amended on 30 April 2005\)](#), the plant material from which *T. ferdinandiana* may be derived for listable goods was preparations that contain only aqueous extracts of the fruit flesh or fruit flesh dry, in line with the evaluation of the ingredient. However, the wording of these specific requirements was slightly changed when the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 1 \(2015\)](#) came into effect.

In 2016, the TGA expanded the ingredient use to cover excipient for dermal use only (not to exceed 0.3%) after an application was received. This evaluation covered the plant part, 'fruit', and 'aqueous extract' preparation.

Although the TGA's ELF System<sup>4</sup> was designed to alert sponsors who select plant preparation types different to those approved by displaying a message upon validation that interprets the current legislation, "*Terminalia ferdinandiana* is listable only when the ingredient used in the fruit flesh dry or aqueous extractions of the fruit flesh", the TGA has recently become aware of a number of products listed on the ARTG containing *T. ferdinandiana* as an excipient with preparation types other than those approved by the TGA.

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<sup>4</sup>The TGA's ELF System sets out the ELF validation rules based on the legislative requirements for the different low risk ingredients as set out in the Determination to ensure that listed products are compliant with the current legislation.

As of 19 June 2023, out of 120 listed medicines that contain *T. ferdinandiana* on the ARTG, there is one medicine with fruit flesh oil fixed and 10 medicines with fruit flesh oil infused.

The current wording in the Determination for *T. ferdinandiana* is unclear in reflecting the original evaluation for the ingredient, specifically in relation to which preparation types are permitted for use in listed medicines.

## Consultation

The TGA has investigated the available literature and has not found sufficient information to establish the safety of *T. ferdinandiana* preparations other than when it is used as the fruit flesh (fresh or dry) and an aqueous extract of the fruit flesh (liquid or dry/powdered) as evaluated by CMEC.

**Therefore, the TGA invite stakeholders to comment on an amendment to the requirements of the ingredient below included in the Permissible Ingredients Determination to align with the CMEC's original evaluation of *T. ferdinandiana*. Sponsors who are using *T. ferdinandiana* particularly other preparation types including oil fixed and oil infused, are also invited to submit information they hold that is relevant to the safety of their ingredients. This will allow the TGA to evaluate the safety of these preparations and consider amending the Determination to allow usage of these preparations if they are low-risk.**

If insufficient information is received to establish the safety of other preparations, the TGA proposes to clarify the specific requirements wording for *T. ferdinandiana* in the Determination to align with the CMEC recommendation and original listing notice.

Following consideration of comments received for this consultation, and subject to evaluation of any safety information submitted, any revisions of the proposals and consideration by the Delegate of the Minister, sponsors of existing listed and assessed listed medicines containing the affected ingredient below will have until the end of the transition period to amend their products in line with any new specific requirements.

## Affected ingredients

### 1. TERMINALIA FERDINANDIANA

As of 19 June 2023, there were 120 listed medicines included in the ARTG that contained *T. ferdinandiana*. 12 of these medicines contain *T. ferdinandiana* as an excipient.

## Proposed specific requirements

Ingredient name	Existing specific requirements	Proposed specific requirements
<p>TERMINALIA FERDINANDIANA</p>	<p>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.</p> <p>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.</p> <p>When used as an excipient, the concentration in the medicine must be no more than 0.3%.</p>	<p>Only for use when the plant part is fruit flesh, <b>and the plant preparation is fresh, fruit flesh</b> dry, or <del>the preparation is as an aqueous extract of the fruit flesh.</del></p> <p>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.</p> <p>When used as an excipient, the concentration in the medicine must not be more than 0.3%.</p>

## Making a submission

The TGA is requesting comments that will help ensure that the proposed requirements are appropriate and support the quality and safety of listed and assessed listed medicines. To provide feedback on this consultation, please provide your submission using the file upload function on the [Consultation Hub web page](#). You do not have to address all proposals. However, when responding, please clearly identify the proposal you are responding to.

Submissions may include any further data or information that may assist the Delegate to make an informed decision. Submissions may also include, for example, suggested improvements or an assessment of how the proposed change will affect you.

All submissions will be considered after the consultation period ends and may be published on the Consultation Hub web page with your consent.

## Privacy and your personal information

The TGA collects your personal information in this submission in order to:

- Contact you if the TGA wants to seek clarification of issues raised in your submission or to check whether you consent to certain information that you have provided being made publicly available; and
- Help provide context about your submission (e.g. to determine whether you are an individual or a director of a company or representing an interest group).

The TGA may disclose your name, work title, company, and submission on the Internet (i.e. make this information publicly available) with your consent. You may specify whether there is anything in your submission which you would prefer to not be published online (e.g. names, email addresses, proprietary information) by:

- Providing an additional, redacted copy of your submission; or
- Providing details of content not to be published e.g. “Do not publish pages 3-5”, “Please redact contact details”; or
- Identifying any text within your submission to remain confidential by having it clearly marked 'IN CONFIDENCE' and highlighted in grey.

**Please do not** include personal information about other individuals in the body of your submission. Personal information in this context means information or an opinion about an individual whose identity is apparent, or can reasonably be ascertained, from the information or opinion. The TGA will not publish personal information about you/others without your/their consent unless authorised or required by law.

## Timetable

This consultation opened on **Thursday 3 August 2023**.

Interested parties should respond by close of business **Thursday 14 September 2023**. Please note that late submissions after this date may not be considered.

Following consideration of public submissions, outcomes of these proposals will be published to the [Consultation Hub web page](#) by **Friday 1 December 2023**.

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

The transition period of 1 year 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: [listed.medicines@health.gov.au](mailto:listed.medicines@health.gov.au).

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