Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Proposed changes to requirements for listed medicine ingredients: Annual low-negligible risk changes 2024-25

Consultation paper

Version 1.0, August 2024

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Contents

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 2025 (see schedule for low-negligible risk changes for 2024-2025). 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.

The final decision document will include transition provisions for sponsors concerning Australian Approved Names (AANs) as it is sponsors' responsibility to ensure their medicines comply with the Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines.

Proposed changes to requirements for listed medicine ingredients

1. Herbal ingredients with pregnancy contraindications and other toxic effects

Introduction

There are over 80 ingredients approved for use in listed medicines that currently require a label warning statement about pregnancy. However, as part of an ongoing review, we have identified evidence related to potential concerns related to use in pregnancy for several ingredients, which do not currently require a pregnancy warning on the label.

Safety concerns for use during pregnancy include:

- traditional use to induce pregnancy termination (abortifacient),
- traditional use to induce menstruation (emmenagogue) or to stimulate contractions of the uterus,
- established contraindication during pregnancy;
- by an overseas regulatory authority,
- in traditional reference texts, and/or
- in referenced herbal databases,
- recognised oxytocic, embryotoxic or teratogenic effects and/or demonstrated reproductive toxicity in non-clinical studies,
- the presence of constituents known to have any of the above effects, and/or
- reported cases of adverse pregnancy outcomes in humans.

These safety concerns have the potential for catastrophic outcomes in pregnancy, such as miscarriage, foetal death, teratogenicity, neonatal death, adverse developmental effects, or other harm. If not appropriately mitigated, these risks are not consistent with the low-risk listed medicines regulatory framework. Listed medicines are only permitted to contain low-risk ingredients unless any higher risks are appropriately mitigated.

A pregnancy contraindication on the medicine label to advise consumers not to use during pregnancy or if planning to become pregnant would reduce the risks described above.

We consider a precautionary approach may be warranted for ingredients associated with these concerns in this vulnerable population group, including where some uncertainty or evidence gaps remain. This ensures that any avoidable adverse pregnancy outcomes related to ingredients of concern are prevented and that these ingredients remain sufficiently low-risk for use in listed medicines.

We are aware of a general consumer perception that herbal medicines are thought to be safer than conventional medicines. This perception can extend to use during pregnancy. Evidence indicates Australian women use complementary medicines to treat common ailments during pregnancy[1, 2]. Listed/complementary medicines may be selected by consumers during pregnancy as an alternative to other medicines, due to an assumption that herbal/complementary medicines are safe or low-risk[3, 4].

While there are public health recommendations for pregnant women to consult a healthcare professional prior to using any medicines, including complementary medicines[5] (many of which are listed medicines), their use may not always be discussed or disclosed[4]. Evidence suggests that use of herbal medicines by women during pregnancy in Australia is self-prescribed[4]. In addition, it is noted

that there are a number of indications for listed/complementary medicines for common health issues that also frequently occur during pregnancy, such as muscle and joint aches and pains, nausea, constipation, indigestion, headaches, anxiety, fatigue and insomnia. Studies have shown that women in Australia use complementary medicines during pregnancy for many of these health issues[1, 2, 4]. Therefore, self-selection and use of listed/complementary medicines by pregnant women without healthcare professional advice can be expected and must be considered when determining appropriate risk mitigation.

Previous responses to consultations regarding risks for listed medicine ingredients have often placed emphasis on the number and quality of adverse event reports. Spontaneous adverse event reporting systems such as the TGA's Database of Adverse Event Notifications (DAEN) – medicines, cannot be solely relied on to detect safety signals for herbal ingredients, particularly for pregnancy-related concerns. Consumers' awareness of risks posed by particular herbal ingredients during pregnancy is not assured and, with the general perception that herbal ingredients are thought to be safe, may result in under-reporting of pregnancy-related adverse events. As miscarriage is estimated to occur in approximately 1 in 4 confirmed pregnancies in Australia[6], it is possible that cases that relate to the use of herbal medicines may go unreported against a high background rate of 'expected' miscarriage. The role of herbal ingredients in cases of poor neonatal outcomes or neonatal abnormalities may also be difficult to detect. The delay between taking the ingredient and the outcome may contribute to this difficulty. Therefore, a low number or absence of adverse event reports does not establish safety or that pregnancy-related adverse events have not occurred.

As a result of the first stage of our ongoing review into the safety of permitted herbal ingredients during pregnancy, we are proposing to introduce label warnings that contraindicate use in pregnancy for the following ingredients available for use in listed medicines:

- *Ruta graveolens* (common Rue), *Ruta graveolens* Oil,
- Parsley Herb Dry, Parsley Herb Oil, Parsley Herb Powder, Parsley Seed Oil, and *Petroselinum crispum* (parsley).

During our review, additional safety concerns were identified for *Ruta graveolens* and *Ruta graveolens* Oil to warrant further restrictions on how these ingredients can be used in low-risk listed medicines.

As our review is ongoing, restrictions for additional ingredients with concerns for use during pregnancy may be proposed in future consultations.

As a broader risk mitigation response, the TGA intends to increase consumer education about the importance of consulting a healthcare professional prior to taking complementary medicines during pregnancy.

1.1 *Ruta graveolens* (Common Rue)

Background

The following key safety concerns were identified for *Ruta graveolens* during the TGA review:

- traditional use to induce pregnancy termination (abortifacient) and to induce menstruation;
- potential for maternal death when used as an abortifacient;
- reference texts and databases contraindicate use during pregnancy;
- plausible toxicity based on the constituents and animal studies; and
- reported photocontact dermatitis following topical use.

In light of the significant toxicity associated with *Ruta graveolens,* the TGA has reviewed this ingredient and considered:

a. whether it should require a label warning contraindicating use during pregnancy and lactation; and

b. whether it should remain on the Permissible Ingredients Determination for use other than as a homeopathic ingredient.

Ruta graveolens (rue), is a member of the Rutaceae family, native to southern Europe.

Ruta graveolens has been used both topically and orally in medicines for a wide range of indications, and along with its essential oil has been used as a flavouring agent in foods and beverages and as a fragrance in soaps and cosmetics[16]. *Ruta graveolens* is traditionally used in both herbal medicine preparations as well as in homoeopathic preparations. It may be present as a single active ingredient or in combination with other ingredients.

Risk in pregnancy

Review of traditional use identifies that *Ruta graveolens* was cited in the Hippocratic treatises as part of a recipe that includes a mixture of herbs as an 'abortive'[7]. It was also used to help expel the placenta after birth. Various texts and articles note *Ruta graveolens*'s actions as an emmenagogue and abortifacient[8,9,10,11].

The dose at which *Ruta graveolens* does not present a risk to pregnancy is not clear from traditional literature and there appears to be a wide variation in the information available. Most texts concur that higher doses of the plant are likely to have the abortifacient properties, although what constitutes a 'higher dose' has not been well-defined.

Phototoxicity from topical exposure

Ruta species have been reported to cause photocontact dermatitis. They contain photosensitising compounds which can result (after cutaneous use) in a cutaneous phototoxic inflammation on exposure to sunlight. Furanocoumarins, which are compounds present in *Ruta* species, are thought to be responsible for this reaction in human skin. Significant toxicity has been reported following topical use of *Ruta graveolens*, with symptoms including burns, pain, bradycardia, acute renal failure with hyperkalaemia, coagulopathy, and possibly cardiotoxicity, nephrotoxicity and hepatotoxicity[12].

Adverse event reports

As of 27 June 2024, the TGA has not received any adverse event reports related to pregnancy, embryotoxicity or poor neonatal outcomes involving *Ruta graveolens* or rue oil.

However, the TGA has received five adverse event reports associated with topical use of *Ruta graveolens*, with reported reactions including rash, pruritis, application site pain and application site reactions. All reports are confounded by a multi-ingredient formulation which contained other ingredients that can cause skin reactions. Therefore, it is not known if the reactions were caused by or exacerbated by *Ruta graveolens*.

A review of the WHO VigiBase[i] data up to 25 June 2024 located 11 cases involving single ingredient medicines that contained *Ruta graveolens.* Five of these reported no other suspected medicines. One of these five cases reported hypotonia with a fatal outcome in an infant after topical application to the infant's skin. Other reports with *Ruta graveolens* as the sole suspected medicine and ingredient included a case of phototoxicity after topical use, and cases of tachycardia and hypotonia after oral use.

[i] VigiBase is the WHO global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre. Information in VigiBase 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 WHO.

The only pregnancy-related case in WHO VigiBase included a report of labour stimulation in a 17-year-old female involving two suspected medicines: *Ruta graveolens* (route of administration not reported) and oral Nifedipine. The case was considered serious and caused prolonged hospitalisation.

There was insufficient information in the WHO VigiBase for further assessment.

Literature review

There is agreement between the traditional herbal texts reviewed that *Ruta graveolens* is contraindicated during pregnancy[13, 14, 15]. The available literature identifies a number of compounds that may contribute to the toxicity of *Ruta graveolens*, including its specific emmenagogic, abortifacient and teratogenic properties, such as rutin[9], furoquinoline alkaloids[16] and quinolone alkaloids[17].

Oral use

There is limited information regarding dosing for *Ruta graveolens*. Dosing instructions in traditional herbal texts are inconsistent. The Natural Medicines Database monograph for rue is unable to provide dosing and administration instructions noting that 'Research is limited: typical dosing unavailable.' It also notes that there is insufficient reliable information available about the standardisation of *Ruta graveolens*. The database states that fresh *Ruta graveolens* and rue oil are 'likely unsafe' when used orally, or when large doses of dried herb are used orally. Overdose can cause severe abdominal pain, vomiting, liver damage, kidney damage, vertigo, respiratory distress, delirium and possibly death[16].

Specifically, regarding pregnancy, the monograph states that it is 'likely unsafe' when used orally, and that '*Ruta graveolens* has uterine stimulant and abortifacient effects; avoid using. Deaths have been reported in women who used *Ruta graveolens* as an abortifacient.'[16].

Animal studies of *Ruta graveolens* have found significant reproductive toxicity, including anti-implantation activity[18], and altered blastocyst formation and development[19]. Extracts of *Ruta graveolens* have been found to be mutagenic in experimental mutagenicity screens although the clinical importance of these findings has not been established[20, 21].

Topical use

The Natural Medicines Database considers *Ruta graveolens* as 'likely unsafe' when fresh *Ruta graveolens* is applied topically, as it can cause contact dermatitis and severe photodermatitis after exposure to sunlight or UVA light. The database also reports dermatologic adverse effects as a common occurrence, and notes multiple case reports of patients who developed pruritus, erythema, and severe blistering on the back of the hands and wrists, equivalent to a partial thickness burn, after contact with the fresh plant leaves and exposure to sunlight[16].

There are a number of reported cases of phototoxic reactions caused by the *Ruta* species[12]. The reports described the development of hyperpigmentation after sun exposure in a girl treated with rue ointment[22] and burn injury[23] with skin loss[24]. These symptoms were accompanied by increasing pain and a reduced range of movement[24].

International regulation

In the United States rue (*Ruta montana, Ruta graveolens, Ruta bracteosa*, and *Ruta calepensis*) has been assigned a Generally Recognised as Safe (GRAS) status for use in foods at low concentrations only, not exceeding 2 parts per million (ppm). It is noted that the GRAS status for *Ruta graveolens* was assigned in 1978 and was based on available evidence at the time.

Other safety assessments by international agencies could not be located.

Advisory Committee on Complementary Medicines

The safety of *Ruta graveolens* was considered by the Advisory Committee on Complementary Medicines (ACCM) at their 31st meeting in May 2023. They concluded that based on the available evidence, as a minimum a label warning should be applied to medicines containing these ingredients contraindicating use during pregnancy or if planning to become pregnant, regardless of dose or route of administration.

However, the Committee also recommended that, given the significant risk during pregnancy and the reports of severe adverse reactions following topical use, consideration should be given to whether it is appropriate for *Ruta graveolens* to remain on the Permissible Ingredients Determination.

Consultation

There are currently nine products listed on the ARTG containing *Ruta graveolens*. Based on the available information, it appears that the use of this ingredient is as a homoeopathic in all nine medicines. Seven of which are for topical application only and the remaining two products being indicated for oral routes of administration. There are currently no listed products containing rue oil.

The TGA is proposing to limit the use to homoeopathic, as this reflects the apparent use of these ingredients in listed medicines. As the available evidence regarding phototoxicity largely relates to the use of fresh plant matter, this is likely to sufficiently mitigate this risk for topical medicines.

Given the limited information available to establish appropriate use during pregnancy, the TGA is unable to determine a dose where the risk in this vulnerable population is appropriate. Therefore, it is proposed that all medicines containing *Ruta graveolens* or rue oil (including those using homoeopathic preparations) to carry the following warning statement on the product label:

- 'Do not use if pregnant or likely to become pregnant, or during lactation.'

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

- RUTA GRAVEOLENS
- RUE OIL

Proposed specific requirements

Ingredient name	Existing availability	Proposed availability	Existing specific requirements	Proposed specific requirements
RUTA GRAVEOLENS	A, E, H	~~A, E,~~ H	None	The following warning statement is required on the medicine label: - 'Do not use if pregnant or likely to become pregnant, or during lactation.'
RUE OIL	A, H	~~A,~~ H	None	The following warning statement is required on the medicine label: - 'Do not use if pregnant or likely to become pregnant, or during lactation.'

1.2 *Petroselinum crispum* (parsley)

Background

The TGA safety review identified the following key concerns for *Petroselinum crispum*:

- traditional use to induce pregnancy termination and to induce menstruation;
- there is a plausible mechanism of toxicity based on evidence related to constituents in *P. crispum;* and
- reference texts and databases contraindicate use during pregnancy.

Petroselinum crispum (parsley) is widely used in food and medicinal preparations. Use in food is not considered to be a safety concern. In Australia, foods containing parsley do not require a pregnancy warning. When used in preparations for medicinal purposes, there may be increased exposure to certain constituents of concern. These constituents could be more concentrated in medicinal preparations, leading to potential safety considerations.

P. crispum is consistently documented to induce abortion/miscarriage in traditional literature when used medicinally. Evidence describes the traditional use of *P. crispum* to induce abortion using a decoction of the aerial (i.e. above ground) parts of the plant, which includes leaf, flower and seed/fruit, for oral administration[25]. Topical application of the leaf to induce abortion has also been described[26]. Several authors report the naturally-occurring essential oils apiol and myristicin as the constituents responsible for the abortifacient effects of *P. crispum*[27, 28, 29, 30, 31]. These two constituents are reportedly found in all plant parts, albeit in highest concentration in seed/fruit oil (see further detail below).

Adverse event reports

As of 25 June 2024, there have been no adverse events reported to the TGA or the WHO VigiBase[ii] involving *P. crispum* or parsley and related to pregnancy, embryotoxicity or poor neonatal outcomes. However, as noted above, this may be due to lack of awareness of the risks of herbal products, and the background rate of miscarriage.

Literature review

A review of herbal references and the scientific literature showed a clear consensus that parsley has emmenagogic and uterine stimulant properties and has been traditionally used to induce abortion. These effects may be due to the constituents apiol and/or myristicin.

One herbal monograph[31] states that the tonic effect on the uterine muscle has been attributed to the apiol content, but has also been observed with apiol-free aqueous extracts[32]. The monograph states that myristicin has been reported to cross the placenta and can lead to foetal tachycardia and should not be taken during pregnancy and lactation at doses that exceed amounts used in foods. The monograph refers to low concentrations of myristicin in parsley leaf (less than 0.05%) but mentions that parsley seed is potentially hazardous in view of its higher volatile oil content (2-7%) which contains apiol and myristicin[31].

Another herbal reference includes a monograph for *P. crispum* which includes several references for traditional use of parsley as an emmenagogue and abortifacient. This monograph attributes abortifacient activity to apiole, found primarily in the seed but also in lesser concentrations in the leaf

[ii] VigiBase is the WHO global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre. Information in VigiBase 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 WHO.

and root. The monograph states that parsley essential oil and parsley seed should not be used during pregnancy, although moderate use of parsley leaf is thought to be safe[30].

A third herbal text refers to the fruit (i.e. seed) being known as an emmenagogue and abortifacient, and that use as an emmenagogue is based on volatile oil content, varying from less than 0.1% in the root, 0.3% in the leaf, to 2-7% in the fruit. The monograph describes apiol and myristicin as being similar both chemically and in their physiological action, with both being uterine stimulants accounting for the use of parsley volatile oil as an emmenagogue and misuse as an abortifacient. The monograph states that parsley volatile oil should under no circumstances be administered to pregnant women[29].

The composition of herbs and their oils varies significantly between studies, as well as different plant parts and varieties. A review reported the concentrations in parsley seed oil ranged from 11-67.5% (apiol) and 0.7-37.0% (myristicin), and in parsley leaf oil from 0.2-5.2% (apiol) and 1.9-8.8% (myristicin)[33].

The toxic effects of myristicin are dose-dependent. It has been reported that neuropsychological symptoms occur after ingestion of approximately 400 mg of myristicin from nutmeg (6-7 mg/kg bw), with anti-cholinergic effects occurring at higher doses[34].

International regulation

P. crispum was historically assigned a GRAS status by the US FDA for use in foods, as one of several spices and other natural seasonings and flavourings. A published report of this evaluation suggests that assessment of reproductive toxicity (risk during pregnancy) was not required, as the estimated intake from food was low[35].

The requirement for a pregnancy warning by other regulatory authorities for medicines that contain *P. crispum* could not be located, noting *P. crispum* may be regulated as a food rather than as a medicine in other jurisdictions.

Advisory Committee on Complementary Medicines

The safety of *P. crispum* was considered by ACCM at their 34th meeting in March 2024. They agreed that there was sufficient evidence of risk to contraindicate the use of parsley in listed medicines during pregnancy, with the greatest risk being from parsley seed oil. They also advised that indications relating to pregnancy should not be permitted for these ingredients. The Committee recommended that the label warning should apply to both oral and topical use, given that essential oils can be absorbed through the skin.

Consultation

In the therapeutic goods framework, there is no established dose of an ingredient where pregnancy risks are not required to be assessed. Based on the available evidence of the abortifacient properties of these herbs and in the absence of a safe dose for use in medicines, the TGA is proposing to require that medicines containing *P. crispum* or related ingredients include the following warning statement on the product label:

- (PREGNT2) ‘Do not use if pregnant or likely to become pregnant.’

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

- PARSLEY HERB DRY
- PARSELY HERB OIL

- PARSLEY HERB POWDER
- PARSELY SEED OIL
- PETROSELINUM CRISPUM

As of 5 July 2024, the ARTG includes the following entries related to parsley:

- One medicine containing parsley herb oil as an active ingredient.
- Two medicines containing parsley seed oil as an active ingredient.
- 52 medicines containing *Petroselinum crispum*, with two as excipient ingredients and 50 as active ingredients.
- No medicines containing either parsley herb dry or parsley herb powder.

Proposed specific requirements

Ingredient name	Existing specific requirements	Proposed specific requirements
PARSLEY HERB DRY	None	The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant.'
PARSELY HERB OIL	None	The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant.'
PARSLEY HERB POWDER	None	The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant.'
PARSELY SEED OIL	None	The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant.'
PETROSELINUM CRISPUM	None	The following warning statement is required on the medicine label: - (PREGNT2) 'Do not use if pregnant or likely to become pregnant.'

References – herbal ingredients with pregnancy contraindications

[1] Frawley J. et al (2013). Prevalence and determinants of complementary and alternative medicine use during pregnancy: results from a nationally representative sample of Australian pregnant women - PubMed (nih.gov) Aust N Z J *Obstet Gynaecol.* Aug;53(4):347-52. doi: 10.1111/ajo.12056. Epub 2013 Mar 8. PMID: 23472704.

[2] Adams J, Sibbritt D, Lui CW. The use of complementary and alternative medicine during pregnancy: a longitudinal study of Australian women - PubMed (nih.gov). *Birth*. 2011 Sep;38(3):200-6. doi: 10.1111/j.1523-536X.2011.00480.x. Epub 2011 May 20. PMID: 21884228.

[3] Barnes LAJ, Barclay L, McCaffery K, Aslani P. Women's health literacy and the complex decision-making process to use complementary medicine products in pregnancy and lactation. *Health Expect*. 2019; 22: 1013–1027. https://doi.org/10.1111/hex.12910

[4] Frawley J, Adams j, Steel A, Broom A, Gallois C, Sibbritt D. Women's Use and Self-Prescription of Herbal Medicine during Pregnancy: An Examination of 1,835 Pregnant Women, *Women's Health Issues*. 2015; 24 (4): 396-402. https://doi.org/10.1016/j.whi.2015.03.001.

[5] Medicines during pregnancy. Healthdirect https://www.healthdirect.gov.au/medicines-during-pregnancy

[6] Miscarriage Australia Updated 20 October 2022 https://miscarriageaustralia.com.au/understanding-miscarriage/what-is-miscarriage/

[7] Pollio, A., De Natale, A., Appetiti, E., Aliotta, G. & Touwaide, A. 2008. Continuity and change in the Mediterranean medical tradition: Ruta spp.(rutaceae) in Hippocratic medicine and present practices. *Journal of ethnopharmacology,* 116**,** 469-482.

[8] Ciganda, C. & Laborde, A. 2003. Herbal infusions used for induced abortion. *Journal of Toxicology: Clinical Toxicology,* 41**,** 235-239.

[9] Asgarpanah, J. & Khoshkam, R. 2012. Phytochemistry and pharmacological properties of Ruta graveolens L. *J Med Plants Res,* 6**,** 3942-3949.

[10] Brinker, F. J. 2010. *Herbal Contraindications & Drug Interactions: Plus Herbal Adjuncts with Medicines*, Eclectic Medical Publications. P: 278.

[11] Verissimo, L. F., Bacchi, A. D., Zaminelli, T., Paula, G. H. O. D. & Moreira, E. G. 2011. Herbs of interest to the Brazilian Federal Government: female reproductive and developmental toxicity studies. *Revista Brasileira de Farmacognosia,* 21**,** 1163-1171.

[12] Coimbra, A. T., Ferreira, S. & Duarte, A. P. 2020. Genus Ruta: A natural source of high value products with biological and pharmacological properties. *Journal of ethnopharmacology,* 260**,** 113076.

[13] Gruenwald, J., Brendler, T. & Jaenicke, C. 2000. *Physicians Desk Reference for Herbal Medicines*. Gunn, T. & Wright, I. 1996. The use of black and blue cohosh in labour. *The New Zealand Medical Journal,* 109**,** 410-411.

[14] Williamson, E. W. & Wren, R. C. 2003. *Potter's herbal cyclopaedia: the authoritative reference work on plants with a known medical use*, Daniel Company.

[15] Hoffmann, D. 1990. The new holistic herbal: a herbal celebrating the wholeness of life. London: Harper Collins Publishers.

[16]Natural Medicines Database (2024). Natural Medicines Professional Monograph - Rue. Available at: https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=885. [Online. Accessed: 04 July 2024].

[17] Costa, K. C. D. S., Bezerra, S. B., Norte, C. M., Nunes, L. M. N. & Olinda, T. M. D. 2012. Medicinal plants with teratogenic potential: current considerations. *Brazilian Journal of Pharmaceutical Sciences,* 48**,** 427-433.

[18] Prakash, A. O., Saxena, V., Shukla, S., Tewari, R., Mathur, S., Gupta, A., Sharma, S. & Mathur, R. 1985. Anti-implantation activity of some indigenous plants in rats. *Acta Europaea Fertilitatis,* 16**,** 441-448.

[19] Gutiérrez-Pajares, J. L., Zúñiga, L. & Pino, J. 2003. Ruta graveolens aqueous extract retards mouse preimplantation embryo development. *Reproductive Toxicology,* 17**,** 667-672.

[20] Paulini, H., Popp, R., Schimmer, O., Ratka, O. & Röder, E. 1991. Isogravacridonchlorine: a potent and direct acting frameshift mutagen from the roots of Ruta graveolens. *Planta medica,* 57**,** 59-61.

[21] Paulini, H. & Schimmer, O. 1989. Mutagenicity testing of rutacridone epoxide and rutacridone, alkaloids in Ruta graveolens L., using the Salmonella/microsome assay. *Mutagenesis,* 4**,** 45-50.

[22] Morais, P., Mota, A., Cunha, A. P., Peralta, L. & Azevedo, F. 2008. Phytophotodermatitis due to homemade ointment for Pediculosis capitis. *Contact Dermatitis (01051873),* 59.

[23] Furniss, D. & Adams, T. 2007. Herb of grace: an unusual cause of phytophotodermatitis mimicking burn injury. *Journal of burn care & research,* 28**,** 767-769.

[24] Radotra, I., Gardiner, S. & Barnes, D. 2018. A phytophototoxic injury at a burns unit: the ungraceful after-effects of the “common rue” plant. *Journal of Burn Care & Research,* 39**,** 1064-1066.

[25] Montesano, V., Negro, D., Sarli, G., De Lisi, A., Laghetti, G. & Hammer, K. 2012. Notes about the uses of plants by one of the last healers in the Basilicata Region (South Italy). *Journal of ethnobiology and ethnomedicine,* 8, 1-10.

[26] Benítez, G., González-Tejero, M. & Molero-Mesa, J. 2010. Pharmaceutical ethnobotany in the western part of Granada province (southern Spain): Ethnopharmacological synthesis. *Journal of Ethnopharmacology,* 129**,** 87-105.

[27] Mills, S. Y. & Bone, K. 2004. *The essential guide to herbal safety*, Elsevier Health Sciences.

[28] Van Wyk, B.-E. & Wink, M. 2018. *Medicinal plants of the world*, 2004. Briza. South Africa. p. 235.

[29] Foster, S. 1999. *Tyler's honest herbal: a sensible guide to the use of herbs and related remedies*, Routledge.

[30] Gardner, Z. & Mcguffin, M. 2013. *American Herbal Products Association’s botanical safety handbook*, CRC press.

[31] Newall, C. A., Anderson, L. A. & Phillipson, J. D. 1996. *Herbal medicines. A guide for health-care professionals*.

[32] Mcguffin, M. 1997. *Botanical safety handbook*, CRC press.

[33] Dosoky, N. S. & Setzer, W. N. 2021. Maternal reproductive toxicity of some essential oils and their constituents. *International journal of molecular sciences,* 22**,** 2380.

[34] Seneme, E. F., Dos Santos, D. C., Silva, E. M. R., Franco, Y. E. M. & Longato, G. B. 2021. Pharmacological and therapeutic potential of myristicin: A literature review. *Molecules,* 26**,** 5914.

[35] Davidsen, J. M., Cohen, S. M., Eisenbrand, G., Fukushima, S., Gooderham, N. J., Guengerich, F. P., Hecht, S. S., Rietjens, I. M., Rosol, T. J. & Harman, C. L. 2023. FEMA GRAS assessment of derivatives of basil, nutmeg, parsley, tarragon and related allylalkoxybenzene-containing natural flavor complexes. *Food and Chemical Toxicology,* 175**.**

2. *Garcinia* species, hydroxycitric acid, hydroxycitrate complex and salts, and risk of liver injury

Background

Liver injury associated with the use of supplements containing medicinal herbal ingredients is a growing concern globally. An increase in liver injury attributed to dietary supplements has been reported in the literature along with an increase in severe outcomes[36, 37]. Concerns have been identified in the literature that a lack of information for consumers and a reactive regulatory approach without rigorous pre-market scrutiny do not provide adequate consumer protection and safety[36, 38].

Liver injury within Australia's low-risk regulatory framework

In Australia, the TGA's role as the medicine regulator is to safeguard and enhance the health of the Australian community. Most supplements containing medicinal herbal ingredients are regulated in Australia as low-risk listed medicines. We take a risk-based approach to regulation, which means higher risk medicines have more rigorous controls than lower risk medicines. Although listed medicines are not individually assessed prior to supply in Australia, they can only contain pre-approved low-risk ingredients and make low level health claims. A clearly-established risk of severe liver injury is not consistent with the low-risk listed medicines framework unless effective risk mitigation strategies are implemented. For listed medicines, the risks may be mitigated through informing consumers which can be achieved through the medicine label. The key components of risk mitigation are:

- a description of symptoms, which is necessary to enable consumers to recognise the early signs of liver injury, and
- a call to action, such as an instruction to stop use and see a doctor if symptoms occur which can prevent a severe outcome.

Both parts of the warning are critical, as early identification and discontinuation of the offending agent reduces the risk of severe outcomes in cases of drug induced liver injury (DILI).

The TGA has previously addressed liver injury risks for several ingredients permitted for use in listed medicines. Stakeholders have raised concerns about the increasing number of required warnings. However, the number of affected ingredients remains low (8 herbal-based ingredient groups affecting 16 related permitted ingredients in total[iii]) compared to the total number of ingredients permitted in listed medicines (over 5200 in total, with over 2300 active ingredients). The TGA is committed to ensuring emerging risks are managed appropriately to protect consumers and will continue to take actions to ensure listed medicines remain low-risk.

In general, ingredients with a clearly-established risk of severe liver injury are not considered appropriate for use in listed medicines unless the risk can be reduced through restrictions or limits. Higher risk ingredients must undergo full evaluation prior to use in medicines in Australia. Appropriate controls on use are applied to ensure the risk-benefit profile remains appropriate for the intended use. For example, it may be appropriate for medicines with life-saving benefits to be higher risk. For some medicines, risk of liver injury is addressed through restrictions, such as limits on the allowable daily dose, on duration of use or, for some listed medicine ingredients, on how a herbal ingredient is prepared. However, adequate evidence to establish these types of restrictions for effective risk mitigation is rarely available for listed medicine ingredients.

Previous responses to similar consultations have drawn comparisons to other self-selected products (such as paracetamol) and food (such as alcohol and sugar) which can also harm the liver but which

[iii] *Actaea racemosa*, Black cohosh dry, Black cohosh powder, *Camellia sinensis*, *Chelidonium majus*, *Curcuma longa*, *Curcuma aromatica*, *Curcuma zanthorrhiza*, *Curcuma zedoaria*, Curcumin, *Khaya senegalensis, Larrea tridentata*, *Piper methysticum*, *Valeriana officinalis*, Valerian Powder, Valerian root.

may not have the same label requirements. Unlike listed medicines, paracetamol is in registered medicines and is subject to tighter regulatory controls than listed medicines. The risk of liver injury from paracetamol is well-established with toxicity predictable based on dose and duration of use, and has been mitigated by other means including limits on duration of use and instructions for suspected overdose (which refers to potential liver injury). The TGA does not regulate foods and acknowledges 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.

Frequency of adverse events

The occurrence of liver injury for most ingredients permitted in listed medicines that require a label warning cannot be predicted based on dose, duration of use or individual susceptibility. This type of liver injury is termed idiosyncratic[39]. For medicines known to cause idiosyncratic liver injury, the frequency has been estimated to occur somewhere between 1 per 10,000 to 1 per 100,000 subjects who take the medicine[40]. To reliably detect a rare adverse event in a clinical trial (for example 1 case per 10,000 subjects), the number of patients needed would be 30,000[41]. Clinical trials of this size are rare, and idiosyncratic DILI is usually only discovered through post-market monitoring of adverse events.

Spontaneous adverse event reporting systems are foundational to global safety surveillance. However, a major drawback of reliance on spontaneous adverse event reporting systems for detecting safety signals is under-reporting[42]. Multiple factors contribute to under-reporting. For healthcare professionals, uncertainty around the potential causal relationship between a medicine and an adverse event can contribute to under-reporting of events that appear to be related to the use of a medicine but for which explanation for the causal association is lacking[42].

Therefore, many cases associated with lesser-known medicines, such as complementary medicines, may go unreported due to lack of awareness of an association and/or lack of readily available information of a possible causal association. Under-reporting is likely further exacerbated for Australian complementary medicines, where patients, when questioned on their medication history, may not disclose to their treating healthcare professionals[43].

Consequently, a low number of spontaneous adverse event reports cannot be considered evidence of the absence a safety signal. The TGA considers multiple sources in addition to adverse event cases reported in Australia when investigating safety signals. This includes published literature (including but not limited to literature case reports), international regulatory action, international cases reported to other authorities as well as disproportionality algorithm results applied to global adverse event data[44].

The true rate of occurrence of an adverse event cannot be determined from spontaneous adverse event reporting systems, due to both under-reporting and lack of usage data. Therefore, it is not appropriate to apply a ‘threshold’ number of cases above which a label warning or other regulatory action is needed. Instead, regulators consider the weight of evidence available in the context of the regulatory framework.

Consideration of quality issues

Responses to previous, similar consultations have suggested that the low number of liver injury reports in Australia is indicative that Australian medicines are less likely to cause liver injury. Respondents consider this could be in part due to the more rigorous regulation of herbal medicines in Australia compared with some other countries and have suggested that problems with quality may have contributed to overseas cases. Similarly, previous consultation responses have raised concerns that product analysis was not conducted in most cases to confirm the presence and quality of the active ingredient and the absence of adulterants or contaminants.

The TGA acknowledges that product analyses are ideal when considering causality for adverse events. However, the absence of analyses is not sufficient justification to negate a causal relationship. This is particularly the case where multiple cases are observed over several years, and in a number of

different countries, with no clusters of cases observed to suggest a quality issue. This pattern of reporting indicates an ingredient-related effect is more likely than a quality issue.

The TGA has been aware of literature reports of liver injury associated with multi-ingredient formulations containing *Garcinia gummi-gutta* (synonym *Garcinia cambogia*[iv]) for some time. These earlier reports involved cases which also included *Camellia sinensis* (green tea) or other known hepatotoxins, making the causal role of *Garcinia gummi-gutta* unclear. More recently, an increasing number of case reports have been published that involved products with *Garcinia gummi-gutta* as the only reported suspect ingredient. Many reports included causality assessments which support a causal association.

Garcinia gummi-gutta fruit is commonly consumed as part of a traditional Asian diet[45], while the dried fruit rind has a history of culinary use and in Ayurvedic medicine[46]. The fruit rind or epicarp is rich in hydroxycitric acid (HCA) at a concentration of 20-30% dry weight[45]. HCA is reported as the primary constituent responsible for purported therapeutic effects, and also as the constituent of concern in liver injury[37, 4646, 47]. *Garcinia quaesita* also naturally contains HCA and has been considered synonymous with *Garcinia gummi-gutta*[48].

There are currently no required risk mitigation measures in place that sufficiently address the risk of liver injury with *Garcinia gummi-gutta* or other HCA-containing ingredients when used in listed medicines in Australia.

Garcinia gummi-gutta was not permitted in listed medicines until 2014. Prior to this, *Garcinia quaesita* was the only permitted *Garcinia* species in listed medicines. The TGA's risk assessment for *Garcinia gummi-gutta* in 2014 identified five case reports of hepatotoxicity. However, at the time, the multi-ingredient nature of the suspected products with poor documentation of concomitant medicines and other possible confounders made it difficult to conclude that *Garcinia gummi-gutta* played a causative role.

Since 2014 the number of cases reported in the literature has increased, many of which did not report other suspected hepatotoxins, including five serious cases that resulted in liver transplant.

Literature review

Published case reports

A literature review of articles published after 2014 identified a total of 19 case reports of liver injury associated with *Garcinia gummi-gutta* where no other hepatotoxins or confounders were suspected (for further details and discussion on confounders, see Appendix A and Appendix B).

Patients were hospitalised in 79% of cases (15/19). Where the pattern of liver injury was reported it was mostly hepatocellular (five cases), while two cases reported a cholestatic pattern of liver injury. Positive de-challenge (where liver enzymes returned to normal, and not just decreased) was reported in 58% of cases (11/19) with the time taken to recover ranging from 'several' days to 180 days. One case also reported a positive re-challenge strengthening the evidence for a causal relationship. Of the 13 cases that included a causality assessment score using RUCAM[v], three were highly probable, nine were probable, and one was possible.

The time to onset of liver injury after consuming *Garcinia gummi-gutta* ranged from 1 week to 5 months. Where dosage information was reported it ranged from 160 mg – 2800 mg *Garcinia gummi-gutta* extract per day, while HCA daily doses ranged from 200 mg – 561 mg per day.

Of particular concern, five cases resulted in liver transplantation. Two of these cases reported the suspected product as containing either *Garcinia gummi-gutta* as the single active ingredient, or in a formulation containing no other known hepatotoxins[49, 50]. The other three liver transplantation cases reported no other known hepatotoxins but did not provide formulation details for the suspected

[iv] Although most literature refers to *Garcinia cambogia*, the Australian Approved herbal name (AHN) *Garcinia gummi-gutta* is used in this consultation document.

[v] Roussel Uclaf Causality Assessment Method

Garcinia gummi-gutta products[51, 52, 53]. Another case resulted in liver transplantation from a product containing *Garcinia gummi-gutta* 'alone', however there was insufficient information to assess whether this case was a duplicate of other cases, and whether other ingredients were present in the formulation[54]. Therefore, this case was not included in Appendix A and is not counted as one of the five cases resulting in liver transplant mentioned above.

There are some limitations in the published case reports, including limited information regarding the products used including composition and dose. Analysis of product quality was also limited[54, 55] or absent. However, the number of published studies with causality assessment provides a strong body of evidence supporting the safety concern.

We note that, in some of the above published case studies, there was mention of either concomitant medicines that have possible hepatotoxic effects in some circumstances[50, 56, 57, 58], or unexpected contaminants identified on analysis of the suspected medicine[55]. In all but one case[55], these factors were not identified as suspected confounders by the study authors. Our review of available information indicates these factors are unlikely suspects in the reported liver injury cases. Further discussion can be found in Appendix B.

It is important to note that several cases described that the patient did not initially disclose use of a *Garcinia gummi-gutta*-containing product, and only revealed this on further questioning[49, 58, 59, 60, 61]. In one case this was associated with continued product use and ultimately a catastrophic liver injury requiring a liver transplant[49]. The lack of patient disclosure regarding supplement use suggests that the number of cases occurring may be far greater than represented in the literature and adverse event databases. Similarly, publication bias is likely to favour those cases with more remarkable clinical features and a named cause of liver injury, with transient/mild cases unlikely to be published.

One case was Australian, and resulted in liver transplant, however as the suspect product was not described it was not possible to ascertain if the product was included on the ARTG[53]. Concomitant medicines were also not reported. This case was not reported to the TGA and is therefore not included in the Australian adverse event cases discussed below.

The TGA identified several additional liver injury case reports in the literature that involved products containing *Garcinia gummi-gutta*/HCA but that also reported co-suspected ingredients associated with liver injury or other confounding factors. It is unclear in these cases whether *Garcinia gummi-gutta* caused or contributed to the liver injury. Therefore, these cases are not considered to have contributed to the evidence base for this safety concern.

Other literature

As described above, recent case studies identify an increased number of reports supporting a causal link, whereas many earlier case reports were confounded[45, 62, 63, 64]. Similarly, there are some other recent study types which are identifying potential signals of liver injury. This contrasts with earlier human and non-clinical studies which did not report hepatotoxic effects and did suggest some evidence of hepatoprotective effects of HCA.

Human studies

Only one clinical trial was located that reported adverse liver findings[65]. This study reported HCA supplementation (1122 mg/day for 8 weeks) accompanied by calorie restricted diet (CRD) resulted in a significant increase in serum alanine transaminase (ALT), and non-significant increase in aspartate transferase (AST). The control group showed a significant decrease in serum ALT and non-significant decrease in AST, which resulted in significant inter-group differences observed in serum levels of ALT (p=0.001) and AST (p=0.001). However, mean ALT and AST levels remained within the normal range, although it appears some individuals experience ALT levels exceeding upper limit of normal. The study included 40 women with non-alcoholic fatty liver disease (NAFLD) who were randomly assigned to two groups: HCA group (n=21) who received a low-calorie diet plus 2 HCA tablets before meals (6/day), and control group (n=19) who received a low-calorie diet only. The HCA supplement contained 312.5 mg *Garcinia gummi-gutta* bark leaf extract, and consisted of 187 mg HCA, 4.7 mg

vitamin B1, and 5 mg vitamin C[vi]. The small number of participants in this study is insufficient to detect rare adverse events, nevertheless the significant increase in ALT levels after eight weeks in the treatment group, albeit within the normal range, suggests liver damage is possible in participants consuming a HCA-containing supplement.

In an earlier review article, authors commented that none of the reviewed human intervention studies found serious adverse events[45]. However, no details were provided about the number of these studies that collected and reported adverse event data. Furthermore, the combined number of subjects in the individual studies was not a sufficient study population to support the detection of rare adverse events.

Non-clinical studies

A recent *in vitro study* explored possible mechanisms responsible for *Garcina gummi-gutta* induced hepatotoxicity. It reported a moderate dose-dependent reduction in cell viability (normal human [H69] cholangiocytes), as well as a significant and dose-dependent increase in reactive oxygen species (ROS)[66].

An earlier study published in 2013 examined the long-term effects of *Garcinia gummi-gutta* on adiposity and non-alcoholic liver disease in obese mice[67]. *Garcinia gummi-gutta* was found to increase markers related to oxidative stress and inflammatory responses as well as plasma ALT and AST levels.

Another non-clinical study examined the effects of a *Garcinia gummi-gutta*/HCA extract on lipid profile, liver and testes in male rats[68]. This study found that treatment with a *Garcinia gummi-gutta*/HCA extract for three weeks caused negative histological changes in the liver. The possible role of chromium was not discussed by the authors, possibly because chromium doses in this study equated to 14 micrograms (mcg)/kg/day and 28 mcg/kg/day, which are well below the no observed adverse effect level (NOAEL) and the lowest observed adverse effect level (LOAEL) in toxicological animal studies[vii].

Although authors of a review article commented that non-clinical toxicity studies have shown Garcinia/HCA to have positive safety profiles, only one of the above studies was included in their review[45,67]. Further, the low number of non-clinical studies with adverse liver findings cannot be equated to reassurance of safety, considering liver injury can be difficult to replicate in animal models, particularly if idiosyncratic[69]. On the contrary, two animal studies and one *in vitro* study with adverse liver findings suggest that hepatoxicity from *Garcinia gummi-gutta* is plausible. However, it should be noted that while supportive of the safety concern, these studies do not form the basis of the TGA's proposal which is centred on the clinical case reports.

Mechanism and pattern of liver injury

Available evidence suggests that liver injury from *Garcinia gummi-gutta*/HCA is idiosyncratic[37, 46]. Patients suffering from *Garcinia gummi-gutta* induced liver injury usually present with hepatocellular liver injury, although cases with cholestatic damage have been reported[70, 71].

Animal and *in vitro* studies indicate that *Garcinia gummi-gutta* can induce ROS which can play a role in liver injury[66, 67], with oxidative stress a proposed mechanism of action for liver injury from *Garcinia gummi-gutta*[36]. This may be of particular relevance in obese individuals as growing evidence

[vi] Authors did not discuss the use of the plant part 'bark leaf' and the possible presence of constituents other than HCA that may be absent in the fruit rind (which is the only permitted plant part for *Garcinia gummi-gutta* in listed medicines). However, we note that HCA is common to both plant parts and was the subject of this study.

[vii] Agency for Toxic Substances and Disease Registry (ATSDR) – Toxicological profile for Chromium. The lowest observed adverse effect level (LOAEL) for haematological effects from intermediate oral exposure (22 days – 6 months) to chromium (VI) in male rats was 0.77 mg/kg/day, while the NOAEL was 0.21 mg/kg/day. LOAELs for hepatotoxicity effects were higher than those producing hematopoietic effects. In humans the oral minimum risk level for intermediate exposure (15-362 days) to hexavalent chromium compounds has been established as 0.005mg/kg /day, which equates to 250 micrograms (mcg) /day in a 50 kg adult. https://www.atsdr.cdc.gov/ToxProfiles/tp7-c2.pdf [Accessed: 29 April 2024].

suggests obese patients may have an excessive production of ROS[66], which could place them at higher risk of liver injury. Furthermore, overweight/obese individuals are at increased risk of NAFLD which can be silent with few or no symptoms[72]. Therefore, it is possible that one of the main target populations for *Garcinia gummi-gutta* and HCA containing products could be at greater risk of liver damaging effects, although this requires further research to confirm. We acknowledge that not all people seeking assistance with weight management are overweight or obese, and the target population for *Garcinia gummi-gutta* and HCA containing products is broad. As it is not clear that the risk only applies to overweight or obese individuals, risk mitigation measures should not be limited to specific population groups.

It has been postulated that certain patients could have genetic predisposition leading to hepatotoxicity, such as cytochrome P450 polymorphisms promoting toxic accumulation of metabolites[49, 56]. Others have suggested the presence of the HLA B*35:01 allele could play a role[54, 66]. This allele was found to be significantly greater in patients who experienced DILI after consuming *Garcinia gummi-gutta* compared to DILI patients who consumed other herbal dietary supplements and conventional drugs[54]. Even if these risk factors were confirmed in future, consumers cannot be expected to be aware of any predisposing genetic polymorphisms prior to the safe use of a listed medicine. Such an approach is inconsistent with the low-risk framework where medicines are available for self-selection and self-administration.

Adverse event reports

Cases reported to the TGA Australia

Only a small number of possible liver injury cases associated with HCA-containing ingredients have been reported to the TGA. While this may seem reassuring, it is possible that cases are going unreported. Notably, one published literature case resulting in liver transplant that occurred in Australia was not reported to the TGA.

The possible DILI cases reported to the TGA (up to 24 May 2024) included six cases associated with *Garcinia gummi-gutta* or calcium hydroxycitrate. Four of these were confounded by other suspected hepatotoxins while for the remaining two cases, there was insufficient information reported to identify the suspected *Garcinia gummi-gutta* products. All six possible DILI cases either involved products not on the ARTG or did not include enough information to identify the *Garcinia gummi-gutta*-containing medicine (reported by ingredient name only). One case with a fatal outcome was significantly confounded by concomitant medicines and medical history. An additional seven liver-related cases were identified that were either not DILI cases or did not include enough information to assess against DILI criteria.

In addition, one case of possible DILI associated with *Garcinia quaesita* has been reported to the TGA, however this case involved another suspected hepatotoxin (*Camellia sinensis*). Another liver-related case associated with *Garcinia quaesita* reported autoimmune hepatitis[viii], while three additional liver-related cases associated with *Garcinia quaesita* were unclear and/or did not include sufficient data to assess against DILI criteria.

As discussed in the background section above (Frequency of adverse events), we do not consider that a low number of cases reported to the TGA is evidence that liver injury from *Garcinia gummi-gutta*/HCA does not warrant risk mitigation in Australia. Similarly, there is insufficient information to conclude that this safety concern is not relevant to the Australian population and/or Australian products, as discussed in the background section above (Consideration of quality issues) and further discussed below (Quality issues as a possible cause).

[viii] According to LiverTox, drug induced autoimmune hepatitis resembles idiopathic autoimmune hepatitis, but typically resolves completely once the medication is withdrawn, although recovery may be slow and lead to a limited course of corticosteroid therapy [accessed 6 May 2024]. There was insufficient information to assess whether this case may have been drug induced autoimmune hepatitis, therefore it was not considered a possible DILI case.

International cases

A review of VigiBase[ix] data up to 5 May 2024 revealed a positive disproportionality score for *Garcinia gummi-gutta* when paired with the Standardised MedDRA[x] Query (SMQ) Drug related hepatic disorders - comprehensive search (Broad) using the information component (IC) model[xi]. This reveals a higher-than-expected number of reports compared with all reported reactions for *Garcinia gummi-gutta* and all reports of drug related hepatic disorders for all active ingredients.

As of 5 May 2024, there had been 27 hepatobiliary cases involving *Garcinia gummi-gutta* reported to WHO VigiBase (applying the SMQ Drug related hepatic disorders - comprehensive search (Broad)), with eight of these from Australia. Of the 19 international cases, three reports involved *Garcinia gummi-gutta* as the only suspected ingredient while another seven were reported as a suspected interaction with quetiapine. Another case reported a fatal outcome, however this case involved multiple suspected ingredients and reported multiple co-morbidities. Available data in VigiBase was limited for further detailed case assessment.

The European Commission's Rapid Alert System for Food and Feed (RASFF) have published two alerts reporting serious liver-related adverse events after consuming *Garcinia gummi-gutta* containing products, one that resulted in death[73], the other in liver transplantation[74].

International regulation

While this signal has not yet led to broad regulatory action by authorities in other jurisdictions, there is a growing awareness of the safety concern and the association between *Garcinia gummi-gutta* and liver injury.

LiverTox[46] has assigned a likelihood score of B (likely rare cause of clinically apparent liver injury) to *Garcinia gummi-gutta*. The LiverTox entry for *Garcinia gummi-gutta* notes that more recently there have been cases of acute liver injury when taking products labelled as containing *Garcinia gummi-gutta* alone. It also states that while the frequency is not known it is likely uncommon and in less than 1:10,000 persons, noting Livertox was last updated in February 2019. It states:

> *Patients typically present with fatigue, nausea, elevations in serum aminotransferase levels, and jaundice 1 to 4 weeks after starting the product, although the latency to onset has been longer (3 to 12 months) in some cases. The pattern of enzyme elevations is hepatocellular, and immune features are not common. Some cases have been severe, resulting in acute liver failure and either death or need for urgent liver transplantation.*

LiverTox also states that while *in vitro* studies suggest HCA may be toxic to the liver in high doses, the rare instances suggest an idiosyncratic form of injury.

The National Institute of Health (NIH) Dietary Supplement Fact Sheet for Health Professionals and Health Information for consumers identifies liver injury risks from *Garcinia gummi-gutta*[75, 76].

The Natural Medicines Therapeutic Research Centre (NatMed) professional monograph for *Garcinia* also recognises liver injury as a possible adverse effect of *Garcinia gummi-gutta* and HCA[77].

[ix] VigiBase is the WHO global database of reported potential side effects of medicinal products. Information in VigiBase 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 WHO.
[x] Medical Dictionary of Regulatory Activities (MedDRA)
[xi] 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).

Quality issues as a possible cause

One author has suggested that improper processing could increase the toxicity of HCA calcium salts[62] and questioned the quality of extract used in an animal study with adverse liver findings[67]. However, the use of a poorly processed extract in the animal study was speculative, and the author's affiliation with a company supplying HCA suggests a possible conflict of interest.

A small number of liverinjury cases included details of product analyses[54, 55] with only one reporting unexpected findings[55]. Our assessment of the reported findings concluded that the impurities that were detected were not expected to have contributed to the liver injury (see Appendix B for further details).

Therefore, our review was unable to locate sufficient evidence to support that liverinjury concerns are due to widespread quality issues. Further, the number of cases reported over several years from different regions with no clear clusters suggests that quality issues are not likely to play a significant role in liver injury concerns for *Garcinia gummi-gutta* and HCA.

Advisory Committee on Complementary Medicines

The TGA sought advice on this issue from the Advisory Committee on Complementary Medicines ('the Committee') at their 33rd meeting in November 2023. The Committee advised that while the available evidence has some limitations, it was still sufficient to support a causal link and the need for risk mitigation. The Committee advised that a label warning is appropriate risk mitigation noting the importance of describing symptoms and what actions to take should a consumer develop any of these.

Listed medicines containing *Garcinia gummi-gutta*, *Garcinia quaesita* and Hydroxycitrate complex

Garcinia gummi-gutta

When used in listed medicines, the existing specific requirements of *Garcinia gummi-gutta* specify that the ingredient cannot include directions for use in children, or pregnant or lactating women. The route of administration can only be oral, and the plant part can only be fruit rind, when used in listed medicines.

As of 16 May 2024:

- there are 39 listed medicines for oral use in the ARTG that contain *Garcinia gummi-gutta*, often indicated for assistance with weight management, to support metabolism and/or to support energy levels.
- all list the plant part as fruit peel or fruit peel outer (as per the restriction on this ingredient).
- all contain concentrated extracts of *Garcinia gummi-gutta*, which range from 4:1 to 12:1 in concentration.
- the quantity of extract in the maximum daily dose (MDD) (where provided) ranges from 1 mg to 1667 mg.
- the equivalent quantity of *Garcinia gummi-gutta* fruit peel in the MDD (where provided) ranges from 6.5 mg to 20 g.
- the HCA content (naturally occurring in *Garcinia gummi-gutta*) is quantified in the ARTG entry for 26 of these 39 listed medicines.
- the HCA content in the MDD (where provided) ranges from 50 mg to 1000 mg.
- there are no medicines in the ARTG that use *Garcinia gummi-gutta* as a non-active (excipient) ingredient, or that are for routes of administration other than oral (as per restrictions for this ingredient).

Garcinia quaesita

There are currently no restrictions specific to the ingredient *Garcinia quaesita* when used in listed medicines.

As of 16 May 2024:

- there are 10 listed medicines for oral use in the ARTG that contain *Garcinia quaesita*, mostly indicated for assistance with weight management and/or to support metabolism and energy.
- the plant part is mostly fruit (9), one lists fruit peel.
- all contain concentrated extracts of *Garcinia quaesita*, which range from 6:1 to 10:1 in concentration.
- the quantity of extract in the maximum daily dose (MDD) (where provided) ranges from 240 mg to 2750 mg.
- the equivalent quantity of *Garcinia quaesita* fruit/fruit peel in the MDD (where provided) ranges from 1440 mg to 16.5 g.
- the HCA content (naturally occurring in *Garcinia quaesita*) is quantified in the ARTG entry for 7 of the 10 listed medicines that contain *Garcinia quaesita*.
- the HCA content in the MDD (where provided) ranges from 130 mg to 1375 mg.
- there are no medicines in the ARTG that use *Garcinia quaesita* as a non-active (excipient) ingredient, or that are for routes of administration other than oral.

Hydroxycitrate complex

When used in listed medicines, hydroxycitrate complex must contain one or more of the three salts (calcium, sodium or potassium hydroxycitrate) of hydroxycitric acid.

The TGA compositional guideline[78] for hydroxycitrate complex states that it is derived from the fruit rind of *Garcinia quaesita*, *Garcinia zeylanica*[xii] and can also be derived from *Garcinia gummi-gutta.* The guideline specifies a concentration of no less than (NLT) 50% HCA on assay, and that remaining plant material should not exceed 10%.

As of 16 May 2024, there are four listed medicines for oral use in the ARTG that contain hydroxycitrate complex, mostly indicated for assistance with weight management, to support metabolism and/or to support energy levels. Only one of these medicines has provided a MDD of 4.7 g, equivalent to 2.8 g HCA. There are no medicines on the ARTG that contain hydroxycitrate complex as a non-active (excipient) ingredient.

Calcium hydroxycitrate, Sodium hydroxycitrate, and Potassium hydroxycitrate, hydroxycitric acid

There are currently no restrictions specific to the ingredients calcium hydroxycitrate, sodium hydroxycitrate, potassium hydroxycitrate or hydroxycitric acid when used in listed medicines.

Calcium hydroxycitrate, sodium hydroxycitrate and potassium hydroxycitrate are not currently included as single active ingredients in any listed medicines but may be present in listed medicines that contain hydroxycitrate complex.

Hydroxycitric acid is not currently included as an active ingredient in any listed medicines, only as a component of *Garcinia gummi-gutta*, *Garcinia quaesita* and Hydroxycitrate complex.

Dosage considerations

According to Andeuza et al., (2021) the NOAEL of 2800 mg/day for HCA in humans was established in 2004, based on toxicological studies at the time[45]. However, cases of liver damage have

[xii] *Garcinia zeylanica* is not currently permitted as a separate ingredient in listed medicines.

subsequently been reported at doses well below this (160 mg to 2800 mg *Garcinia gummi-gutta* extract per day, 240 mg to 561 mg HCA per day [see Appendix A]).

Further, as liver injury associated with *Garcinia gummi-gutta* and HCA appears to be idiosyncratic, it cannot be predicted based on dose. In addition, not all reported cases included dose. Therefore, there is insufficient evidence to support a threshold dose below which the risk of liver injury is mitigated without a warning statement.

Active or excipient ingredient

We are proposing that the warning will apply to use of the ingredients regardless of whether as active or excipient, noting there are currently no medicines on the ARTG that contain these ingredients as excipients. Therefore, there is no current impact on industry by applying the warning to excipient use. Any future use of the ingredients as excipients would then need to comply with any new specific requirements.

Wording of the proposed warning statement

The proposed warning statement includes a description of symptoms commonly experienced during both hepatocellular and cholestatic liver injury, as both have been reported in association with *Garcinia gummi-gutta*/HCA. Most symptoms in the warning statement have also been reported in liver injury cases specifically related to *Garcinia gummi-gutta*/HCA. A description of symptoms is important for consumers who may not know common symptoms of liver injury. This includes some non-specific symptoms that commonly occur in liver injury but in a more persistent or unusual way, that may be the first signs, such as nausea, fatigue or abdominal pain. The call to action, to stop use and see a doctor, sends a clear message to consumers not to ignore these symptoms. The importance of this message cannot be overstated, as early recognition and discontinuation reduces the risk of severe outcomes. This wording has been endorsed by relevant medical specialist groups in previous consultations.

The frequency of occurrence of adverse events cannot be determined based on spontaneous reporting and literature reports. However, considering supplements that contain *Garcinia gummi-gutta* or HCA appear to be widely advertised, it is possible that the occurrence of liver injury is rare or very rare.

We have considered the relatively small number of listed medicines on the ARTG (58) containing these ingredients compared to listed medicines containing other ingredients that require the liver warning, as well as the total number of case reports both in the literature and in adverse event databases. We consider that the wording ‘rare’ is appropriate for *Garcinia gummi-gutta* and other HCA-containing ingredients.

Affected ingredients

Liver injury concerns apply to *Garcinia gummi-g*utta and to the constituent HCA[37, 46, 47, 77], which is naturally-occurring in *Garcinia quaesita* and present in hydroxycitrate complex and salts of HCA. We note hydroxycitrate complex and salts of HCA should be derived from *Garcinia* species when used in listed medicines in accordance with TGA guidance[78]. Therefore, the proposed liver warning applies to ingredients that contain HCA.

The existing requirement that *Garcinia gummi-gutta* cannot be used in listed medicines that include directions for use in children, or pregnant or lactating women was put in place in 2014 due to an absence of information on use in these vulnerable populations. Considering the newly identified risk of possible liver injury, and the continued absence of evidence of safe use in these populations, it appears appropriate that this requirement be extended to other HCA-containing ingredients. Therefore, we are proposing that *Garcinia quaesita*, hydroxycitrate complex, hydroxycitric acid, calcium hydroxycitrate, sodium hydroxycitrate and potassium hydroxycitrate also must not contain any directions for use for children or pregnant or lactating women.

The proposed new requirements apply to the following ingredients:

- CALCIUM HYDROXYCITRATE
- GARCINIA GUMMI-GUTTA
- GARCINIA QUAESITA
- HYDROXYCITRATE COMPLEX
- HYDROXYCITRIC ACID
- POTASSIUM HYDROXYCITRATE
- SODIUM HYDROXYCITRATE

We are also proposing minor amendments to the wording of the existing specific requirements for *Garcinia gummi-gutta* to improve clarity without changing the requirements.

We are aware that HCA is also reported to naturally occur in the permitted ingredient *Hibiscus sabdariffa*, although reportedly in lower quantities than in *Garcinia* species[79], and is possibly also present in other *Hibiscus* species. Although HCA in *Hibiscus sabdariffa* is reported to occur in a slightly different chemical configuration than in *Garcinia* species, it is still thought likely to have similar pharmacological effects[79]. The risk of liver injury from HCA in *Hibiscus* species is under separate consideration by the TGA and is not part of this consultation.

Consultation

This proposed risk mitigation is critical to ensure that listed medicines containing *Garcinia gummi-gutta*/HCA-containing ingredients remain low-risk to allow consumers to self-select and self-administer these medicines.

We are inviting interested stakeholders to comment on the proposal and to submit additional information to support any suggested changes to the proposed requirements.

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.

Proposed specific requirements

Ingredient name	Existing specific requirements	Proposed specific requirements
CALCIUM HYDROXYCITRATE	-	When used in oral medicines, the following warning statement is required on the medicine label: 'In rare cases, calcium hydroxycitrate 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.' Medicines containing calcium hydroxycitrate must not be indicated for use in children, or in pregnant or lactating women.

Ingredient name	Existing specific requirements	Proposed specific requirements
GARCINIA GUMMI-GUTTA	Only for use in oral medicines. Must be obtained from the rind of the fruit only. Must not contain any directions for use for children or pregnant or lactating women.	The route of administration for medicines that contain *Garcinia gummi-gutta* must be limited to oral. The plant part must be limited to fruit peel. The following warning statement is required on the medicine label: 'In rare cases, *Garcinia gummi-gutta* 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.' Medicines containing *Garcinia gummi-gutta* must not be indicated for use in children, or in pregnant or lactating women.
GARCINIA QUAESITA	-	When used in oral medicines, the following warning statement is required on the medicine label: 'In rare cases, *Garcinia quaesita* 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.' Medicines containing *Garcinia quaesita* must not be indicated for use in children, or in pregnant or lactating women.
HYDROXYCITRATE COMPLEX	Hydroxycitrate complex must contain one or more of the three salts (calcium, sodium or potassium hydroxycitrate) of hydroxycitric acid.	Hydroxycitrate complex must contain one or more of the three salts (calcium, sodium or potassium hydroxycitrate) of hydroxycitric acid. When used in oral medicines, the following warning statement is required on the medicine label: 'In rare cases, hydroxycitrate complex 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.' Medicines containing hydroxycitrate complex must not be indicated for use in children, or in pregnant or lactating women.

Ingredient name	Existing specific requirements	Proposed specific requirements
HYDROXYCITRIC ACID	-	When used in oral medicines, the following warning statement is required on the medicine label: 'In rare cases, hydroxycitric acid 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.' Medicines containing hydroxycitric acid must not be indicated for use in children, or in pregnant or lactating women.
POTASSIUM HYDROXYCITRATE	-	When used in oral medicines, the following warning statement is required on the medicine label: 'In rare cases, potassium hydroxycitrate 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.' Medicines containing potassium hydroxycitrate must not be indicated for use in children, or in pregnant or lactating women.
SODIUM HYDROXYCITRATE	-	When used in oral medicines, the following warning statement is required on the medicine label: 'In rare cases, sodium hydroxycitrate 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.' Medicines containing sodium hydroxycitrate must not be indicated for use in children, or in pregnant or lactating women.

References - Garcinia gummi-gutta, Garcinia quaesita, hydroxycitric acid

[36] Carty, J & Navarro, VJ. Dietary Supplement- Induced Hepatotoxicity: A Clinical Perspective, Journal of Dietary Supplements, 25 March 2024. DOI: 10.1080/19390211.2024.2327546

[37] Philips CA, Theruvath AH. A comprehensive review on the hepatotoxicity of herbs used in the Indian (Ayush) systems of alternative medicine. Medicine 2024;103: 16 (e37903).

[38] Li W, Wertheimer A. Narrative Review: The FDA's Perfunctory Approach of Dietary Supplement Regulations Giving Rise to Copious Reports of Adverse Events. [Review] Innovations in Pharmacy. 2023;14(1).

[39] Fontana, R. et al. AASLD practice guidance on drug, herbal, and dietary supplement induced liver injury. Hepatology, 2022; 00: 1-29.

[40] 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). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology, 2008;135(6): 1924–1934. e19344. doi. 10.1053/j.gastro.2008.09.011

[41] Onakpoya, IJ. Rare adverse events in clinical trials: understanding the rule of three. *BMJ Evidence-Based Medicine* 2018;23:6. Available at: Rare adverse events in clinical trials: understanding the rule of three - BMJ EBM Spotlight. [Accessed 1 July 2024].

[42] Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Bruno L, Lista RM, Staltari O, Scuteri A, Scicchitano F, Russo E. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two “challenging” case reports. J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1):S66-72.

[43] Harnett JE, McIntyre E, Steel A*, et al*. Use of complementary medicine products: a nationally representative cross-sectional survey of 2019 Australian adults. *BMJ Open* 2019;9:e024198. doi: 10.1136/bmjopen-2018-024198.

[44] VigiBase, the World Health Organization (WHO) global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC).

[45] Andueza N., et al. Risks associated with the use of garcinia as a nutritional complement to lose weight. *Nutrients.* 2021; 13(2): 1-19. Article Number: 450.

[46] LiverTox . *Drug Record: Garcinia cambogia, Updated 13 February 2019*. [Online] Available from: Garcinia Cambogia - LiverTox - NCBI Bookshelf (nih.gov) [accessed: 13 May 2024]

[47] Calaquian LL, Yau I. Garcinia cambogia-A Supplement-Related Liver Injury. *Cureus*. 2022 Feb;14(2): e22225.

[48] Drugs.com – Garcinia (Hydroxycitric Acid) [accessed 1 July 2024].

[49] Lunsford KE, Bodzin AS, Reino DC, Wang HL, and Busuttil RW. Dangerous dietary supplements: *Garcinia cambogia*-associated hepatic failure requiring transplantation. *World J Gastroenterol.* 2016; 22(45): 10071 – 10076. doi: 10.3748/wjg.v22.i45.10071

[50] Corey R, Werner KT, Singer A, Moss A, Smith M, Noelting J, and Rakela J. Acute liver failure associated with *Garcinia cambogia* use. *Annals of Hepatology*. 2016;15(1): 123 – 126. DOI: 10.5604/16652681.1184287

[51] Flerova E, Ambilil M, Civan JM, Sass DA, Maley WR, Pulinthanathu R, Huang J. Striking Cholestatic Giant Cell Hepatitis Resulting in Fulminant Liver Failure After Garcinia Cambogia Use. International Journal of Surgical Pathology. 2023

[52] Bessone F., Garcia-Cortes M., Medina-Caliz I., Hernandez N., Parana R., Mendizabal M., Schinoni M.I., Ridruejo E., Nunes V., Peralta M., Santos G., Anders M., Chiodi D., Tagle M., Montes P., Carrera E., Arrese M., Lizarzabal M.I., Alvarez-Alvarez I., Caballano-Infantes E., Niu H., Pinazo J., Cabello M.R., Lucena M.I., Andrade R.J. Herbal and Dietary Supplements-Induced Liver Injury in Latin America: Experience From the LATINDILI Network. *Clinical Gastroenterology and Hepatology*. 2022; 20(3): e548-e563.

[53] McCarthy R.E., Bowen D.G., Strasser S.I., McKenzie C. The dangers of herbal weight loss supplements: a case report of drug-induced liver injury secondary to Garcinia cambogia ingestion. *Pathology.* 2021; 53(4): 545-547.

[54] Vuppalanchi R., Bonkovsky H.L., Ahmad J., Barnhart H., Durazo F., Fontana R.J., Gu J., Khan I., Kleiner D.E., Koh C., Rockey D.C., Phillips E.J., Li Y.-J., Serrano J., Stolz A., Tillmann H.L., Seeff L.B., Hoofnagle J.H., Navarro V.J. Garcinia cambogia, Either Alone or in Combination With Green Tea, Causes Moderate to Severe Liver Injury. *Clinical Gastroenterology and Hepatology*. 2022; 20(6): e1416-e1425.

[55] Philips C.A. and Augustine P. Chemical Analysis of Weight Loss Herbal Supplement Safe LeanTM Associated With Acute Liver Injury - A Concern for Spurious Drug, Misbranding and Adulteration. *Journal of Clinical and Experimental Hepatology*. 2018; 8(4) :471-473).

[56] Crescioli G, Lombardi N, Bettiol A, Marconi E, Risaliti F, Bertoni M, Ippolito FM, Maggini V, Gallo E, Firenzuoli F, and Vannacci A. Acute liver injury following *Garcinia cambogia* weight-loss supplementation: case series and literature review. *Internal and Emergency Medicine*. 2018;13: 857 – 872. https://doi.org/10.1007/s11739-018-1880-4

[57] Sharma A, Akagi E, Njie A, Goyal S, Arsene C, Krishnamoorthy G, Ehrinpreis M. Acute Hepatitis due to Garcinia Cambogia Extract, an Herbal Weight Loss Supplement. *Case Reports in Gastrointestinal Medicine*. 2018: 9606171.

[58] Melendez-Rosado J, Snipelisky D, Match G, and Stancampiano F. Acute hepatitis induced by pure *Garcinia cambogia*. *J Clin Gastroenterol*. 2015; 49(5): 449 – 450.

[59] Mas Ordeig A., Bordon Garcia N. Hepatotoxicity caused by Garcinia cambogia. Hepatotoxicidad por Garcinia cambogia. *Gastroenterologia y Hepatologia*. 2020; 43(3):134-135.

[60] Gavric A, Ribnikar M, Smid L, Luzar B, and Stabuc B. Fat burner-induced acute liver injury: case series of four patients. *Nutrition*. 2018; 47: 110 – 114.

[61] Smith R.J., Bertilone C., Robertson A.G. Fulminant liver failure and transplantation after use of dietary supplements. Medical Journal of Australia. 2016 (Jan); 204(1): 30-32.e1.

[62] Clouatre DL and Preuss HG. Hydroxycitric acid does not promote inflammation or liver toxicity. *World J Gastroenterol*. 2013; 19(44): 8160 – 8162.

[63] Stohs SJ, Preuss HG, Ohia SE, Kaats GR, Keen CL, Williams LD, and Burdock GA. No evidence demonstrating hepatotoxicity associated with hydroxycitric acid. *World J Gastroenterol*. 2009; 15(32): 4087 – 4089. doi: 10.3748/wjg.15.4087

[64] Jakopin Z. Risks associated with fat burners: A toxicological perspective. *Food and Chemical Toxicology.* 2019; 123: 205-224.

[65] Arefhosseini S, et al., The effect of hydroxy citric acid supplementation with calorie-restricted diet on metabolic, atherogenic and inflammatory biomarkers in women with non-alcoholic fatty liver disease: a randomized controlled clinical trial. *Food & Function*. 2022; 13(9): 5124-5134.

[66] Di Giacomo S, Di Sotto A, Percaccio E, Scuotto E, Battistelli C, Mazzanti G, Menniti-Ippolito F, Ippoliti I. Interaction of Garcinia cambogia (Gaertn.) Desr. and Drugs as a Possible Mechanism of Liver Injury: The Case of Montelukast. *Antioxidants.* 2023 Sep 16; 12(9):1771.

[67] Kim YJ, Choi MS, Park YB et al.*Garcinia Cambogia* attenuates diet induced adiposity but exacerbates hepatic collagen accumulation and inflammation. *World J Gastroenterol* 2013; 19: 4689–4701.

[68] Mahmoud G. and Amer A., Effect of natural extract of Hydroxycitric acid on lipid profile, liver and testes of adult male rats, *AAMJ* 2013; 11: 161–182.

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

[70] Ballotin V.R., et al., Herb-induced liver injury: Systematic review and meta-analysis. *World Journal of Clinical Cases.* 2021; 9(20): 5490-5513.

[71] Licata A., and Minissale M.G. Weight-loss supplementation and acute liver failure: the case of Garcinia Cambogia. *Internal and emergency medicine*. 2018; 13(6): 833-835.

[72] National Institute of Diabetes and Digestive and Kidney Diseases. Nonalcoholic Fatty Liver Disease (NAFLD) & NASH https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash [accessed 11 September 2023].

[73] European Commission Rapid Alert System for Food and Feed (RASFF). Notification 2020.1614. RASFF Window - Notification detail (europa.eu) [Accessed 22 May 2024]

[74] European Commission's Rapid Alert System for Food and Feed (RASFF). Notification 2021.3300. RASFF Window - Notification detail (europa.eu) [Accessed 22 May 2024]

[75] National Institutes of Health, NIH (2022). *Dietary Supplements for Weight Loss – Fact Sheet for Health Professionals, Updated on 18 May 2022*. [Online] [Accessed: 7 May 2024]. NIH Health Information (2020). *Garcinia Cambogia*, *Updated December 2020.* [Online][Accessed: 7 May 2024].

[76] NIH Health Information. *Garcinia Cambogia*, *Updated December 2020.* [Online] [accessed: 7 May 2024].

[77] Natural Medicines Therapeutic Research (NatMed) – Professional Monograph Garcinia. NatMed Pro - Professional Monograph (therapeuticresearch.com) [accessed: 23 May 2024].

[78] TGA compositional guideline – Hydroxycitrate complex [accessed 6 May 2024]

[79] Izquierdo-Vega JA, Arteaga-Badillo DA, Sánchez-Gutiérrez M, Morales-González JA, Vargas-Mendoza N, Gómez-Aldapa CA, Castro-Rosas J, Delgado-Olivares L, Madrigal-Bujaidar E, Madrigal-Santillán E. Organic Acids from Roselle (*Hibiscus sabdariffa* L.)-A Brief Review of Its Pharmacological Effects. Biomedicines. 2020 Apr 28; 8(5):100. doi: 10.3390/biomedicines8050100. PMID: 32354172; PMCID: PMC7277581.

3. *Xanthium* species

Background

Xanthium is a genus of plants within the family Asteraceae. *Xanthium* species have been observed on most continents[80], and are considered invasive weeds in Australia[81]. One species within this genus, *Xanthium strumarium* L. (synonym: *Xanthium sibiricum*) is used in Traditional Chinese Medicine (TCM).

Xanthium strumarium burs (often known colloquially as fruits) are traditionally dried and heat-treated for medicinal treatment of headaches, joint stiffness, common cold, sinusitis, and some bacterial skin infections [82, 83, 84]. These burs are also known as 'Fructus Xanthii' in TCM texts. Aside from the burs, fresh aerial parts of the plant are used as an ingredient in a traditional fermented herbal preparation known as 'Massa Medicata Fermentata[85, 86]. There are currently no listed medicines that use *Xanthium* spp. in this form.

Xanthium strumarium and *Xanthium sibiricum* are currently permitted for use in listed medicines without any restrictions. Current listed medicines in the ARTG are categorised as 'fruit'; however, we note that 'bur' is not available as a plant part in the TGA Code Tables.

In 2023, a literature report was published describing a fatal poisoning in China caused by *Xanthium sibiricum*[87]. The case report recorded that a 55-year-old man had consumed unprocessed burs of *Xanthium sibiricum* for two months which caused anorexia, nausea, abdominal pain, general weakness and signs of liver dysfunction. Although he was treated in hospital, his condition worsened to coma and death. Following identification of this report, a further investigation was initiated by the TGA into the safety of *Xanthium strumarium* and *Xanthium sibiricum*.

Xanthium species are known to produce carboxyatractyloside (CATR) and its analogue, atractyloside (ATR), which are known to be toxic to humans and animals due to their inhibition of mitochondrial function[88, 89]. Preparation techniques, such as those used in TCM practices, have been shown to reduce the amount of these two components in *Xanthium* burs[90]. This is reflected in the case reports detailed below; with most cases of poisoning in humans by *Xanthium* species due to consumption of unprocessed/raw plant parts that have high concentrations of these compounds. Similarly, ingestion of unprocessed bur and young plants by livestock has been reported as fatal[91, 92, 93, 94, 95].

CATR and ATR have been reported to be the primary toxic components of *Xanthium* species, as studies indicate that these compounds in isolation produce similar signs and internal injury as those seen in cases of poisoning by *Xanthium* burs[92, 96, 97]. Studies of these compounds have found effects including toxic hypoglycaemia and impaired mitochondrial oxidative phosphorylation by direct inhibition of adenosine diphosphate (ADP)/adenosine triphosphate (ATP) carrier proteins, and have been reported to cause nephrotoxicity, hepatotoxicity, cardiotoxicity, organ failure and death[89, 98, 99, 100].

While traditional methods of processing the bur for medicinal use are known to reduce the amounts of CATR and ATR, analysis has found these components are not completely removed[90, 101]. Random testing of commercial medicinal products that include *Xanthium* revealed levels of CATR and ATR did not meet the concentration limits recommended by the Pharmacopoeia of the People's Republic of China[89, 90, 102].

Literature review

Published case reports

Internationally, there have been multiple reports of toxicity due to consumption of *Xanthium* plants or medicinal products containing the herb.

In English-language medical literature, there are 28 cases of fatal poisoning published between 1962 and 2023 which were attributed to consumption of *Xanthium* herb[87, 98, 99, 103, 104, 105]. Most commonly,

these are cases where people have ingested the herb mistakenly believing it was edible, though two cases were under direction of traditional medicine practitioners[87, 104]. The amount of herb ingested is rarely reported, so it is difficult to determine the amount that causes fatality in humans. Cases are most often of acute poisoning with onset of symptoms within 1-2 days, with the exception of two cases reporting fatality following long-term use[87, 104]. Symptoms common among reports are nausea, gastrointestinal issues, weakness, liver and kidney damage, and coma prior to death. Cases are clinically addressed by supportive symptomatic treatment, as there is currently no antidote for CATR or ATR poisoning[87, 98, 106].

Additional case reports in literature record non-fatal toxicity due to consumption or medicinal administration of *Xanthium*. Common symptoms in these case reports are nausea and vomiting[98, 105] and altered mental state[105, 107]. While most of these cases made a recovery without significant complications, one patient required a liver transplant[106].

Common to nearly all cases of *Xanthium* poisoning, fatal and non-fatal, are reports of elevated liver enzymes or physical changes to the liver, indicating liver injury or complete liver failure[87, 98, 99, 104, 105, 106, 107]. Kidney dysfunction or failure are also common among these cases[98, 99, 106,107]. Damage to the heart is also reported in some cases of *Xanthium* toxicity[95, 98, 99]. Children appear to be more susceptible than adults to poisoning[105].

Mechanism and pattern of organ toxicity

ATR and CATR are direct inhibitors of mitochondrial ADP/ATP carrier proteins[88] thus blocking oxidative phosphorylation in mitochondria, a critical process necessary for cellular function[88, 89]. Subsequent increase in generation of reactive oxygen species within the mitochondria becomes toxic to the cells[89]. Organs with high energetic demands, such as the kidney and liver, are susceptible to damage due to mitochondrial dysfunction, hence the nephrotoxicity and hepatotoxicity seen in cases of *Xanthium* toxicity[89, 91, 92, 96, 97, 98, 100, 108, 109]. Aside from local cellular damage, ATR and CATR also cause toxic hypoglycaemia due to blockade of oxidative phosphorylation and thus aerobic glycolysis.

Xanthium echinosum, which also produces CATR and ATR, raw seeds removed from within the bur have been demonstrated to be fatally toxic at doses as low as 0.22% body weight[93], equivalent to 154 g of seeds for a 70 kg human. Comparatively, this is well above the recommended dose of 3-10 g *Xanthium strumarium* that is used medicinally[110].

A study investigated organ damage due to ATR and CATR extracted from *Xanthium strumarium* in mice[100]. Three dosage points were investigated for each ATR (50, 125, 200 mg/kg) and CATR (50, 100, 150 mg/kg), which was administered once a day for five days via intraperitoneal injection. After this, microscopic examination revealed no visible injury to the lung, spleen, heart, kidney or central nervous system. However, extensive liver injury was seen in the high dose ATR group and CATR groups, including hepatocellular degeneration, necrosis, inflammatory cell infiltration and cytoplasmic vacuolation. Serum levels of liver injury markers alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase were higher in all ATR- and CATR-treated groups compared to control, which occurred in a dose-dependent manner. The authors also quantified the downstream effects of oxidative stress in the liver, which were worse in CATR and ATR treated mice including increased malondialdehyde (an end-product of lipid peroxidation due to abundant reactive oxygen species) and decreased activities of the antioxidant enzymes superoxide dismutase, glutathione and catalase.

Another *in vivo* study investigated medium-term effects of extracts of commercial raw and processed (heat-treated) *Xanthium sibiricum* burs in male mice[111]. This study administered 120 g/kg extract per day for 10, 20 or 30 days then quantified ATP, ADP, adenosine monophosphate (AMP), CATR and ATR in the liver. After 30 days, raw bur-treated mice had significantly reduced liver levels of both ATP and AMP with concurrent increase in ADP, which were not seen in the mice treated with processed bur extract or control, indicating mitochondrial dysregulation. Furthermore, mice treated with raw bur had accumulating presence of both ATR and CATR in the liver, while CATR and ATR levels were undetectable in mice treated with processed burs. These results indicate that repeated exposure to this herb may have cumulative toxic affects due to deposition in body tissues.

Further evidence that these glycosides may accumulate in the body with repeated dosing is a study which investigated effects of 12-week administration of aqueous extract of the raw or processed (heat-treated) bur of *X. sibiricum* at doses 0.585, 1.755 and 5.265 g/kg body weight (equivalent to one, three and nine times human recommended dose) to rats[108]. Four of 24 raw bur-treated and six of 24 processed bur-treated rats died over the course of administration, and postmortem examination of liver and kidney showed congestion and focal necrosis in the liver and renal tubules. Body weights of rats treated with mid- and high-dose processed bur extracts were lower than saline-treated after week eight, though statistical significance was mixed. Serum creatinine and blood urea nitrogen, which are typical kidney function tests, were also affected by administration of raw bur and processed bur, but without clear dose-dependent or manufacture-dependent trends. This appears to be the only study to investigate long-term safety of this herb in humans or animals.

Regarding the use of *Xanthium* products during pregnancy, there is a lack of safety studies in humans. A study indicated that aqueous extract of burs of *Xanthium sibiricum* decreased the hatch rate and increased mortality rate of zebrafish embryos[112]. There has also been a genotoxicity study performed on *Xanthium strumarium* extract, which demonstrates *in vitro* genotoxicity in mammalian cells but did not show evidence of *in vivo* genotoxicity in a mouse bone marrow micronucleus assay[113]. The results of this study may underestimate the risk from existing preparations, as the extract was prepared using the whole adult plant rather than the bur. Thus, the possibility of *in vivo* genotoxicity cannot be excluded.

The young leaves of *Xanthium strumarium* have been reported to be toxic, with toxicity decreasing with age of the plant[92]. *Xanthium* leaves are used traditionally in Massa Medicata Fermentata preparations[114]. While fermentation process similar to those used in this preparation has been found to degrades certain compounds[115, 116], no evidence was found to indicate whether CATR or ATR are affected by this method of processing.

Adverse event reports

The Database of Adverse Event Notifications (DAEN) for medicines includes one confirmed adverse event related to *Xanthium* spp. in Australia. This report from April 2017 described a 26-year-old female who experienced eye swelling and pruritic rash suspected to be caused by a medicine that contained *X. sibiricum*. The medicine contained *X. sibiricum* among four other active ingredients, and causality was not confidently established to any single ingredient.

A search of WHO's global Individual Case Safety Report database, VigiBase[13], indicated 12 reports associated with medicines with either *X. strumarium* or *X. sibiricum* as an active ingredient (*X. strumarium* and *X. sibiricum* searches returned the same results; accessed 3 April 2024). However, only two of these reports related to oral medicines; pollen from these herbs is commonly used in allergy tests, which are not of concern in the context of *Xanthium* toxicity or poisoning. One of the two oral *Xanthium* product reports listed dyspepsia, diarrhoea and asthenia (generalised weakness) as symptoms, although the case is confounded by 22 other ingredients in the suspected product and so the causality of *Xanthium* in this case is not clearly established. The second case, which only involved *Xanthium sibiricum* in the formulation, reported dizziness, nausea and vomiting after a single 100-gram dose, symptoms which may be consistent with CATR/ATR toxicity.

One adverse event is recorded in the Canada Vigilance adverse reaction online database (data from 1 January 1965 to 31 January 2024) for products containing 'xanthii fructus' and/or 'xanthii fructus sibirici'. This adverse event notification was received in February 2012 and reports that a 36-year-old female experienced eye disorder, eye discharge and eye pruritus suspected to be caused by a Bi Yan Pian product (a preparation containing *Xanthium* fruit/bur among other herbal ingredients, further product identification not provided).

[13] 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.

While there is only one record of an adverse event occurring in Australia due to *Xanthium*-containing medicines, this does not necessarily mean these medicines are safe. It is likely that adverse events are under-reported, especially as *Xanthium* is included in complementary medicines often used without professional oversight. Consequently, the low number of Australian adverse event reports cannot be considered evidence of the absence a safety signal, especially considering the published international case reports discussed above.

International regulation

Several regulatory agencies internationally have classified *Xanthium strumarium* or *Xanthium sibiricum* (herein considered the same herb) as representing a health risk:

- In 2009, the European Food Safety Authority (EFSA) included *Xanthium strumarium* as well as all species in the *Xanthium* genus within the 'EFSA Compendium of botanicals that have been reported to contain toxic, addictive, psychotropic or other substances of concern'. Within this document, the flowering tops of all *Xanthium* species are noted to contain CATR, and the leaves, fruit, herb and root of *Xanthium strumarium* as containing CATR and the alkaloid xanthatin[117]. This was ratified in the 2012 version, 'Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements'[118], which also notes: 'toxicosis usually associated with the consumption of the seedlings in the cotyledon stage which contain a high concentration of carboxyatractyloside. Seeds also known to contain the toxin.'
- The Norwegian Medical Products Agency has explicitly listed *Xanthium strumarium* in a list of herbs that are banned from personal import due to being poisonous, containing narcotic substances or having strong effects or health risks[119].

Under Canadian regulation, *Xanthium sibiricum* and Fructus Xanthii are only permitted when prepared according to the specifications outlined in Health Canada's Natural Health Product Ingredients Database. The entries for 'Xanthium sibiricum' and 'Fructus Xanthii' were most recently updated on the 15 March 2023, to stipulate that:

> 'In order to reduce toxicity, the following ingredient must be processed before use as a medicinal ingredient in Massa Medicata Fermentata and Fructus Xanthii: Xanthium sibiricum fruit must have the spines removed and be stir-baked.'

Furthermore, the Health Canada's entry limits administration to oral route of administration.

Of note, the preparation of the fruit/bur involving spine removal and stir-baking aligns with the monograph of the Pharmacopoeia of the People's Republic of China[110].

Consultation

Considering the available information and the risk of toxicity even when the burs are prepared according the TCM preparation methods, the TGA is proposing to remove *Xanthium strumarium* and *Xanthium sibiricum* from the Determination. This would disallow the use of these ingredients in listed medicines.

Given the toxicological information available, it does not appear possible to scientifically estimate an appropriate level for ingestion of CATR or ATR by humans. While heat processing is known to reduce the amount of these compounds, heat-treating the burs during preparation has been found to ensure absence in commercially available medicines. While the burs are of the most concern from a toxicological perspective, aerial parts of the plant have been found to be toxic. As such, it cannot be assured that these preparations are free of CATR and ATR. However, it is noted that, as of July 2024, there were no listed medicines declaring *Xanthium* spp. leaves as ingredients.

As preparation methods have not been found to entirely remove these components and as there does not appear to be an antidote currently available for CATR or ATR poisoning, the use of these ingredients does not appear to align with the low-risk framework for listed medicines.

The TGA is inviting interested stakeholders to comment on the TGA proposal and submit additional information to support a safe dose and preparation method for *Xanthium* species to mitigate the risk of toxicity.

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

- XANTHIUM SIBIRICUM
- XANTHIUM STRUMARIUM

As of the 24 April 2024, there were 16 listed medicines on the ARTG that included either *Xanthium* species, the majority using *Xanthium sibiricum*. These medicines are all for oral administration, and all list the plant part used as 'fruit' (or 'fruiting body'), indicating that the bur is likely the commonly used medicinal part of the plant. Notably, currently no listed medicines use the leaves of this plant, indicating that this plant is not currently used in fermented form within Massa Materia Medica preparations.

Proposed changes

Ingredient name	Existing specific requirements	Proposed specific requirements
~~XANTHIUM SIBIRICUM~~		NA
~~XANTHIUM STRUMARIUM~~		NA

References – Xanthium species and risk of toxicity

[80] USDA-ARS National Plant Germplasm System. *Germplasm Resources Information Network (GRIN Taxonomy), entry for Xanthium strumarium L.* 2024 17 May 2024; Available from: https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomydetail?id=42072.

[81] Centre for Invasive Species Solutions. *Weeds Australia: Xanthium strumarium L.* 2024 17 May 2024]; Available from: https://weeds.org.au/profiles/noogoora-burr-cockleburr/.

[82] Yang, S.-Z., *The divine farmer's materia medica: a translation of the Shen Nong Ben Cao Jing*. 1998: Blue Poppy Enterprises, Inc.

[83] World Health Organization, *Medicinal plants in Viet Nam.* 1990.

[84] Zhao, Z., *An illustrated Chinese materia medica in Hong Kong*. 2004: World Scientific.

[85] Hsu, H., et al., *Oriental materia medica: a concise guide.* 1996.

[86] Fu, F.Q., et al., *Biostudy on Traditional Chinese Medicine Massa Medicata Fermentata.* ACS Omega, 2020. **5**(19): p. 10987-10994.

[87] Li, Y., et al., *Multiorgan failure caused by Chinese herbal medicine Xanthii Fructus poisoning: a case report.* BMC Complementary Medicine and Therapies, 2023. **23**(1): p. 273.

[88] Mavridou, V., et al., *Substrate binding in the mitochondrial ADP/ATP carrier is a step-wise process guiding the structural changes in the transport cycle.* Nature Communications, 2022. **13**(1): p. 3585.

[89] Woyda-Ploszczyca, A.M., *Direct and indirect targets of carboxyatractyloside, including overlooked toxicity toward nucleoside diphosphate kinase (NDPK) and mitochondrial H+ leak.* Pharmaceutical Biology, 2023. **61**(1): p. 372-390.

[90] Nikles, S., et al., *Influence of processing on the content of toxic carboxyatractyloside and atractyloside and the microbiological status of Xanthium sibiricum fruits (Cang'erzi).* Planta Medica, 2015. **81**(12/13): p. 1213-1220.

[91] Witte, S.T., et al., *Cocklebur toxicosis in cattle associated with the consumption of mature Xanthium strumarium.* Journal of Veterinary Diagnostic Investigation, 1990. **2**(4): p. 263-267.

[92] Stuart, B.P., R.J. Cole, and H.S. Gosser, *Cocklebur (Xanthium strumarium, L. var. strumarium) intoxication in swine: review and redefinition of the toxic principle.* Veterinary Pathology, 1981. **18**(3): p. 368-383.

[93] Marsh, C.D., A.B. Clawson, and G.C. Roe, *Cockleburs (species of Xanthium) as poisonous plants*. Vol. no.1274 (1924). 1924, Washington, D.C: U.S. Dept. of Agriculture.

[94] Martin, T., E.L. Stair, and L. Dawson, *Cocklebur poisoning in cattle.* Journal of the American Veterinary Medical Association, 1986. **189**(5): p. 562-563.

[95] Roh, S., et al., *A case of carboxyatractyloside intoxication by ingestion of the cocklebur (Xanthium strumarium) in a Korean native cow.* Veterinární medicína, 2022. **67**(10): p. 538.

[96] Cole, R.J., et al., *Isolation and redefinition of the toxic agent from cocklebur (Xanthium strumarium).* Journal of Agricultural and food Chemistry, 1980. **28**(6): p. 1330-1332.

[97] Obatomi, D.K. and P.H. Bach, *Biochemistry and Toxicology of the Diterpenoid Glycoside Atractyloside.* Food and Chemical Toxicology, 1998. **36**(4): p. 335-346.

[98] Turgut, M., et al., *Carboxyatractyloside poisoning in humans.* Annals of Tropical Paediatrics, 2005. **25**(2): p. 125-134.

[99] Zhang, Y.-g. and G.-z. Huang, *Poisoning by toxic plants in China: report of 19 autopsy cases.* The American Journal of Forensic Medicine and Pathology, 1988. **9**(4): p. 313-319.

[100] Wang, Y., et al., *Hepatotoxicity of kaurene glycosides from Xanthium strumarium L. fruits in mice.* Die Pharmazie-An International Journal of Pharmaceutical Sciences, 2011. **66**(6): p. 445-449.

[101] Su, T., et al., *Comparison of the toxicities, activities and chemical profiles of raw and processed Xanthii Fructus*, in *BMC complementary and alternative medicine*. 2016, BioMed Central: England. p. 24.

[102] Jiang, H., et al., *Chemometrics coupled with UPLC-MS/MS for simultaneous analysis of markers in the raw and processed Fructus Xanthii, and application to optimization of processing method by BBD design.* Phytomedicine, 2018. **57**: p. 191-202.

[103] Ji, S.X., et al., Acta Academiae Medicinae Jilin, 1962. **1**(75).

[104] Wu, M., et al., *Abstracts of the 2005 North American Congress of Clinical Toxicology Annual Meeting.* Clinical Toxicology, 2005. **43**(6): p. 631-777.

[105] Gurley, E.S., et al., *Fatal outbreak from consuming Xanthium strumarium seedlings during time of food scarcity in northeastern Bangladesh*, in *PloS one*. 2010, Public Library of Science: United States. p. e9756.

[106] Karabiber, H., et al., *Xanthium strumarium poisoning requiring liver transplantation.* Journal of Pediatric Gastroenterology and Nutrition, 2014. **58**(1): p. e6-e9.

[107] Mofidi, M. and H. Saidi, *Toxic effect of Xanthium strumarium as an herbal medicine preparation.* EXCLI Journal, 2009.

[108] Yu, J., et al., *In Vitro Cytotoxicity and In Vivo Acute and Chronic Toxicity of Xanthii Fructus and Its Processed Product.* BioMed Research International, 2013. **2013**: p. 403491.

[109] Xue, L.-M., et al., *Hepatotoxic constituents and toxicological mechanism of Xanthium strumarium L. fruits.* Journal of Ethnopharmacology, 2014. **152**(2): p. 272-282.

[110] State Pharmacopoeia Commission of the People's Republic of China, *Pharmacopoeia of the People's Republic of China: 2015*. 2015: China Medical Science Press.

[111] Jiang, H., et al., *A UPLC-MS/MS application for comparisons of the hepatotoxicity of raw and processed Xanthii Fructus by energy metabolites.* RSC advances, 2019. **9**(5): p. 2756-2762.

[112] Chen, X.Q., et al., *Toxicity of Fructus Xanthii extract to the growth and motion behavior of zebrafish embryos.* Shandong Sci, 2014. **27**: p. 10-13.

[113] Piloto Ferrer, J., et al., *Xanthium strumarium L. extracts produce DNA damage mediated by cytotoxicity in in vitro assays but does not induce micronucleus in mice.* Biomed Res Int, 2014. **2014**: p. 575197.

[114] Chen, J.K., Chen, T.T. and Crampton, L., 2004. *Chinese medical herbology and pharmacology* (Vol. 1267). City of Industry, CA: Art of Medicine Press.

[115] Fu, F.Q., Xu, M., Wei, Z. and Li, W., 2020. Biostudy on traditional Chinese medicine massa medicata fermentata. *ACS omega*, *5*(19), pp.10987-10994.

[116] Wang, Z., Okutsu, K., Yoshizaki, Y., Futagami, T., Tamaki, H., Maruyama, T., Toume, K., Komatsu, K., Hashimoto, F. and Takamine, K., 2022. Effects of microbial fermentation on enzyme activity and volatile properties of Massa Medicata Fermentata. *Traditional & Kampo Medicine*, *9*(1), pp.10-17.

[117] ESCO Working Group Members, *EFSA Compendium of botanicals that have been reported to contain toxic, addictive, psychotropic or other substances of concern.* EFSA Supporting Publications, 2009. **6**(6): p. 281R.

[118] European Food Safety, A., *Compendium of botanicals reported to contain naturally occuring substances of possible concern for human health when used in food and food supplements.* EFSA Journal, 2012. **10**(5): p. 2663.

[119] Norwegian Medical Products Agency. *Importing medicines for personal use in the form of consignments*. 2023 26/2/2024 22/5/2024]; Available from: https://www.dmp.no/en/manufacturing-import-and-retailing-of-medicines/importing-medicines-for-personal-use/importing-medicines-for-personal-use-in-the-form-of-consignments#CBD-(cannabidiol)--175595.

4. Phenoxyethanol

Background

2-Phenoxyethanol (phenoxyethanol) is an aromatic ether and has a large spectrum of antimicrobial activity and has been widely used as a preservative in cosmetic products (at a maximum concentration of 1%) for decades. It is effective against various gram-negative and gram-positive bacteria, as well as some yeasts[120]. It may also be used as a fixative for perfumes and soaps, and in the synthesis of fragrance materials.

Phenoxyethanol is currently permitted for use in listed medicines only as an excipient in topical medicines for dermal application. The concentration of phenoxyethanol must not exceed 15% in such preparations. This is consistent with the exceptions for phenoxyethanol in Schedule 6 of the Poisons Standard, as listed medicines cannot contain scheduled substances.

> **Schedule 6**
>
> 2-PHENOXYETHANOL **except**:
>
> a) in cosmetic preparations containing 1% of less of 2-phenoxyethanol; or
> b) in other preparations containing 15% or less of 2-phenoxyethanol.
>
> **Index entry**
>
> Schedule 6
> Appendix E, clause 3
> Appendix F, clause 4

The Cosmetic Ingredient Review (CIR) found that phenoxyethanol is not phototoxic based on clinical studies[121]. Historically, allergic contact dermatitis related to phenoxyethanol was attributed to 'compound allergy' with the allergenicity being attributed to methyldibromo glutaronitrile. However, recent large patch testing trials have demonstrated low sensitisation rates to phenoxyethanol, ranging from 0.1 to 0.24%[122].

In 2013, the Australian Industrial Chemicals Introduction Scheme (AICIS) completed a human health tier II assessment of phenoxyethanol. In this assessment, it was observed that there was no evidence of the substance having reproductive or developmental toxicity, and it was not genotoxic. However, data on carcinogenicity was absent. The critical health effects included acute toxicity by oral exposure and local effects such as eye irritation; sensitisation may occur in susceptible individuals. To further support this point, phenoxyethanol is included in Appendix F, Part 3 of the Poisons Standard as an irritant, and contact with eyes should be avoided. It has low acute toxicity by dermal and inhalation exposure. Additionally, due to its high dermal absorption rate in leave-on formulations, it is recommended that this substance should be avoided in products that come into contact with the eye[123]. AICIS recommended that consideration should be given to the fact that internationally the chemical is allowed as a preservative in cosmetic products at a maximum concentration of 1%.

In over the counter (OTC) medicines, phenoxyethanol is only permitted for topical use with its concentration in the medicine not exceeding 2%. Therefore, the current use of phenoxyethanol in the Permissible Ingredients Determination exceeds the use allowed in registered OTC medicines.

Adverse event reports

As of 25 June 2024, there were three case reports in the Database of Adverse Event Notifications (DEAN) in relation to products containing phenoxyethanol. However, as the adverse event reports recorded in DAEN relate to active ingredients these reports are linked to other medicines or off-label products not included on the Australian Register of Therapeutic Goods (ARTG), as phenoxyethanol is restricted for use only as an excipient in listed medicines. In addition, there were eight reports attributed to phenoxyethanol when used as an active ingredient in VigiAccess.

International regulation

In Europe, cosmetics are regulated via Regulation (EC) No 1223/2009 of the European Parliament and of the Council. Phenoxyethanol is present in Annex V, the list of preservatives allowed in cosmetic products, at a maximum concentration of 1%.

This was written into European legislation following the risk assessment and safety Opinion on phenoxyethanol (the Opinion) published by the European Scientific Committee on Consumer Safety (SCCS) (the Committee) in 2016[124].

The Committee concluded that phenoxyethanol was not an irritant or sensitiser (rare sensitiser), nor was there evidence that the substance was genotoxic or a carcinogen when used at 1% in cosmetic formulations. In addition, the Committee considered phenoxyethanol as being safe for all consumers, including children of all ages, when used as a preservative in cosmetic products at a maximum concentration of 1%. Further, adverse effects observed in toxicological studies have only occurred when levels of exposure have been higher (200-fold higher) than those to which consumers are exposed.

In 1990, the CIR Expert Panel (the Expert Panel) completed a safety assessment of phenoxyethanol and concluded that it was safe as a cosmetic ingredient in the present practices of use and concentration[121]. In 2007, the Expert Panel reviewed more newly available studies along with updated information regarding types and concentration of use. The Expert Panel reaffirmed their initial findings that phenoxyethanol was safe in the present practices of use and concentrations[125].

The safety information presented by the SCCS and AICIS is also consistent with regulation in New Zealand (NZ) and the Health Canada monograph, where phenoxyethanol is restricted to a maximum concentration of 1%.

Consultation

Considering the available information, the TGA is proposing to reduce the maximum permitted concentration to 1% in topical listed medicines for dermal application. This would align with phenoxyethanol in the Poisons Standard for cosmetic (topical) preparations. In addition, amending the restrictions to exclude the use of medicines intended for use in the eye. Reducing the permitted concentration to 1% in topical listed medicines would be commensurate with a risk-based approach, where the permitted concentration of phenoxyethanol in OTC topical medicines is 2%. In addition, the implemented change will also align with European legislation, NZ legislation, Health Canada's monograph, CIR Expert Panel reports and the SCCS safety information.

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 ingredient

- PHENOXYETHANOL

As of 24 April 2024, there were 536 medicines included on the ARTG containing phenoxyethanol, with only two of these containing more than 1% phenoxyethanol. 453 of these listed medicines are sunscreens and none of these are reported to contain more than 1% phenoxyethanol. None of these medicines are specified as being for use in the eye.

Proposed specific requirements

Ingredient name	Existing specific requirements	Proposed specific requirements
PHENOXYETHANOL	Only for use in topical medicines for dermal application. The concentration of phenoxyethanol in the preparation must not exceed 15%.	Only for use in topical medicines for dermal application and not to be included in medicines intended for use in the eye. The concentration of phenoxyethanol in the preparation must not exceed 1~~15~~%.

References - Phenoxyethanol

[120] Dréno. 2019. Safety review of phenoxyethanol when used as a preservative in cosmetics. Journal of the European Academy of Dermatology and Venereology. Wiley Online Library.

[121] REV, E.P.C.I., 1990. Final report on the safety assessment of phenoxyethanol. *Journal of the American College of Toxicology*, *9*, pp.259-278.

[122] Roh, J. and Cheng, H., 2022. Ultraviolet filter, fragrance and preservative allergens in New Zealand sunscreens. *Australasian Journal of Dermatology*, *63*(1), pp.e21-e25.

[123] Sullivan, D.A., da Costa, A.X., Del Duca, E., Doll, T., Grupcheva, C.N., Lazreg, S., Liu, S.H., McGee, S.R., Murthy, R., Narang, P. and Ng, A., 2023. TFOS Lifestyle: Impact of cosmetics on the ocular surface. *The Ocular Surface*, *29*, pp.77-130.

[124] Bernauer, U., Bodin, L., Celleno, L., Chaudhry, Q.M., Coenraads, P.J., Dusinska, M., Duus-Johansen, J., Ezendam, J., Gaffet, E., Galli, C.L. and Granum, B.B., 2016. SCCS OPINION ON Phenoxyethanol.

[125] Andersen, F.A., 2011. Annual review of cosmetic ingredient safety assessments: 2007-2010. *International Journal of Toxicology*, *30*(5_suppl), pp.73S-127S.

5. Clarification of hydration state for Rutoside

Background

Rutoside (rutin) is a flavonoid glycoside commonly found in various fruits, vegetables and plants. The major medical sources of rutoside include buckwheat, Japanese pagoda tree and *Eucalyptus macrorhyncha*. Other dietary sources include black tea and apple peels. Rutoside belongs to the flavonoid class of compounds, known for their antioxidant and anti-inflammatory properties[126].

Rutoside is currently permitted for use in listed medicines both as an active ingredient and excipient, without any restrictions.

In April 2004, rutoside was approved for use in listed medicines on recommendation from the Complementary Medicines Evaluation Committee (CMEC) during its 45th Meeting[127]. The evaluation noted that rutin is an Australian Approved Name (AAN) referenced in the Merck Index. The commercially available form of rutoside is typically the trihydrate rather than an anhydrous form. Furthermore, in 2022, rutoside trihydrate was added to the Ingredients Repository, however, is not currently available for use in listed medicines.

As such, there appears to be a discrepancy between what was considered at CMEC 45 and what is currently on the Determination.

Consultation

The TGA is proposing to change 'rutoside' to 'rutoside trihydrate' to align with the original CMEC evaluation.

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 ingredient will have until the end of the transition period to amend their products in line with the name change.

Affected ingredient

- RUTOSIDE

As of 21 June 2024, there were 89 medicines included on the ARTG containing rutoside. Among these rutoside was an active ingredient in 86 products and an excipient in three others.

Proposed change

Existing ingredient name	Proposed ingredient name	Existing specific requirements	Proposed specific requirements
RUTOSIDE	RUTOSIDE TRIHYDRATE	-	-

References - Rutoside

[126] Ganeshpurkar, A. and Saluja, A.K., 2017. *The Pharmacological Potential of Rutin*, Saudi Pharmaceutical Journal, 2017. 25(2): P. 149-164. (https://www.sciencedirect.com/science/article/pii/S1319016416300263)

[127] Complementary Medicines Evaluation Committee (CMEC) Extracted Ratified Minutes, Forty-fifth Meeting, 23 April 2004: https://www.tga.gov.au/sites/default/files/cmec-minutes-45.pdf.

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 **Friday 2 August 2024**

Interested parties should respond by close of business **Friday 13 September 2024.** 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 **Monday 2 December 2024.**

The confirmed changes to the Determination will commence on **Saturday 1 March 2025**.

The transition period of 1 year will end on **Sunday 1 March 2026** 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.

Appendices

Appendix A – liver injury case reports

Table 1: Liver injury case reports in the literature for *Garcinia gummi-gutta* with no other suspected hepatotoxins

Study details (region)	Sex	Age (yrs)	Suspected product and dose	Other medicines	Type of liver injury	Symptoms	Onset time	Positive de-challenge*	Hospital-isation	Causality
Flerova *et al* 2023[51] (United States)	F	65	*Garcinia gummi-gutta* (not further described)	NR	Hepato-cellular	Fatigue, dark urine, acholic stool, elevated liver enzymes, jaundice.	2.5 months	No - proceeded to LT	Yes	RUCAM 8 (Probable)
Calaquian *et al,* 2022[47] (South Korea)	F	45	SERY BOX Seryburn Day Triple *Garcinia gummi-gutta* supplement (dose NR)	None	NR	Yellowing of skin and sclera, fatigue, malaise, anorexia.	3 months	NR (AST & ALT decreased by over 50% after 2 weeks)	Yes	NR
Bessone *et al,* 2022[52] **Case 15** (Latin America)	F	48	Lisopresol (dose NR)	Levothyroxine	Acute liver failure	Jaundice	11 days	No - proceeded to LT	Yes	RUCAM 7 (Probable)

Study details (region)	Sex	Age (yrs)	Suspected product and dose	Other medicines	Type of liver injury	Symptoms	Onset time	Positive de-challenge*	Hospital-isation	Causality
Bessone *et al*, 2022[52] **Case 14** (Latin America)	M	16	Lisopresol (dose NR)	None	Hepato-cellular	Jaundice	23 days	Yes (180 days)	No	RUCAM 5 (Possible)
Bessone *et al*, 2022[52] **Case 13** (Latin America)	F	46	Lipo On Fire	None	Hepato-cellular	Hyper transaminasemia	31 days	Yes (30 days)	No	RUCAM 8 (Probable)
McCarthy *et al*, 2021[53] (Australia)	F	54	*Garcinia gummi-gutta* (not further described)	NR	Acute liver failure	malaise, jaundice and dark urine.	2 months	No - proceeded to LT	Yes	NR
Mas Ordeig & Bordon Garcia, 2020[59] (Spain)	F	64	*Garcinia gummi-gutta* product 1000mg-2000mg/ day	Nil regular	NR	moderate non-colicky pain in epigastrium and right hypochondrium, nausea, vomiting and dark urine.	15 days	Yes (8 weeks)	Yes	RUCAM 9 (highly probable)

Study details (region)	Sex	Age (yrs)	Suspected product and dose	Other medicines	Type of liver injury	Symptoms	Onset time	Positive de-challenge*	Hospital-isation	Causality
AL-Khazraji *et al,* 2020[128] (United States)	F	39	Slimming herbal tea supplement containing pure *Garcinia gummi-gutta*	NR	auto-immune hepatitis	fatigue, dark coloured urine	5 weeks	No - required immune-suppressive therapy before LFTs normalised (5 months)	Yes	NR
Yousaf *et al,* 2019[129] (United States)	F	21	*Garcinia gummi-gutta* 1400mg / day	None	Acute liver failure	Severe abdominal pain, nausea, vomiting, anorexia, and myalgias.	4 weeks	Yes (42 days after discharge).	Yes	RUCAM 9 (highly probable)
Kothadia *et al,* 2018[130] (United States)	F	36	*Garcinia gummi-gutta* not further described	NR	Hepato-cellular	Low-grade fever, nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice.	4 weeks	Yes (2 weeks later)	Yes	RUCAM 8 (Probable)

Study details (region)	Sex	Age (yrs)	Suspected product and dose	Other medicines	Type of liver injury	Symptoms	Onset time	Positive de-challenge*	Hospital-isation	Causality
Crescioli *et al,* 2018[56] **Case 1** (Italy)	F	61	'Super Ananas Slim' 1 'envelope' daily *Garcinia gummi-gutta* extract (60% HCA) *Ananas comosus* (bromelain 334 GDU) *Ilex paraguariensis* (2% caffeine)	Levothyroxine	Cholestatic hepatitis	Abdominal pain, nausea, progressive weakness, jaundice, dark urine acholic stools.	~7weeks	Yes (4 months)	Yes	CIOMS (RUCAM) 7 (probable)
Crescioli *et al,* 2018[56] **Case 3** (Italy)	F	47	THERMO GIALLO® 2 capsules / day, each containing: *Garcinia gummi-gutta* 400mg extract (200mg HCA), Chromium 50mcg	Levothyroxine 100mcg daily, Enalapril 20mg daily	Acute hepatitis	Severe abdominal pain (right hypochondrial)	1 month	NR (rapid improvement on cessation)	Yes	RUCAM 6 (probable)

Study details (region)	Sex	Age (yrs)	Suspected product and dose	Other medicines	Type of liver injury	Symptoms	Onset time	Positive de-challenge*	Hospital-isation	Causality
Crescioli *et al*, 2018[56] **Case 4** (Italy)	F	52	'Jill Cooper Be Slim' 1 capsule daily, each containing: *Garcinia gummi-gutta* extract 400mg 60% (240mg HCA) 'Jill Cooper Be Slim' 1 capsule daily, each containing Green Coffee extract 400mg 50% (200mg chlorogenic acid)	NR	acute hepatitis	NR	1 month	Yes (completely resolved during the days following cessation)	ED	RUCAM 6 (probable)
Sharma *et al,* 2018[57] (United States)	F	57	*Garcinia gummi-gutta* extract 1400mg/cap Dose: 2/day	Vitamins A & D	NR	Abdominal pain & vomiting.	~ 1 month	Yes (1 month) Positive rechallenge.	NR	RUCAM 11 (highly probable)
Philips & August-ine, 2018[55] (India)	F	33	Safe Lean 2 capsules / day, each containing: *Garcinia gummi-gutta* (600 mg), *Allium sativum* (250 mg) and *Trigonella foenum graecum* (100 mg) (Elemental impurities and traces of ethylhydrazine detected)	Vitamin D, Folic acid (5mg/day).	Severe hepatitis	Nausea, loss of appetite.	1 month	Yes (1 month)	NR	RUCAM 8 (probable)

Study details (region)	Sex	Age (yrs)	Suspected product and dose	Other medicines	Type of liver injury	Symptoms	Onset time	Positive de-challenge*	Hospital-isation	Causality
Lunsford *et al,* 2016[49] (United States)	M	34	Swanson Premium Brand Garcinia Cambogia 5:1 Extract, 2 capsules / day, each containing *Garcinia gummi-gutta* 5:1 extract 80mg (equivalent 400mg 'standard preparation')	None	Hepato-cellular	Nausea, vomiting, abdominal pain, and dark urine. 6 weeks later; asterixis, jaundice, and confusion.	5 months	No – proceeded to LT	Yes	NR
Corey *et al*, 2016[50] (United States)	F	52	*Garcinia gummi-gutta* (USA Nutra Labs) 2 capsules/ day, total 50 capsules consumed. 2 caps contained *Garcinia gummi-gutta* extract 936mg (60% HCA), calcium 50mg, chromium 200mcg, potassium 50mg.	> 12-month duration: melatonin, dicyclomine, topical Bi-Estrogen/ progesterone/ DHEA, 'dancing willow' (topical antifungal nail oil)	Severe acute hepatitis, liver failure	Jaundice, abdominal distension, worsening fatigue, appetite loss, confusion.	NR (estimated 25 days based on dose)	No – required LT	Yes	RUCAM 7 (probable)
Cavacio-cchi *et al.*, 2016[131] (Italy)	F	61	*Garcinia gummi-gutta*	NR	Chole-static hepatitis	Mild upper abdominal pain, nausea, progressive weakness, dark urine, acholic stools	2 months	Yes – (3 months)	Yes	NR

Study details (region)	Sex	Age (yrs)	Suspected product and dose	Other medicines	Type of liver injury	Symptoms	Onset time	Positive de-challenge*	Hospital-isation	Causality
Melendez-Rosado J., *et al* 2015[58] (United States)	F	42	Pure *Garcinia gummi-gutta* supplement	Paracetamol/ hydrocodone, hydralazine.	NR	Right upper quadrant abdominal pain, nausea.	1 week	Yes (several days)	Yes	NR

NR = not reported; LT = liver transplant; * = positive de-challenge was only considered positive if liver enzyme levels returned to normal (not just decreased).

Table 1 includes key data from 20 liver injury case reports published in the literature involving products that contained *Garcinia gummi-gutta* with no other suspected hepatotoxins reported. Data includes the study details, sex of patient, age of patient, description of the suspected products and dose, any other medicines, type of liver injury, symptoms, onset time, whether there was a positive de-challenge and if so, when this occurred, whether the patient was hospitalised, and the results of causality assessment if this was done. The data has been summarised in the section titled *Published case reports*.

References – Appendix A

[128] AL-Khazraji A., Novikov A., Ahmed M., Singh B., Syed U., Sharma R., Bansal R., Baum J., Aron J., Gurram K., Walfish A. First case of garcinia cambogia (GC)-induced autoimmune hepatitis (AIH). *American Journal of Gastroenterology.* Conference: 2020 Annual Scientific Meeting of the American College of Gastroenterology, ACG 2020. Nashville, TN United States. 115(SUPPL) (pp S1368-S1369), 2020.

[129] Yousaf MN, Chaudhary FS, Hodanazari SM, Sittambalam CD. Hepatotoxicity associated with Garcinia cambogia: A case report. World Journal of Hepatology. 11(11):735-742, 2019.

[130] Kothadia JP, Kaminski M, Samant H, and Olivera-Martinez M (2018). Hepatotoxicity associated with use of the weight loss supplement *Garcinia cambogia*: a case report and review of the literature. *Case Reports in Hepatology*. Article ID 6483605. https://doi.org/10.1155/2018/6483605

[131] Cavaciocchi L., Bertoni M., Guarducci L., Lotti P., Risaliti F., Di Natale M.E. Acute liver failure following food supplements: An escalating warning for clinicians. *Italian Journal of Medicine.* Conference: 21st Congresso Nazionale della Societa Scientifica FADOI. Roma Italy. 01 May 2016:10 (Supplement 2): 23 (Conference abstract only).

Appendix B – review of possible confounders

The TGA's review of literature cases involving *Garcinia gummi-gutta* with no other suspected hepatotoxins identified some possible confounding factors, although only one of these was reported by study authors as having a suspected causal role[55]. Our review concluded that none were expected to contribute to the reported liver injuries, including the one case where authors reported that contaminants may have played a possible contributory role.

For this one case, the authors reported that results of analysis of the suspected medicine found high levels of thallium (4.21 mg/kg), cadmium (16.64 mg/kg), chromium (2.84 mg/kg), vanadium (1.86 mg/kg), barium (7.73 mg/kg) and lead (1.57 mg/kg) as well as traces of ethylhydrazine. None of these components were disclosed on the packaging. Authors considered that chromium, cadmium, barium, thallium, vanadium and hydrazine derivatives could all play a contributory role in liver injury. However, comparison of the levels detected against permitted daily exposure (PDE) limits specified in the ICH guideline Q3D (R2) on elemental impurities[132] found all levels to be below oral PDEs except cadmium and thallium (see Table 2 below). This was based on an estimated weight of each Safe Lean capsule as 1 gram, based on the quantity of reported active ingredients (950 mg), with 2 capsules per day consumed as reported in the case study.

Table 2 – Elemental impurities detected in Safe Lean – comparison with ICH Q3D

Elemental Impurity	Amount detected (mg/kg = mcg/g)	ICH Q3D oral conc. limit up to 10 g/day (mcg/g)	ICH Q3D oral PDE (mcg/day)	Estimated exposure from 2 g Safe Lean (mcg/day)
Cadmium	16.64	0.5	5	33.3 (6.6× PDE)
Lead	1.57	0.5	5	3.1
Thallium	4.21	0.8	8	8.4 (1.05× PDE)
Vanadium	1.86	10	100	3.7
Barium	7.73	140	1400	15.5
Chromium	2.84	1100	11,000	5.7

Table 2 shows elemental impurities detected in Safe Lean capsules compared with ICH Q3D limits, based on an estimated exposure of 2 grams per day of Safe Lean. The table shows the amount detected in red text for cadmium and thallium which exceeded PDE limits. However, exposure to these levels for 1 month is not expected to lead to liver injury, further discussed in the body of text.

According to ICH Q3D, sensitive endpoints to oral exposure to cadmium are skeletal and renal effects. The renal toxicity endpoint was used to establish the oral PDE for cadmium and was based on the minimum risk level[xiv] (MRL) of 0.1 mcg/kg for chronic oral exposure as recommended by the Agency for Toxic Substances and Disease Registry (ATSDR). However, the oral MRL for cadmium for intermediate exposure (15-364 days) established by ATSDR[133] is 0.5mcg/kg/day which equates to 25 mcg in a 50 kg adult, with kidneys being the most sensitive organ to cadmium toxicity. Therefore, oral exposure to 33.3 mcg/day cadmium for 1 month is not expected to result in liver abnormalities, particularly in the absence of renal effects.

Similarly for thallium, the most sensitive target of toxicity from oral exposure appears to be the skin, particularly the hair follicles. Exposure to an additional 0.4 mcg/day above the PDE (which is based on a lifetime/chronic exposure) for 1 month is not expected to result in liver abnormalities.

The only mention of ethylhydrazine by study authors was that traces were detected, and that the presence of hydrazine derivatives may have exacerbated the severe hepatitis seen in the patient.

[xiv] The MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure.

Therefore, no exposure value could be estimated. Further, scientific literature on liver toxicity due to ethylhydrazine could not be readily located. Therefore, we consider it unlikely that trace amounts were causative in this case.

Paracetamol use was noted in another case[58], however authors noted that the prescribed dose had not been exceeded, and that other causes of liver injury were excluded including paracetamol levels which were found to be within the normal range. Authors did not comment on possible causative role of hydralazine in this case, which has been assigned a likelihood score of A in the LiverTox entry for hydralazine (well established cause of clinically apparent liver injury). Both short (2 to 6 weeks) and long (2 months to more than a year) latency periods have been described. In this case there was no mention that hydralazine, that was taken for hypertension, was discontinued. The positive de-challenge with return to normal of liver enzymes four months after discontinuing the *Garcinia gummi-gutta* supplement, as well as the authors comments that the diagnosis of acute hepatitis secondary to *Garcinia gummi-gutta* was very likely, supports that hydralazine was not a suspected medicine in this case. Nevertheless, we note that this case did not report a RUCAM causality assessment score therefore it is not considered a pivotal case, but still contributes to the body evidence that supports the safety signal.

One case[56] reported concomitant use of enalapril, which is associated with rare cases of liver injury, according to LiverTox. However, there was no cessation of treatment reported, rather authors commented that levels of total bilirubin spontaneously declined after the cessation of the weight loss supplement, and that 'symptoms and liver function tests rapidly improved without the need of therapies'. Further this case reported a RUCAM score of 6 (probable). Assessment using RUCAM takes into account concomitant medicines. Therefore, it appears appropriate that enalapril was not considered a suspected medicine by study authors in this case.

Two other cases reported that chromium was present in the suspected formulations, one reported 100mg mcg per day for 1 month[56], the other reported 200 mcg per day for approximately 25 days[50]. Chromium from dietary supplements is expected to be in the trivalent form, which is not documented to adversely effect the liver based on toxicity studies in animals[134]. Furthermore, the doses taken and duration of use are below minimum risk levels for intermediate oral exposure to hexavalent chromium[134].

One case referred to concomitant use of Vitamin A[57], which is also associated with liver injury but only at high doses (see LiverTox entry for Vitamin A). In this case authors reported that the patient had normal vitamin A and D levels, ruling out hypervitaminosis as the cause of hepatitis. Therefore, Vitamin A was not considered a suspected ingredient in this case.

One case reported positive hepatitis B virus and Epstein-Barr virus (EBV) blood test results however these findings were consistent with past infection[47]. Blood markers of acute hepatitis B or EBV were not detected. Further, the rapid clinical improvement after discontinuing the *Garcinia gummi-gutta* supplement supports that *Garcinia gummi-gutta* was the suspected agent.

References – Appendix B

[132] Q3D (R2) Step 5 Elemental impurities (europa.eu) [Accessed: 14 June 2024].

[133] Agency for Toxic Substances and Disease Registry (ATSDR) – Toxicological profile for Cadmium. https://www.atsdr.cdc.gov/toxprofiles/tp5.pdf [Accessed: 14 June 2024].

[134] Agency for Toxic Substances and Disease Registry (ATSDR) – Toxicological profile for Chromium. https://www.atsdr.cdc.gov/ToxProfiles/tp7-c2.pdf [Accessed: 29 April 2024].

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Complementary Medicines Evaluation Section	2 August 2024

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

Reference D24-1104257