Technical Alert

TGA NEW Scheduling Consultation:

- **Amygdalin & hydrocyanic acid – increased 'limit' proposal for most herbs**
- **Wild Cherry Bark proposed for Schedule 10 – a ban on all supply**
- **Green Tea (*Camellia sinensis*) caution for oral use in some products**

The TGA has released a public consultation on amending the Poisons Standard regarding amygdalin and hydrocyanic acid, including Wild Cherry Bark closing **Friday 12 April 2024**. There is also a consultation for any *Camellia sinensis* (tea/green tea) that is not on products on the ARTG or in foods. CMA strongly encourages all stakeholders (sponsors, manufacturers, raw material suppliers, practitioners, consumers, etc) whose interests are affected by this consultation to provide a response, which may be given by TGA online survey.

Previously, proposals to amend the Poisons Schedule for green tea extracts and amygdalin and hydrocyanic were referred to TGA expert advisory committees. Consultations on the proposals and interim decisions were also undertaken. Through this feedback, the TGA is now proposing changes that are different to the original scheduling proposals. The new proposals suggested by the TGA are in summary:

- **Amygdalin and hydrocyanic acid, to permit an increased limit cutoff for most herbs** in recognition of the low risk of misuse of preparations containing these substances as a minor component, impurity or contaminant, *however*;
    - **A NEW Schedule 10 entry for Wild Cherry Bark - which specifically bans all supply of this herb.**
- **Cautionary statements for *Camellia sinensis* (green tea) and extracts thereof, for oral use, other than products that are foods or are listed in the ARTG.**

➢ **PLEASE NOTE:** CMA considered that the public consultation proposals published by the TGA on 1 March 2024 were difficult to understand. CMA sought clarification from the TGA: this alert provides further information for CMA stakeholders in relation to the TGA Delegate's newly proposed changes and the intent of their effect.

1. Amygdalin & Hydrocyanic Acid for most herbs; S10 for Wild Cherry Bark

Clarification of TGA's proposal

The TGA consultation page states the consultation is in relation to a proposal to: '*Amend the scheduling for amygdalin and hydrocyanic acid to exempt these substances when present as a component of Wild Cherry Bark.*' The TGA have clarified this statement relates to the previous proposal outlined in the original application for amygdalin and hydrocyanic acid (**HCN**) consulted in Apr-May 2023; **it is not what the TGA are proposing in the current consultation**.

The current consultation includes a proposal fora Schedule 10 entry with a 10mg/kg limit (exemption) for amygdalin and a Schedule 7 entry for HCN in preparations for therapeutic use. This means that most herbs which may contain very low levels of amygdalin and/or HCN would be permitted for continued supply in therapeutic preparations. This proposal is a higher amount than is currently allowed (amygdalin has no cutoff currently) and so this positively affects over21 ingredients, outlined in Table 1 of this alert. CMA has advocated for a reasonable cutoff applying to medicines, cosmetics, and raw materials and are in support of increased amounts such as those in this proposal.

However, the intent of the newly proposed specific Schedule 10 entry for Wild Cherry Bark for therapeutic use is *not* to exempt Wild Cherry Bark from scheduling in the same way as other substances at a concentration of 10mg/kg of

amygdalin or HCN. Rather, if this proposal proceeds, Wild Cherry Bark as a herb (irrespective of amygdalin and HCN levels) will be classified it as a Schedule 10: substance i.e., **a substance of such danger to health as to warrant prohibition of sale, supply and use. Therefore, this proposal is for a total ban on Wild Cherry Bark for therapeutic use,** and it would remain inaccessible for use by all persons. The sale or supply of Schedule 10 substances is associated with offences under Commonwealth and State/Territory laws.

Practitioner implications

This TGA proposal gives greater certainty to practitioners who prescribe any of the 21 herbs listed in Table 1 of this alert (which does not include Wild Cherry Bark) that the substances are less likely to be scheduled by way of very low amounts of naturally occurring hydrocyanic acid or amygdalin.

However, this TGA proposal also means that Wild Cherry Bark (*Prunus serotina*), whether in complementary medicines available for self-selection by consumers, or in extemporaneously compounded medicines by practitioners (such as herbal extracts), **will not be not permitted under any circumstances**.

Important note: If herbalists, naturopaths, practitioner associations, or healthcare groups advocate that Wild Cherry Bark (or any other ingredient) be allowed to be prescribed or dispensed *only* by healthcare professionals with herbal training, this is essentially representing that the substance belongs in a Schedule of the Poisons Standard (which is inaccessible to those practitioners) because it suggests that the substance is not safe for *general* use. There is no separate pathway within the medicines regulatory and Scheduling framework that allows herbal or naturopathic practitioners to have exclusive access to substances that are not available for general use. The only Scheduling pathways that permit substances to be prescribed by health professionals are those for certain Registered health practitioners, for example, pharmacists (Schedule 3 substances) and medical practitioners (Schedule 4 Prescription Only substances).

Therefore, the representation that an ingredient should be restricted to certain persons means that it is more likely to be restricted to practitioners that do not include herbalists, naturopaths, etc. Through the Scheduling framework, *both* unregistered health professionals and a number of Registered health professionals (such as physiotherapists, chiropractors and osteopaths) can only access substances that are unscheduled (i.e. that are not included at the specified concentration or amount in any Schedule to the Poisons Standard).

CMA's draft position in response to the proposal is outlined below. Herbalists, naturopaths, practitioner associations and healthcare groups are encouraged to consider this information when responding to the consultation.

Practitioners may also wish to consider providing any relevant information in their response to the consultation about their professional experience of the clinical application of Wild Cherry Bark as a traditional medicine; the benefit it has provided to their patients; and the lack of adverse events reported.

TGA PROPOSAL:

Schedule 10 - New Entry

WILD CHERRY BARK for therapeutic use.

Schedule 10 - Amend Entry

AMYGDALIN for therapeutic use **except** in preparations containing 10 mg/kg or less of amygdalin.

Schedule 7 - Amend Entry

HYDROCYANIC ACID, **except**:

(a) when included in Schedule 4;

(b) its salts and derivatives other than cyanides separately specified in this Schedule; or

(c) in preparations containing 10 mg/kg or less of hydrocyanic acid.

The TGA provide that the suggested 10 mg/kg limit for exemption from scheduling for amygdalin and hydrocyanic acid (which will apply to herbs and ingredients that are not otherwise banned) are in recognition of the low risk of misuse of preparations containing these substances as a minor component, impurity or contaminant, particularly in complementary medicines and:

- is considered by the TGA to be sufficiently low to mitigate the risks from toxicity, misuse or diversion to treat unapproved indications; and
- aligns with the general limit for exemption from scheduling that applies to Schedules 1-6 in the Poisons Standard (Part 2, Section 11(d)).

Table 1: Ingredients available to use in Listed medicines that may contain amygdalin or hydrocyanic acid

Botanical name/ ARTG ingredient	Common name(s)
Almond	Almond
Almond oil	Almond oil
Malus domestica	Apple, Domestic apple
Malus sylvestris	Apple, Crab apple, European Crab Apple
Bitter almond oil [*Prunus dulcis* var. *amara*]	Bitter almond oil
Eriobotrya japonica	Loquat, Japanese loquat
Persic oil	Apricot kernel oil or peach kernel oil
Prunus africana	African prune, pygeum
Prunus armeniaca	Apricot
Prunus avium	Sweet cherry
Prunus cerasifera	Cherry plum

Prunus cerasus	Sour Cherry
Prunus domestica	Plum, European plum
Prunus dulcis	Almond, Sweet almond
Prunus humilis	Bush Cherry
Prunus japonica	Japanese bush cherry, Korean Cherry
Prunus laurocerasus	Cherry Laurel, English Laurel
Prunus mume	Japanese Apricot, Japanese Flowering apricot
Prunus persica	Peach, Flowering Peach, Ornamental Peach, Common Peach
Prunus salicina	Japanese Plum, Chinese plum
Prunus spinosa	Sloe, Blackthorn

For Wild Cherry Bark, the proposed ban via the Schedule 10 entry is stated by the TGA to mitigate the risks of misuse of products containing Wild Cherry Bark extract and the potential to deter consumers from seeking medical attention for more serious conditions. The TGA has also provided that the delegate has concerns regarding the high and variable amygdalin (and presumably HCN) content in Wild Cherry Bark. As such, the delegate has suggested its inclusion in Schedule 10, and is seeking further advice from stakeholders.

These concerns are detailed in previous TGA decisions, including the most recent interim decision, which specifically notes:

- increased access to products that containing amygdalin may promote the inappropriate use of amygdalin for the treatment of conditions such as cancer and COVID-19; and
- quality control would be difficult to reliably achieve due to the high variability of amygdalin and hydrocyanic acid content in Wild Cherry Bark.

Based on advice from the Advisory Committee on Medicines and Chemicals Scheduling (ACCM) the delegates interim decision concluded that “industry is not capable at this time to undertake reproducible testing of amygdalin and hydrocyanic acid content in Wild Cherry Bark preparations if a concentration cut-off were implemented in the Poisons Standard” and that:

- Wild Cherry Bark product quality control would be difficult to reliably achieve due to the high variability of amygdalin and hydrocyanic acid content in Wild Cherry Bark.
- A current lack of available hydrocyanic acid testing nationally, and where available, the techniques carry considerable health risk to those conducting the testing, while not being adequately robust or sensitive in their detection.

Responding to the consultation

CMA strongly encourages all interested stakeholders including industry, health professionals and consumers to make a submission to the Scheduling consultation in support of ongoing consumer access to herbal medicines within the remit of appropriate labelling and regulatory controls.

For reference, CMA's *draft* position is included below.

In formulating a response, it is relevant to address the scheduling factors outlined for the different schedules in the Scheduling Policy Framework for Medicines and Chemicals (PDF available on this TGA webpage.)

The consultation closes on **Friday 12 April 2024** and submissions to the public consultation can be made via the online survey available on the Consultation Hub web page. Stakeholders are being asked whether the delegate should amend the Poisons Standard in relation to amygdalin, hydrocyanic acid and Wild Cherry bark; and *Camellia Sinensis* extracts in the manner provided above. The options provided in the online survey for each proposal are:

- SUPPORT: the Poisons Standard should be amended in relation to the proposals as suggested above;
- PARTIAL SUPPORT: the Poisons Standard should be amended in a different way to the suggested entry; or
- DO NOT SUPPORT: the Poisons Standard should not be amended.

Stakeholders also have the ability to provide a text response via the online survey, or upload a PDF submission outlining their response on the assigned page. If submitting a pdf, the text box does not need to be populated.

The TGA have provided that written submissions should:

- include whether or not you support the suggested changes;
- address relevant matters mentioned in section 52E of the *Therapeutic Goods Act 1989*:
    - the risks and benefits of the use of a substance
    - the purposes for which a substance is to be used and the extent of use of a substance
    - the toxicity of a substance
    - the dosage, formulation, labelling, packaging and presentation of a substance
    - the potential for abuse of a substance
    - any other matters necessary to protect public health

Submissions may also include:

- suggested improvements; and/or
- an assessment of how the proposed change will impact you. Specifically, what are the likely benefits or costs to you (these may be financial or non-financial), including your calculations of these costs and benefits, if possible.

Stakeholders are advised to contact the TGA directly if you have difficulty responding, via medicines.scheduling@health.gov.au and include 'Suggested Amendments to the Poisons Standard' in the subject line of the email.

Members may also provide specific feedback on the proposals directly to CMA for consideration and incorporation into an industry response via technical@cmaustralia.org.au, preferred by **Friday 5 April 2024**.

CMA draft position

CMA intends to propose a consistent approach to all permitted herbal ingredients that contain amygdalin and hydrocyanic acid based on the existing evidence base:

- CMA intend to **support** the proposed 10mg/kg limit for hydrocyanic acid.
- CMA intend to **not support** the proposed Schedule 10 entry for Wild Cherry Bark as the same final limits for amygdalin and HCN should apply equally to Wild Cherry Bark, and this substance is not at risk of misuse;
- For amygdalin, CMA are investigating the suitable cutoff level for amygdalin in most herbs and whether 10mg/kg is the most suitable. CMA are further investigating a second risk based limit for amygdalin where additional Scheduling and regulatory controls apply, these may include: a requirement to be on the ARTG, a limited duration of use, an 'adults only' direction for use, a child-resistant closure cap, and any other relevant controls to prevent or suitably minimise any of the stated TGA concerns on possible misuse or quality control.

In support of an industry response and to address these concerns, stakeholders are asked to provide to CMA (technical@cmaustralia.org.au):

- **any specific information and data that demonstrates the availability of safe, robust and reproducible testing methods for amygdalin hydrocyanic acid; and/or**
- **any specific information and data supporting different limit(s) for amygdalin**.

Background

An application was made to amend the Poisons Standard in March 2023 to amend Schedule 10 for amygdalin and Schedule 4 for hydrocyanic acid to exempt these substances from scheduling when present as a component of Wild Cherry Bark, i.e.:

- To amendment to the current entry of AMYGDALIN in Schedule 10, to exempt amygdalin from scheduling when present as a naturally occurring constituent in Wild Cherry Bark (Prunus serotina) at a concentration providing less than 5 mg amygdalin per maximum daily dose; and
- a consequential amendment to the Schedule 4 listing of hydrocyanic acid, because amygdalin can be hydrolysed to hydrocyanic acid (less than 0.3 mg of hydrocyanic acid per MMDR (including the theoretical yield from the complete hydrolysis of any amygdalin present).

This was the third application in as many years relating to the down-scheduling of amygdalin and HCN in various contexts to allow for exemptions for naturally occurring levels of these substances.

In June 2023, the Advisory Committees on Medicines and Chemicals Scheduling considered the application and submissions from a public consultation on the proposed changes.

In October 2023, the Delegate made an interim decision to not amend the existing scheduling of amygdalin and hydrocyanic acid which was followed by a second round of public consultation. After considering all the available information, the Delegate has suggested to amend the Poisons Standard in the manner outlined above.

A timeline of amygdalin scheduling history between 1974 - 2022 can be viewed in CMA's 17 January 2022 Member alert.

Resources

- *Therapeutic Goods (Permissible Ingredients) Determination (No. 1) 2024*
- TGA web page: Scheduling handbook: Guidance for amending the Poisons Standard
- TGA web page: Scheduling policy framework for medicines and chemicals
- **Amygdalin/hydrocyanic acid; Wild Cherry Bark:**
    - TGA Consultation Hub: Public consultation on Camellia sinensis extracts, amygdalin and hydrocyanic acid in the Poisons Standard- Joint ACMS-ACCS NOVEMBER, 2022
    - Proposed amendments to the Poisons Standard – ACMS and Joint ACMSACCS meetings, June 2023 [PDF] – 18 April 2023
    - CMA submission: Public consultation on proposed amendments to the Poisons Standard - Joint ACMS-ACCS, JUNE 2023
    - TGA Notice of interim decisions to amend (or not amend) the current Poisons Standard – 5 Oct 2023
    - CMA [Redacted] submission: Public consultation on interim decisions to amend the Poisons Standard - ACMS, ACCS & Joint ACMS-ACCS JUNE, 2023 – Nov 2023

2. *Camellia sinensis*

TGA PROPOSAL:

Schedule 5 - New Entry

CAMELLIA SINENSIS for oral use **except**:

(a) in products included on the Australian Register of Therapeutic Goods and, where applicable, compliant with the requirements for Camellia sinensis in the current Therapeutic Goods (Permissible Ingredients) Determination [provided in Appendix A of this alert], or

(b) in preparations containing not more than 300 mg of epigallocatechin-3-gallate per maximum recommended daily dose.

Requirements for first aid instructions and warning statements, with a similar intent to those included in the Determination, may also be included in Appendix E and Appendix F of the Poisons Standard.

The TGA provide preparations containing less than the proposed exempt level of epigallocatechin-3-gallate (EGCG) (i.e. 300mg MRDD) are considered sufficiently low risk as to not require control by scheduling.

In their current proposal, the TGA state that:

- "Under the proposed Scheduling changes, preparations containing green tea extract that are not included in the ARTG would require product labels with a CAUTION signal header and associated warning statements"; and

- "as food is exempt from the requirements of the Poisons Standard, the suggested changes would not affect any products regarded as food. The use of *Camellia sinensis* (and extracts thereof) in food is regulated by Food Standards Australia New Zealand (FSANZ), under the Food Standards Code.

However, as green tea products are generally foods (and therefore, not subject to the requirements of the Poisons Standard), or therapeutic goods on the ARTG, CMA sought clarification on which consumer goods are intended to be captured by this proposal. The TGA provided that they hold safety concerns about some classes of consumer goods containing green tea extract e.g. some sports supplements **not** captured by the *Therapeutic Goods (Declared Goods) Order 2019* (therefore, not on the ARTG).

For information on how to respond to the proposal, please see the section above for amygdalin/hydrocyanic acid.

Background

Products containing *Camellia sinensis* (green tea), and more specifically *Camellia sinensis* extracts, have been implicated in cases of liver injury worldwide. Safety concerns have arisen from many published case reports in the literature, including cases in Australia that were reported to the TGA and to other regulators in overseas jurisdictions.

An application was made to amend the Poisons Standard in July 2022 to include *Camellia sinensis* extract in Schedule 2 except when labelled with warnings to take with food and advising consumers to be aware of symptoms of liver injury.

The proposal and public submissions on the proposed changes were considered at a joint meeting of the Advisory Committee on Medicines Scheduling (ACMS) and the Advisory Committee on Chemicals Scheduling (ACCS) in November 2022.

In February 2023, the Delegate made an interim decision to not amend the Poisons Standard in relation to *Camellia sinensis* extracts, and a second round of public consultation on the interim decision was subsequently undertaken.

On 1 December 2023, the TGA amended the Permissible Ingredients Determination to require warning statements for certain listed oral medicines that contain *Camellia sinensis*. These changes are due to commence on 1 March 2024 (see schedule for low-negligible risk changes).

Considering the submissions on the interim decision and the recent changes to the Permissible Ingredients Determination, the Delegate has suggested the above new entry for *Camellia sinensis* in the Poisons Standard.

Resources

Green Tea:

- Proposed amendment referred for scheduling advice to Joint ACMS-ACCS #32: Green Tea extract [PDF] – 1 September 2022
- CMA submission to the Scheduling consultation: Green Tea Extract – 28 Sep 2022
- CMA submission to the TGA consultation: Proposed changes to the Permissible Ingredients Determination - low-negligible risk: Curcuma species/curcumin; Green Tea; Soy-phosphatidylserine enriched ingredients; Kakadu Plum – 14 September 2023
- *Therapeutic Goods (Declared Goods) Order 2019*
- FSANZ web page: Food Standards Code

Appendix A: Permissible Ingredient Determination requirements for *Camillia sinensis*

The requirements for *Camellia sinensis* were recently updated in the Permissible Ingredients Determination, following the annual TGA proposed changes to the Permissible Ingredients Determination: Low-negligible risk changes 2023-24.

The NEW additional specific requirements for *Camellia sinensis* are as follows. Please see the current Permissible Ingredients Determination for all applicable requirements related to *Camellia sinensis*:

When used in oral medicines, the following warning statements are required on the medicine label:

- **'In rare cases, Camellia sinensis may harm the liver. Stop use and see a doctor if you have yellowing skin/eyes, or unusual: fatigue, nausea, appetite loss, abdominal pain, dark urine, or itching.'**
- **(FOOD) 'To be taken with food.'**

  unless when:

  (a) the preparation of Camellia sinensis is derived from an aqueous extract and contains 300 mg or less epigallocatechin-3-gallate per maximum recommended daily dose; or

  (b) Camellia sinensis is used in combination with other permitted ingredients as a flavour proprietary excipient formulation.

  The total concentration of flavour proprietary excipient formulations containing Camellia sinensis must not be more than 5% of the total medicine.