Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Notice of final decision to amend (or not amend) the current Poisons Standard

20 February 2025

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Notice of final decision to amend (or not amend) the current Poisons Standard

This web publication constitutes a notice for the purposes of regulation 42ZCZS of the *Therapeutic Goods Regulations 1990* (the **Regulations**). In accordance with regulation 42ZCZS, this notice publishes:

- the decision made by a delegate[1] of the Secretary of the Department of Health and Aged Care (the **Delegate**) pursuant to regulation 42ZCZR
- the reasons for the final decision and
- the date of effect of the decision.

Defined terms

In this notice the following defined terms are used in addition to those above:

- the Therapeutic Goods Act 1989 (Cth) (the **Act**)
- the Scheduling Policy Framework 2018 (the **SPF**)
- the Scheduling handbook, Guidance for amending the Poisons Standard (the **Handbook**) and
- the Therapeutic Goods Administration (the **TGA**).

Note: additional terms are also defined for individual decisions.

Final decision on proposed amendments referred to the Advisory Committees on Medicines and Chemicals Scheduling in joint session (Joint ACMS-ACCS #34, June 2023)

Final decision in relation to amygdalin, hydrocyanic acid and Wild Cherry Bark

Proposal

The Delegate received a proposal to amend of the Poisons Standard to exclude preparations of Wild Cherry Bark from the Schedule 10 entry for amygdalin and the Schedule 4 entry for hydrocyanic acid. Amygdalin and hydrocyanic acid are naturally occurring constituents of Wild Cherry Bark which is used in traditional medicine as an oral treatment for various self-limiting conditions, including cough suppression. The proposal sought an exclusion for Wild Cherry Bark preparations listed on the listed on the Australian Register of Therapeutic Goods (ARTG) subject to additional labelling requirements and the maximum recommended daily dose being less than 5 mg of amygdalin or 0.3 mg of hydrocyanic acid.

Interim decision

The Delegate made an interim decision to not amend the Poisons Standard in relation to amygdalin and hydrocyanic acid which was published on 5 October 2023. Public consultation on the interim decision was undertaken during 5 October to 3 November 2023.

[1] For the purposes of s 52D of the *Therapeutic Goods Act 1989* (Cth).

Additional consultation

An additional consultation seeking further advice from all interested parties on suggested changes to scheduling of amygdalin and hydrocyanic acid was conducted from 1 March 2024 to 12 April 2024. The suggested changes also included an accompanying new entry for Wild Cherry Bark.

Final decision

Pursuant to regulation 42ZCZR of the Regulations, the Delegate has made a final decision to set aside the interim decision and amend the current Poisons Standard in relation to amygdalin, hydrocyanic acid and Wild Cherry Bark as follows:

Wild Cherry Bark

Schedule 10 – New entry

WILD CHERRY BARK for therapeutic use **except** in preparations containing:

(a) 10 mg/kg or less of amygdalin; and

(b) 10 mg/kg or less of hydrocyanic acid.

Amygdalin

Schedule 10 – Amend entry

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

Hydrocyanic acid

Schedule 7 – Amend entry

HYDROCYANIC ACID **except**:

(a) when included in Schedule 4; or

(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.

Schedule 4 – Amend entry

HYDROCYANIC ACID for therapeutic use **except** in preparations containing 10 mg/kg or less of hydrocyanic acid.

Materials considered

In making this final decision, the Delegate considered the following material:

- the application to amend the current Poisons Standard with respect to amygdalin and hydrocyanic acid (the **Application**)
- the 36 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations
- the advice received from the 34th meeting of the Advisory Committees on Medicines and Chemicals Scheduling in joint session (the **Committee**)
- the interim decision relating to amygdalin and hydrocyanic acid and the materials considered as part of the interim decision, as published on 5 October 2023
- the 5 public submissions received in response to the consultation on interim decision under regulation 42ZCZP of the Regulations
- the 12 public submissions received in response to the additional consultation on the scheduling of amygdalin and hydrocyanic acid conducted between 1 March and 12 April 2024
- The Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2024 (PID)

- Food Standards Australia New Zealand's (FSANZ) survey of cyanogenic glycosides in plant-based foods in Australia and New Zealand (2010-13; the **FSANZ Survey**)
- The Safety evaluation of certain food additives and contaminants prepared by the seventy-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (2012; the **JECFA Report**)
- subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance; and (f) any other matters considered necessary to protect public health.
- pursuant to paragraph 52E(2)(a) of the Act, the SPF, and
- the Handbook.

Reasons for the final decision (including findings on material questions of fact)

I have made a final decision to set aside my interim decision to not amend the current Poisons Standard in relation to amygdalin, hydrocyanic acid and Wild Cherry bark, and instead amend the Poisons Standard in the manner set out above. In making my final decision, I have taken into account the material considered in making the interim decision, the 5 public submissions received in response to the interim decision, and the 12 public submissions received in response to the additional consultation on the scheduling of amygdalin and hydrocyanic acid.

Submissions on the interim decision

Of the submissions received in response to the interim decision, 1 submission was in support and 4 were opposed to the interim decision to not amend the Poisons Standard. The submission in support of the interim decision noted the lack of scientific evidence to support the purported indications for use, and the potential for patients to delay seeking appropriate treatment for serious conditions. It also highlighted the risk of cyanide poisoning or toxicity. Four submissions were opposed to the interim decision and recommended implementing a concentration cut-off for amygdalin and hydrocyanic acid as trace impurities of these substances are unlikely to pose a risk of toxicity. Two of these public submissions supported the creation of a concentration cut-off for the scheduling of amygdalin and hydrocyanic acid. One submission provided a proposed concentration cut-off of 10 mg/kg based on the general exemption for Schedule 1 to 6 substances outlined in part 2, division 1, section 11(d) of the Poisons Standard. The submission highlighted that the proposed cut-offs provided a substantial margin of safety relative to the toxic dose. They also noted that liquid extracts of Wild Cherry Bark for extemporaneous compounding and dispensing have previously been available in Australia without any reported adverse events. There is no evidence of misuse or diversion of Wild Cherry Bark preparations. Finally, these submissions noted that any exempt preparation will still be required to listed on the ARTG.

Submissions received through the additional consultation

The additional consultation suggested that preparations containing less than 10 mg/kg of amygdalin or hydrocyanic acid will be exempted from scheduling while Wild Cherry bark for the therapeutic purposes will be listed as a Schedule 10 substance. The additional consultation also suggested the creation of a Schedule 10 entry for Wild Cherry Bark.

Four submissions were received in support of the suggested changes while 5 were partially supportive. Generally, submissions in support or partial support of the suggested changes considered the 10 mg/kg cut-off to be unnecessarily restrictive. A variety of alternative concentration cut-offs were proposed and are discussed below.

Two submissions opposed the suggested changes. These submissions expressed concern that there is insufficient scientific evidence to support the purported indications for use to justify down-scheduling of amygdalin and hydrocyanic acid. They also highlighted the potential risk that use of therapeutics containing Wild Cherry Bark may delay consumers from seeking appropriate medical treatment for

underlying medical conditions. They also noted that, even low concentrations, these preparations pose a risk of cyanide poisoning.

Responses received during the additional consultation also commented on the suggested scheduling of Wild Cherry Bark. One submission indicated partial support of the creation of a Schedule 10 entry for Wild Cherry Bark, whilst 9 submissions indicated they were opposed to the suggested entry. Submissions in opposition claim that there is no evidence that Wild Cherry Bark is a substance of abuse and that it has a history of safe usage in the traditional medicine paradigm. As such, the risks posed by Wild Cherry Bark are broadly consistent with that of amygdalin and hydrocyanic acid, and therefore should not be included in Schedule 10, but subject to the scheduling of amygdalin and hydrocyanic acid, including their exemptions.

Determination of a cut-off for exemptions

Amygdalin is a natural cyanogenic glycoside that can convert to highly toxic hydrocyanic acid in humans. For chronic or long-term effects, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a provisional maximum tolerable daily intake (PMTDI) of 20 µg HCN/kg body weight. For acute effects, an acute reference dose (ARfD) of 80 µg HCN/kg body weight was established by Food Standards Australia New Zealand (FSANZ). However, FSANZ did not establish a tolerable daily intake for humans (for chronic risk assessment purposes) due to a lack of suitable data.

I acknowledge that the public submissions proposed various alternative concentration cut-offs for amygdalin and hydrocyanic acid, all of which would allow greater than the suggested 10 mg/kg concentration cut-off. These submissions estimated a large margin of safety between the proposed concentration cut-off and the PMTDI or acute reference dose (ARfD) for hydrogen cyanide. However, these submissions failed to consider the potential for both therapeutic and dietary consumption of cyanogenic compounds. Dietary intake of cyanogenic glycoside containing foods can be highly variable and can result in inadvertent high exposures. The FSANZ Report[2] noted that for a small number of foods (raw apricot kernels, cassava roots and bread containing linseed) acute dietary exposure alone could exceed the ARfD.

I remain in agreement with the Committee that there is limited evidence to support defining a ‘safe dose’ of these substances, particularly when considering combined therapeutic and dietary consumption which can be highly variable. To account for the high degree of uncertainty, I have decided to implement a 10 mg/kg concentration cut-off for both amygdalin and hydrocyanic acid. This is in alignment with the general exemption for Schedule 1 to 6 substances in the Poisons Standard. These concentration cutoffs are likely to provide an acceptable margin of safety for the therapeutic use of products containing amygdalin and/or hydrocyanic acid, even in scenarios where a person has a high dietary exposure.

Creation of a Schedule 10 entry for Wild Cherry Bark

Wild Cherry Bark contains amygdalin and hydrocyanic acid and is primarily used in traditional medicines as an expectorant, antitussive, astringent, antispasmodic or anti-inflammatory agent to treat self-limiting conditions. However, amygdalin has also been promoted as an anti-cancer agent based on *in vitro* and animal studies but this indication is not supported by clinical evidence.[3] Further, in one instance, one patient with history of pancreatic adenocarcinoma developed severe cyanide toxicity from the ingestion of amygdalin tablets.[4] It is possible that Wild Cherry Bark preparations could be diverted for treatment of serious conditions and delay appropriate medical intervention for the underlying conditions. I remain of the opinion that there is limited evidence of the therapeutic value

[2] FSANZ survey of cyanogenic glycosides in plant-based foods in Australia and New Zealand 2010-13

[3] Spanoudaki M, Stoumpou S, Papadopoulou SK, Karafyllaki D, Solovos E, Papadopoulos K, Giannakoula A, Giaginis C. Amygdalin as a Promising Anticancer Agent: Molecular Mechanisms and Future Perspectives for the Development of New Nanoformulations for Its Delivery. Int J Mol Sci. 2023 Sep 19;24(18):14270. doi: 10.3390/ijms241814270.

[4] Dang T, Nguyen C, Tran PN. Physician Beware: Severe Cyanide Toxicity from Amygdalin Tablets Ingestion. Case Rep Emerg Med. 2017;2017:4289527. doi: 10.1155/2017/4289527.

and efficacy of Wild Cherry Bark and the risk to public health outweighs the limited evidence of therapeutic value.

I also remain in agreement with the Committee that the bioavailability of hydrocyanic acid and amygdalin present in Wild Cherry Bark can vary considerably and that this variability increases the risk of consumer exposure to toxic levels. Product quality control would be difficult to reliably achieve due to the high variability of amygdalin and hydrocyanic acid content in Wild Cherry Bark. Data provided by the applicant noted the variable concentration of both amygdalin (62-242 mg/kg dried bark) and hydrocyanic acid (100-520 mg/kg dried bark) in Wild Cherry Bark. I note that Wild Cherry Bark also contains high levels of prunazine, another cyanogenic glycoside, compared to other raw ingredients where the amygdalin content is lower (such as Batsch fruit oil and apricot kernels) which further increases the risk of exposure to toxic levels of hydrocyanic acid.[5]

Considering the limited therapeutic value of Wild Cherry Bark, its potential toxicity, and the high and variable amygdalin and hydrocyanic acid I have decided to include Wild Cherry Bark in Schedule 10. An exemption for Wild Cherry Bark preparations containing less than 10 mg/kg of amygdalin and hydrocyanic acid will align with the scheduling entries for amygdalin and hydrocyanic acid. The reasons for setting the 10 mg/kg cut-off for amygdalin and hydrocyanic acid are outlined above.

Interaction with the PID

The PID provides the requirements for use of low-risk ingredients in listed medicine formulations including how an ingredient can be used, any quantity restrictions and if any advisory statement label is required. Amygdalin is a mandatory component for 20 ingredients and the concentration of amygdalin in a listed medicine containing any of these ingredients must be zero. All these ingredients except for bitter almond oil and *Malus domestica* also have a limit of 1 µg/kg on hydrocyanic acid content. Introducing a 10 mg/kg cut-off for amygdalin and hydrocyanic acid is less restrictive than PID and does not impact any of the current listed medicines. Classifying Wild Cherry Bark as Schedule 10 with 10 mg/kg cut-offs for amygdalin and hydrocyanic acid also does impact any listed medicines.

As the decision to amend the current Poisons Standard to introduce concentration cut-offs for amygdalin and hydrocyanic, and list Wild Cherry Bark as a Schedule 10 substance with similar cut-offs, does not impact the industry, I have decided on an immediate implementation date of 1 June 2025.

Implementation date

1 June 2025

[5] Telichowska, Kobus-Cisowska and Szulc, (2020) Phytopharmacological Possibilities of Bird Cherry Prunus padus L. and Prunus serotina L. Species and Their Bioactive Phytochemicals, *Nutrients*

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