Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Notice of final decision to not amend the current Poisons Standard in relation to Symphytum spp. (comfrey)

10 October 2023

This document constitutes a notice of a final decision made by a delegate of the Secretary of the Department of the Health and Aged Care (the **Delegate)** under Regulation 42ZCZX in relation to proposed amendments to the current Poisons Standard which were not referred to an expert advisory committee under subdivision 3D.3 of the Therapeutic Goods Regulations 1990 (the Regulations).

The final decision follows an application to amend the Poisons Standard in relation to Symphytum spp. (comfrey) received on 3 March 2021.

Pursuant to r 42ZCZV of the Regulations, the Delegate made the interim decision to not amend the current Poisons Standard. On the 11 May 2023, the Delegate:

a) made an interim decision on the application having regard to the information provided by the applicant.
b) provided the applicant a written notice setting out the interim decision and the reasons for the decision, and advised that they may, within the period specified in the notice (not being less than 10 business days after the date of the notice), make a written submission to the Delegate about the interim decisions.

A response to the interim decision was received from the applicant on 23 May 2023. After considering this response, the Delegate is making their final decisions to confirm their interim decision in relation to Symphytum spp. (comfrey) in accordance with r 42ZCZW of the Regulations. A notice of the final decision was provided to the applicant on 4 August 2023.

In accordance with r 42ZCZX of the Regulations, this notice provides a publication of the Delegate's decision, and the reasons for the decision.

Background

Current Scheduling

Schedule 10

SYMPHYTUM spp. (Comfrey) in preparations for human or animal use **except** when in Schedule 5

Schedule 5

SYMPHYTUM spp. (Comfrey) for dermal therapeutic or dermal cosmetic use.

Appendix F

31	WARNING – Do not use on face or on anal or genital areas except on doctor's advice.
32	This preparation should be part of an overall treatment plan regularly assessed with your doctor.

Index

SYMPHYTUM spp.
cross reference COMFREY
Schedule 10
Schedule 5
Appendix F, clause 4

Alternative names

Symphytum spp., boneset, knitbone, black wort, wall wort, and slippery root

Proposal

An applicant proposed that the Poisons Standard be amended 'to allow comfrey to be accepted as a safe food, being 0.9% alkaloid' (the **Proposal**).

Final Decision

Pursuant to r 42ZCZX of the Regulations, the Delegate has made a final decision to not amend the current Poisons Standard in relation to *Symphytum spp*. (comfrey). The detailed reasons for the decision are provided within.

Materials considered

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

- the application to amend the current Poisons Standard with respect to comfrey (the **Application**).
- subsection 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (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 (f) any other matters considered necessary to protect public health.
- the scheduling history for comfrey, whereby comfrey was first considered by the Poisons Schedule Standing Committee in 1978 and again in 1983; by the Drugs and Poisons Scheduling Committee in 1990, 1991, and 1992, and by the National Drugs and Poisons Scheduling Committee in 1988. The wording of the scheduling entries for comfrey have been considered as recently as 2016.
- publications as cited throughout the reasons for the interim decision, which was provided to the applicant for response on 11 May 2023
- the applicant's response to the interim decision, received on 23 May 2023.
- the Scheduling Policy Framework 2018 (the **SPF**), and
- the Scheduling handbook: Guidance for amending the Poisons Standard (the **Handbook**).

Reasons for the interim and final decisions (including findings on material questions of fact)

Interim decision reasons

I have made an interim decision not to amend the current Poisons Standard (the **Standard**) in relation to *Symphytum spp.* (comfrey). The basis of my decision is that the substance is already exempt from scheduling when used as a food. In addition, comfrey meets the scheduling factors for inclusion in Schedule 10 for human use as outlined in the SPF. The risks of the substance from its inclusion in any schedule other than Schedule 10 for oral use in humans are unacceptable and substantially outweigh any potential benefits, for which there is a paucity of evidence. The detailed reasons for my decision follow.

On its face, the Proposal seeks to 'allow comfrey as a safe food, being 0.9% alkaloid'. However, Appendix A of the Standard provides that food, except food additives before incorporation into food or when used as a means for administering a poison for therapeutic use, is exempt from scheduling. Therefore, there would be no purpose in amending the Standard as sought on the face of the Proposal. I note that the Food Standard Code includes comfrey (as *Symphytum asperum, Symphytum officinale,* and *Symphytum x uplandicum)* in Schedule 23 as a prohibited plant.

Considering the application as a whole, I have formed the view that the purpose of the application may in effect be to permit access to preparations containing comfrey for human use that are not food, namely therapeutic goods (medicines) for oral use for a range of indications, access to which is currently prohibited by the entry for comfrey in Schedule 10. I have reached this view by virtue of the reference in the application to a variety of claims (the **comfrey claims**):

> The healing properties of Comfrey is wide, heals sprains, bruises, burns, joint inflammation knits bones, skin repairer [allantoin], relieves pain (prosmarinic acid), fights cancer. Orally used to treat ulcers, colitis and diarrhea. Internal consumption is safe as it has been for centuries by humans and animals. Comfrey is high in protein, heals damaged tissue, cartilage production, muscles and tendons. Stimulates digestion, regulates excess menstral flow, heals bleeding gums and thyroid disorders, reduces glandular fever, lung disorders, lupus, lowers blood pressure, malignant growths, asthma and reduces cancer production.

I am satisfied that these claims fall within the meaning of 'therapeutic use' as defined in s 3 of the Act, which relevantly provides:

> "therapeutic use" means use in or in connection with:
>
> *(a) preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons*; or
>
> *(b) influencing, inhibiting or modifying a physiological process in persons*; or
>
> (c) testing the susceptibility of persons to a disease or ailment; or
>
> (d) influencing, controlling or preventing conception in persons; or
>
> (e) testing for pregnancy in persons; or
>
> (f) the replacement or modification of parts of the anatomy in persons.[1]

In section 3 of the Act, the definition of 'therapeutic goods' relevantly provides that these are goods:

> (a) that are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be:
>
> (i) for therapeutic use;
>
> …
>
> but does not include:
>
> …
>
> (e) goods (other than goods declared to be therapeutic goods under an order in force under section 7) for which there is a standard (within the meaning of subsection 4(1) of the *Food Standards Australia New Zealand Act 1991*); or
>
> (f) goods (other than goods declared to be therapeutic goods under an order in force under section 7) which, in Australia or New Zealand, have a tradition of use as foods for humans in the form in which they are presented;

This means that goods that are represented or are likely to be taken to be for any of the comfrey claims would, if they do not fall within the exclusions within paragraphs (e) and (f) of the definition of 'therapeutic good', not be a food for the purpose of Appendix A of the Standard. As a result, they would be within scope of the entry for comfrey in Schedule 10 of the Standard, having the status as therapeutic goods.

[1] Emphasis added.

On this basis, I have considered whether the Standard should be amended to permit oral therapeutic use of comfrey by amending its Schedule 10 entry.

The applicant has provided very limited information to support an assessment according to the criteria I am required to consider in subsection 52E of the Act and the SPF in deciding whether to amend the scheduling of comfrey in the Standard. This is despite requests for further information.

Nevertheless, I have considered the criteria under s 52E of the Act, and have given particular weight to the risks and benefits to the public, the uses of the substance, and the toxicity of the substance pursuant to paragraphs (a), (b) and (c) of s 52E(1) of the Act.

I have considered the work by Dr MacAlister,[2] and Dr Mattock[3,4] as referred to in the application. It is important to note that the report by MacAlister was published in 1936 and consist of various clinical observations, rather than controlled scientific experiments or trials. Similarly, the reports by Mattock were published in 1968 and 1971, and do not disprove the hepatotoxic effects of pyrrolizidine alkaloids within comfrey.

Reflecting on the scheduling history of the substance, the Poisons Schedule Standing Committee (PSSC) considered preliminary evidence in May 1978 demonstrating the toxicity of comfrey, and again in November 1983, the PSSC noted evidence that comfrey contained a carcinogenic alkaloid shown to produce a cumulative toxic effect. It was only from the mid-1980s that publications attributing severe adverse effects, such as acute sinusoidal obstruction syndrome, hepatic injury, and hepatic carcinoma, were published in relation to comfrey and the pyrrolizidine alkaloids within.

In 1990 the Drugs and Poisons Scheduling Committee (DPSC) considered further data on the hazards associated with the presence of pyrrolizidine alkaloids in a number of herbs and deemed these of such severity as to warrant complete prohibition for therapeutic use.

I note that in July 2001 the United States Food and Drug Administration advised dietary supplement manufacturers to remove comfrey products from the market due to health concerns associated with pyrrolizidine alkaloids.[5] I therefore consider that the limited evidence provided to support the claims made by the applicant is outdated and has been superseded by more recent findings.

I now turn to the systemic review by Avila *et al*. demonstrating the potential toxic effects of comfrey consumption in humans.[6] Case reports involving comfrey published between 1985 and 2013 reported adverse events of hepatic veno-occlusive disease and pulmonary arterial hypertension. In some cases, adverse impacts were fatal, and/or detected *in utero*. Literature demonstrates that the metabolic activation of pyrrolizidine alkaloids forms DNA adducts in the liver,[7,8] and is associated with hepatic carcinoma in rodent studies.[9] The lungs may also be affected leading to pulmonary arterial hypertension.[10,11]

On the balance of this evidence before me showing significant hepatotoxicity of comfrey by oral administration, I am not satisfied that access to comfrey for oral use is appropriate, given the toxicity

[2] COMFREY - AN INVESTIGATION CONCERNING AN ANCIENT MEDICINAL REMEDY CJ MACALISTER MD1936.pdf (seleneriverpress.com)

[3] Hepatotoxic Effects due to Pyrrolizidine Alkaloid N-Oxides: Xenobiotica: Vol 1, No 4-5 (tandfonline.com)

[4] https://www.nature.com/articles/217723a0

[5] FDA archive http://wayback.archive-it.org/7993/20171114115012/https://www.fda.gov/Food/RecallsOutbreaksEmergencies/SafetyAlertsAdvisories/ucm111219.htm

[6] https://www.sciencedirect.com/science/article/pii/S0367326X20301015?via%3Dihub

[7] P.P. Fu, Q. Xia, G. Lin, M.W. Chou. Pyrrolizidine alkaloids—genotoxicity, metabolism enzymes, metabolic activation, and mechanisms Drug Metab. Rev., 36 (2004), pp. 1-55, 10.1081/dmr-120028426

[8] R. Moreira, D. Pereira, P. Valentão, P. Andrade. Pyrrolizidine alkaloids: chemistry, pharmacology, toxicology and food safety. Int. J. Mol. Sci., 19 (6) (2018), 10.3390/ijms19061668

[9] B. Dusemund, et al. Risk assessment of pyrrolizidine alkaloids in food of plant and animal origin Food Chem. Toxicol., 115 (2018), pp. 63-72

[10] J.A. Edgar, S.M. Colegate, M. Boppré, R.J. Molyneux. Pyrrolizidine alkaloids in food: A spectrum of potential health consequences Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess., 28 (3) (2011), pp. 308-324

[11] J.A. Edgar, R.J. Molyneux, S.M. Colegate. Pyrrolizidine alkaloids: potential role in the etiology of cancers, pulmonary hypertension, congenital anomalies, and liver disease. Chem. Res. Toxicol., 28 (1) (2015), pp. 4-20

and risks, in particular the hazards of the pyrrolizidine alkaloids. Moreover, the abovementioned information is consistent with the scheduling factors in the SPF for a Schedule 10 substance:

> The substance poses such a high public health risk, including potential risk, that its sale, supply and/or use require very strict control, with access generally being prohibited. The potential health risk does not include potential for abuse, diversion into illicit products or other factors which would warrant inclusion in Schedule 9; and
>
> The substance has a public health risk that substantially outweighs the benefit to the extent that no other Schedule would provide appropriate public access to any proposed or known products. The serious public health risk may be restricted to particular uses.

Turning to the benefits of comfrey for human use, there is minimal evidence of public health benefit. Having considered paragraph 52E(1)(a) and (b) of the Act, I acknowledge the historical use of comfrey as a healing herb, attributed to various components, including allantoin, phenolics, glycopeptides, polysaccharides and pyrrolizidine alkaloids. *In vitro* and *in vivo* animal data demonstrate antioxidant, anti-inflammatory and anti-microbial activity likely to contribute to therapeutic benefit from the use of comfrey.[12,13,14]

I note that three topical creams with comfrey as an active ingredient, being Schedule 5 preparations, are currently included on Australian Register of Therapeutic Goods (ARTG) for relief of minor pain or swelling associated with bruises and mild joint sprains, and to promote suppuration of boils and abscesses, and gangrenous and ill-conditioned ulcers. The indications for these products correspond to some of the indications within the comfrey claims, and they bear the signal headers and labelled warning statements appropriate for Schedule 5.

In contrast, in relation to whether comfrey for oral consumption should be excluded from Schedule 10 in the Standard, it is unclear to me to which of the comfrey claims this should apply, and insufficient evidence of the efficacy of comfrey for such claims—and thus the likelihood of the benefits being realised—has been provided or is otherwise before me. I note particularly that, with reference to paragraph 52E(1)(b) and (d) of the Act, no information has been provided in the application to support the 0.9% cut-off of alkaloid in preparations of comfrey for oral therapeutic use. I reiterate that the application contained no reference to published literature, other than mentioning the names of the two authors referred to above. I therefore conclude that such benefits of comfrey when used for oral use, or a certain concentration of alkaloid, are limited and unsupported, and do not justify amendment the Standard.

In summary, I am satisfied that the risks from oral use of comfrey substantially outweigh the potential benefits of the substance, for which limited evidence or data has been provided, to support the Proposal. Moreover, on the basis of the evidence about toxicity and safety before me and noting the paucity of evidence provided in the application, the risks are consistent with the scheduling factors for a Schedule 10 substance in the Standard. Consequently, I have decided not to amend the Standard in relation to comfrey.

Final decision reasons

I have made a final decision to confirm my interim decision to not amend the Standard in relation to *Symphytum spp*. (comfrey). I have considered the applicant's response to my interim decision to not amend the Standard, which was received on 23 May 2023. I have considered the claims made by the applicant in their response regarding the apparent safety associated with the oral administration of comfrey. These claims include statements from the World Health Organisation (WHO), the Library of Natural Medicine, and the Multidisciplinary Digital Publishing Institute (MDPI) indicating safety associated with the oral consumption of comfrey. However, the applicant has provided insufficient

[12] A Symphytum officinale root extract exerts anti-inflammatory properties by affecting two distinct steps of NF-κB signaling. J. Seigner, et al. Front. Pharmacol., 10 (2019)

[13] Is comfrey root more than toxic pyrrolizidine alkaloids? Salvianolic acids among antioxidant polyphnols in comfrey (Symphytum officinale L.) roots A. Trifan et al. Food Chem. Toxicol., 112 (2018), pp. 178-187

[14] Proliferative and antioxidant activity of Symphytum officinale root extract. I. Sowa, M. Wójciak-Kosior. Natural Product Research, 32 (5) (2018), pp. 605-609

supporting evidence to substantiate these claims. I consider the weight of evidence of the toxicity of the pyrrolizidine alkaloids present within comfrey, as detailed in my interim decision, to be more than sufficient to justify my decision to not change the access to this substance at this time.

The content of pyrrolizidine alkaloids within comfrey is disputed by the applicant, and I acknowledge the natural variability that can occur within comfrey based on environmental factors. However, there is no evidence provided in the application, interim decision response, or otherwise to suggest that the lower levels of pyrrolizidine alkaloids content in comfrey are safe for oral administration.

My decision is further supported by the lack of evidence regarding any public health benefit to be derived from the oral consumption of comfrey. While anecdotal reports of the historical use of comfrey in this manner have been cited by the applicant as evidence to support the proposal, there exists a distinct lack of clinical data demonstrating therapeutic benefit from the oral consumption of the herb. I also reiterate that the use of comfrey as a food is not addressed in the Standard, and is instead governed by the Food Standards Code, which lists three species of comfrey in Schedule 23 as prohibited plants.

I note that comfrey for oral use remains unapproved in many countries, including the United States and many members of the European Union. I remain satisfied that the risks from oral use of comfrey substantially outweigh the potential benefits of the substance, for which limited evidence or data has been provided to support the Proposal. Therefore, I have decided to confirm my interim decision to not amend the Standard in relation to comfrey.

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