Australian Government

Department of Health and Ageing

Application for exclusion of amygdalin as a natural component from Schedule 10 for human therapeutic use

12 March 2021

Chinese Medicine Industry Council of Australia Ltd
Suite 604, 309 Pitt Street
Sydney NSW 2000

CONTENTS

MEDICINE DETAILS

1	Name of medicine requiring scheduling	Chinese herbal medicines
2	Active ingredient name(s)	Amygdalin as a natural component of herbal ingredients used in traditional Chinese medicine
3	Dosage form	Various oral dosage forms (e.g. capsule, tablet, liquid)
4	Container type	Various container types (e.g. bottle, blister pack)
5	Indications of medicine	Indications consistent with traditional Chinese medicine practice
6	Current poisons schedule (if applicable)	Schedule 10 AMYGDALIN for therapeutic use.
7A	Proposed poisons schedule amygdalin	Schedule 10 AMYGDALIN for therapeutic use except when included as a natural component in traditional Chinese medicines for oral use in adults with a maximum daily dose not exceeding 5 mg of amygdalin.
7B	Proposed poisons schedule hydrocyanic acid	Schedule 4 HYDROCYANIC ACID except when present as a natural component in traditional Chinese medicines for oral use in adults with a maximum daily dose not exceeding 0.3 mg of hydrocyanic acid.

Applicant's Details

1	Applicant's [*Sponsor's*] name	Chinese Medicine Industry Council of Australia Ltd (CMIC)
2	Applicant's [*Sponsor's*] Business Address	Suite 604, 309 Pitt Street Sydney NSW 2000
3	Business name (if applicable)	

4	Date of submission	12 March 2021
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Declaration

I, Dr Max Ma, on behalf of the Chinese Medicine Industry Council of Australia Ltd:

- declare that the information provided in this application is true and current;
- undertake to treat as confidential information, and not publicly disclose, the notice of interim decision in respect of this application, until (if relevant i.e. following referral to an expert advisory committee) the interim decision is published pursuant to subsection 42ZCZP of the Therapeutic Goods Regulations 1990, or the final decision is published pursuant to subsection 42ZCZS of the Therapeutic Goods Regulations 1990.

Dr Max Ma
President, Chinese Medicine Industry Council of Australia

12 March 2021

PART 1 - Summary of the Application

Background

An initial application to amend the scheduling of amygdalin and hydrocyanic acid to meet the needs of Australian Chinese medicine practitioners and consumers was not supported at the November meeting of the ACMS.

Major concerns were the potential for illicit use in cancer therapy (both medically prescribed and by consumers); accidental poisoning (especially in children) or deliberate self-poisonings and chronic overuse of products containing amygdalin.

This application addresses these concerns by limiting the use of amygdalin to products for therapeutic use when included as a natural component in traditional Chinese medicines for oral use in adults with a maximum daily dose not exceeding 5 mg of amygdalin.

An associated change would limit the use of hydrocyanic acid to products for therapeutic use when present as a natural component in traditional Chinese medicines for oral use in adults with a maximum daily dose not exceeding 0.3 mg of hydrocyanic acid. This change is necessary to prevent low dose amygdalin products being caught by schedule 4 by virtue of their hydrocyanic acid content.

This application is largely based on the application considered at ACMS #32 (November 2020) except that the proposal for a schedule 4 entry for amygdalin at doses exceeding 5 mg of amygdalin has been withdrawn and additional justification included in Part 2.

Proposed Scheduling / Rescheduling or other Change to the poisons standard

Suggested scheduling

Amending words in red and underlined

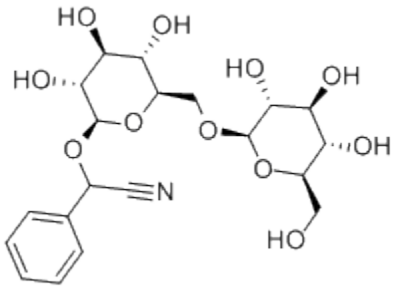
Schedule 10
AMYGDALIN for therapeutic use except as a natural component in traditional Chinese medicines for oral use in adults with a maximum daily dose not exceeding 5 mg of amygdalin.

Schedule 4
HYDROCYANIC ACID for therapeutic use except as a natural component in traditional Chinese medicines for oral use in adults with a maximum daily dose not exceeding 0.3 mg of hydrocyanic acid.

Substance summary

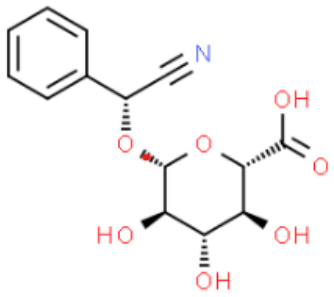
Amygdalin

Amygdalin (D-mandelonitrile-β-D-glucoside-6-β-glucoside; mandelonitrile-β-gentiobioside) is a cyanogenic glycoside found naturally in bitter almonds, apricot kernels and seeds of other plants in the *Prunus* genus. The structure of amygdalin is displayed below.



Chemical structure of amygdalin

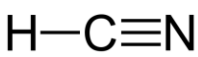
Amygdalin is also referred to as Vitamin B17, although it is not a vitamin, and often as laetrile, although laetrile and amygdalin are not identical, since laetrile is actually a semi-synthetic form of amygdalin, with the chemical composition D -mandelonitrile- β-glucuronide.



Chemical structure of laetrile

Amygdalin for therapeutic use is currently included in Schedule 10 of the Poisons Standard (substances of such danger to health as to warrant prohibition of sale, supply and use).

Hydrogen cyanide (hydrocyanic acid, formonitrile, Prussic acid) (HCN) is a colourless to blue liquid, which exists as a gas at temperatures above approximately 26°C. HCN is a simple molecule with the following structure:



Chemical structure of hydrogen cyanide

HCN has a range of industrial uses, particularly as a fumigant, and in the production of industrial chemicals. The principal natural sources of HCN are cyanogenic glycosides (including amygdalin) found in many plants including cassava, sorghum, lima beans and members of the *Prunus* species.

Hydrogen cyanide for therapeutic use is currently included in Schedule 4 of the SUSMP, with non-therapeutic use included in Schedule 7.

Overview

This application is founded in the theory and practice of Traditional Chinese Medicine (TCM) which is a medical system based on theory, pathology, diagnosis, treatment and herbal pharmacology principles that differ from those of orthodox medicine or Western naturopathy and has developed from knowledge accumulated through clinical observation and treatment over several millennia. In this instance it is based on a scientific review by independent toxicologist Dr Susan James (included in its entirety in Part 3) and a further review by an independent expert engaged by the TGA. Both experts agreed that "on the basis of animal studies, and as assessed by a wide range of regulatory and expert committees, oral intake of 5 to 20 µg/kg/d cyanide (equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult) is considered to present no appreciable risk to consumers".

Amygdalin is a cyanogenic glycoside found naturally in many plants including cassava, sorghum, lima beans, bitter almonds, apricot kernels and seeds of other plants in the *Prunus* genus. Food Safety Australia New Zealand (FSANZ) has set a limit of 10 mg HCN/kg in ready-to-eat cassava chips (FSANZ 2008, 2016). Limits of HCN in other foods and drinks (FSANZ 2015) include:

- 25 mg/kg in confectionery
- 5 mg/kg in stone fruit juices
- 50 mg/kg in marzipan
- 1 mg/kg per 1% alcohol in alcoholic beverages.

By way of comparison, 100 g of confectionary can legally contain up to 2.5 mg of HCN (see above). On a molecular basis this is equivalent to 42.5 mg of amygdalin, more than 8 times the

proposed maximum adult daily dose in unscheduled traditional Chinese medicines. Similarly one standard drink (100 mL) of red wine (13% alcohol) could legally contain up to 22 mg of amygdalin, more than 4 times the proposed daily maximum adult daily dose in unscheduled traditional Chinese medicines.

It is recognised that Maximum Levels (ML) in foods are considered in relation to Acute Reference Doses (ARfD), however other factors are also relevant. The foods listed above are consumed on a regular ongoing basis by a significant proportion of the Australian population. Traditional Chinese medicines, on the other hand, are used to treat disease according to their diagnosed syndrome pattern, when the symptoms are gone the medication must stop ('Zhong Bing Ji Zhi' in Chinese).

Traditional Chinese medicine (TCM) has an established history in Australia and now accounts for more than 3% of the total use of complementary medicines in Australia (Li 2003). In TCM, herbal substances such as bitter apricot seed (Kuxingren) and peach seed (Taoren) are always used in combination with other traditional Chinese herbs, whether in individual dose forms (e.g. tablets, pills or capsules) or as a collection of raw herbs dispensed by a TCM practitioner. In TCM each herbal ingredient contributes to the safety and efficacy of the combination.

TCM has not used amygdalin-containing natural ingredients to treat cancer in the past, nor will it in the future. This is totally irrelevant to the clinical practice and protocols of Chinese medicine.

Under the current scheduling arrangements, products that contain amygdalin in any quantity cannot be used in therapeutic goods. Sponsors of listed medicines that contain *Kuxingren* for example, must declare that the concentration of amygdalin in the medicine is zero (which is not possible) and that the concentration of hydrocyanic acid in the medicine is no more than one part per billion. This means that formulated TCM products with very low levels of amygdalin that are freely available in other countries are not available to Australian TCM consumers.

The effect of the proposed changes would be to make legitimate TCM products containing very low doses of amygdalin available to Australians via the TGA's 'listing' system (subject to TGA approval). <u>These changes will not affect the scheduling status of products containing amygdalin (or 'laetrile') as a stand-alone ingredient or in a medicine that is not a traditional Chinese medicine for oral use in adults. These products will remain in Schedule 10</u>.

Part 2 – Body of the Application

Background

Current scheduling status

Amygdalin is currently included in Schedule 10. Hydrocyanic acid is currently included in Schedules 4 and 7 and in Appendices F, G and J.

Historical context

The available scheduling history of amygdalin follows[1]:

"In November 1974 the Poisons Schedule (Standing) Committee (PSSC) recommended that a new entry for '*amygdalin including defatted kernals of bitter almonds, apricots and peaches containing amygdalin*' be created in the prohibited list of the Uniform Poisons Standard on the basis of its supply as a new drug for the treatment of cancer (Laetrile).

In May 1975 the PSSC considered evidence provided by the Australian Drug Evaluation Committee which indicated that there was no evidence that amygdalin had any effect against cancer and no evidence of its safety. No apparent action regarding the scheduling of amygdalin was taken by the committee at this time.

In November 1977 the PSSC considered a proposal to amend the scheduling of amygdalin to Schedule 7 to allow compassion use in Victoria in certain cancer patients under very close and strict control and only upon a special request from a physician treating such a person. New toxicity data was examined and determined to be adequate. The committee recommended that in view of the action taken in Victoria to make amygdalin available primarily on compassionate grounds to eliminate the exploitation of cancer patients, the production of amygdalin in Australia under proper supervision, and its distribution under strict controls, as proposed in Victoria, free of charge, should be investigated as a matter of urgency. In making this statement the PSSC in no way implies the admission of efficacy or any therapeutic value of amygdalin. [*Details regarding the wording of the proposed Schedule 7 entry were not provided].*

In August 1986 the Drugs and Poisons Schedule Committee (DPSC) noted that amygdalin was still being imported on an individual patient usage basis despite the opinion that there is no evidence of its efficacy in the treatment of advanced cancer. [The scheduling of amygdalin at this time was noted to be Schedule 7. Available documentation does not explicitly state when the change from prohibited substance to Schedule 7 occurred but we assume this recommendation occurred in November 1977. No information is available regarding the wording of the Schedule 7 nor reasons for its inclusion).

[1] Information in an e-mail from the Medicines Scheduling Secretariat Team to Julie Emery dated 23 November 2017

In August 1992 the Drugs and Poisons Scheduling Committee (DPSSC) recommended the inclusion of amygdalin for therapeutic use in Appendix C of the SUSDP due to its serious toxicity profile and lack of efficacy data.

In November 1999 the National Drugs and Poisons Scheduling Committee (NDPSC) considered a request seeking clarification on whether the Appendix C entry of amygdalin are intended to apply to sweet almond oil, which is obtained from 'sweet almonds' (*Prunis dulcis var. dulcis seed*). The Committee clarified that the SUSDP entry for amygdalin acid does not apply to sweet almond oil.

In February 2000 the NDPSC recommended to the NZ Minister Of Health that amygdalin be moved into Part 1 of the Medicines Regulations.

In February 2005 the NDPSC considered the availability of certain substances for therapeutic use listed in Appendix C of the SUSDP. The committee noted that amygdalin for the treatment of terminal cancers appeared to be the Appendix C substance most often accessed through the Special Access Scheme (SAS) (under Category A notification for "lifethreatening conditions") and agreed that, given the condition for which amygdalin accessed through the SAS was being used, no action to limit its availability should be taken at this time. The committee did express concern however over the apparent contradiction that certain substances which had been included in Appendix C on the grounds that they present such danger to health as to warrant prohibition should be made available for therapeutic use under special circumstances."

Basic chemistry facts

Basic chemistry facts are presented in the 'Substance summary' on pages 7 and 8 above.

Detailed Claims Against the Requirements of the Scheduling Policy framework

PART 2.1A – Scheduling factors in SPF Chapter 3 "CLASSIFICATION OF MEDICINES AND CHEMICALS INTO THE SCHEDULES"

This application proposes amendments to Schedules 10 and 4 of the Poisons Standard. The factors for these schedules and for 'unscheduled' are addressed below.

Schedule 10

The factors for Schedule 10 from the AHMAC Scheduling Policy Framework[2] are copied below in *italics* with bolding retained as in the SPF. Responses to each factor are presented in regular font.

Factors for substances of such danger to health as to warrant prohibition of sale, supply and use (schedule 10):

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.

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.

The Secretary may establish a cut-off from Schedule 10 where the substance no longer meets the factors for inclusion in this Schedule or in any other Schedule in the Poisons Standard.

CMIC agrees that Schedule 10 remains appropriate for amygdalin (including 'laetrile') as a stand-alone ingredient in medicines for therapeutic use. These medicines could attract excessive use by people who have or have had cancer who are seeking alternative treatments. This will not apply to the traditional Chinese medicines that are proposed. These will be low-dose, multi-ingredient, herbal formulations that are specifically presented for use as traditional Chinese medicines.

For deliberate self-poisoning concerns, the maximum daily dose limit of naturally presented 0.3 mg of HCN will prevent such a rare behaviour. According to USA EPA intentional / accidental poisoning case report (ATSDT,COT, 2006) (page 33 of TGA assessor's report), the fatal dose of cyanide in adults range from 0.5 to 3.5mg /kg BW. Based on the lowest dose of 0.5mg/kg, (equiv. to 30mg for 60kg adult) to reach the self- poisoning threshold need to consume 100 times the daily dose of natural products (0.3mg x 100 = 30mg). Natural preparations containing the proposed maximum daily limit of 0.3mg of HCN require a considerable weight of herbal powder. For example, a TCM typical dosage form of water-honey pills would require 60 pills x 3 times = 18 g of pills to attain the 0.3 mg HCN limit. For self-poisoning, a consumer would need to take 1800 g of pills in one time). Such a large volume of natural medicine cannot fit into one's stomach in one time.

[2] https://www.tga.gov.au/book-page/scheduling-factors (accessed 12 June 2020)

For concerns for chronic of overuse of these products, please note that TCM treats diseases based on their diagnosed syndrome pattern. Once the pattern has changed, the prescribed formula must be changed. And once the symptoms have gone the medication must stop (Zhong Bing Ji Zhi in Chinese). In addition, neither amygdalin nor HCN accumulate in the body.

For products containing very low levels of amygdalin and HCN, the proposed limits are well within the safety range based on the independent toxicologist report. In addition, the proposal is only applicable for preparations in TCM. The TCM profession is well regulated under AHPRA for national accreditations and registrations, and its manufactured products are well monitored by the TGA via the Good Manufacturing Practice (GMP), the safety of permissible ingredients, adverse event reporting and the post market review processes. This is totally different from the cases where adults or children accidentally consumed large volume of RAW bitter apricot. Please note that apricot kernels or peach kernels used in Chinese medicine preparations are always pre-processed via cooking and peeling to reduce the HCN toxicity.

CMIC submits that amygdalin and HCN limits as proposed in this application do not meet the factors for Schedule 10 or any other Schedule in the Poisons Standard.

Schedule 4

The application proposes a change to the Schedule 4 entry for hydrocyanic acid. This is to ensure that products which are excluded from Schedule 10 are not inadvertently caught by Schedule 4 on the basis of the very low level of hydrocyanic acid that may be present in finished products by hydrolysis from amygdalin.

Unscheduled

In accordance with the cascading principle, exemption of a particular medicinal preparation to allow supply from general sales outlets (such as supermarkets) means that it does not meet the factors for Schedules 2, 3, 4 or 8. Medicinal preparations exempted from scheduling must be determined to be able to be supplied, with reasonable safety, without any access to health professional advice.

Amygdalin as a natural component in the low doses proposed for exclusion from Schedule 10 in traditional Chinese medicines for oral use in adults has no appreciable safety risk as agreed in the submitted report by toxicologist Dr Susan James and an independent expert report commissioned by the TGA. At these low doses it does not meet the factors for Schedules 2, 3, 4 or 8 and can be used with reasonable safety, without any access to health professional advice.

The term ‘with reasonable safety’ means:

- *The consumer is able to identify and self-manage the condition for which the medicine is intended without health professional input.*

  The classification of these medicines as 'unscheduled' may make them eligible for 'listing' on the Australian Register of Therapeutic Goods (ARTG) subject to TGA agreement to changes to the *Therapeutic Goods (Permissible Ingredients) Determination*[3]. Controls within the listing system will ensure that only indications that do not require health professional input are available for use with these medicines.

  If the medicine cannot be listed it must be 'registered' and will be subject to full evaluation by the TGA. Again, this will ensure that only indications that do not require health professional input are approved for use with these medicines (unless they have a specific exemption from TGA).

- *The risk of the consumer confusing their condition with more serious diseases or conditions is very small.*

  Controls within the listing / registration system will ensure that indications for more serious disease or for conditions that could be confused with more serious disease are not available / approved for use with these medicines.

  The reference in the scheduling delegate's initial decision to indications of amygdalin as "cough and wheezing, profuse sputum, masses, lung abscess and internal abscess" appears to have come from the Chinese Pharmacopoeia (CP) entries for Kuxingren and / or Taoren. References from the CP often use terms that are familiar to TCM practitioners but not in use in Western medicine. In any case, the TGA's 'listing' system will limit indications / claims to those that do not require health professional advice and for which the sponsor holds traditional or scientific evidence of efficacy.

- *The risks to health from the medicine are small and can be managed with packaging and labelling. Risks to be assessed include, but are not limited to, risks from adverse reactions, drug/food interactions and contraindications.*

  Controls within the listing / registration system will ensure that any risks from herbal ingredients that include amygdalin at very low dose are appropriately managed by packaging and labelling (e.g. by mandatory label warnings).

- *The risk of inappropriate use and misuse is negligible.*

[3] https://www.legislation.gov.au/Series/F2020L00666

We are not aware of any reports of inappropriate use or misuse of traditional Chinese medicines. Please see comments under the 'Schedule 10' and 'Unscheduled' headings above.

- *There is little need to take any special precautions in handling.*

  CMIC is not aware of any need *t*o take special precautions in handling traditional Chinese medicines.

- *There is net public health benefit from wider availability for the consumer.*

  We submit that there is a substantial public health benefit from availability of a full range of traditional Chinese medicines to consumers, including those that contain very low doses of amygdalin as a natural component of herbal substances for oral use in adults.

PART 2.1B Criteria Which Must Be Addressed – proposals to change Part 4 of the Poisons Standard – scheduling or rescheduling of substances

(A) Risks and Benefits Associated with the Use of a Substance

Amygdalin is a cyanogenic glycoside found naturally in many plants including cassava, sorghum, lima beans, bitter almonds, apricot kernels and seeds of other plants in the *Prunus* genus. Food Safety Australia New Zealand (FSANZ) has set a limit of 10 mg HCN/kg in ready-to-eat cassava chips (FSANZ 2008, 2016). Limits of HCN in other foods and drinks (FSANZ 2015) include:

- 25 mg/kg in confectionery
- 5 mg/kg in stone fruit juices
- 50 mg/kg in marzipan
- 1 mg/kg per 1% alcohol in alcoholic beverages.

Many traditional Chinese medicines are formulated to include one or more of these plant ingredients, usually in combination with other traditional Chinese herbs. The proposed limitation to TCM use only will ensure that these products are well within established safety margins. For example, 100 g of confectionery could legally contain up to 2.5 mg of HCN. On a molecular basis this is equivalent to 42.5 mg of amygdalin, more than 8 times the proposed maximum adult daily dose of amygdalin in unscheduled traditional Chinese medicines. Similarly, one standard drink (100 mL) of red wine (13% alcohol) could legally contain up to 22 mg of amygdalin, more than 4 times the proposed maximum adult daily dose for unscheduled traditional Chinese medicines.

It is recognised that Maximum Levels (ML) in foods are considered in relation to Acute Reference Doses (ARfD), however other factors are also relevant. The foods listed above are consumed on a regular and ongoing basis by a significant proportion of the Australian population including various groups of consumers such as children, elderliness, pregnant women, people with medical conditions etc. Traditional Chinese medicines, on the other hand, are used to treat disease according to their diagnosed syndrome pattern, when the symptoms are gone the medication must stop (‘Zhong Bing Ji Zhi’ in Chinese).

The effect of the proposed changes would be to make legitimate TCM products containing very low doses of amygdalin available to Australians via the TGA’s ‘listing’ system (subject to TGA approval). These changes will not affect the scheduling status of products containing amygdalin (or ‘laetrile’) as a stand-alone ingredient or in a medicine that is not a traditional Chinese medicine for oral use in adults. These products will remain in Schedule 10.

CMIC accepts that hydrocyanic acid can be present at low levels as a natural component of amygdalin in herbal materials used in TCM and that its toxicity can vary with a number of factors including the preparation of the herb, the status of gut flora, the nutritional status of

the individual and concomitant administration of other nutrients such as vitamins. It is also recognised that toxicity is evident at doses over 2 g per day and that fatalities have occurred at doses of 0.5 g to 2.5 g, particularly in children. However, reports by independent toxicologist Dr Susan James (Part 3) and an independent expert engaged by the TGA agreed that "on the basis of animal studies, and as assessed by a wide range of regulatory and expert committees, oral intake of 5 to 20 µg/kg bw/d/ cyanide (equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult) is considered to present no appreciable risk to consumers".

In terms of benefits, the availability of a full range of legitimate TGA-listed TCM products, including those containing low doses of amygdalin, would be greatly valued by the Chinese community in Australia. As stated in the Overview, TCM is a medical system based on theory, pathology, diagnosis, treatment and herbal pharmacology principles that differ from those of orthodox medicine or Western naturopathy. The practice of TCM has developed from knowledge accumulated through clinical observation and treatment over several millennia and has an established history in Australia.

In the 2016 Australian census, 509,555 people (2.2% of the population) reported their country of birth as China with 2.5% of the population speaking Mandarin at home[4]. In March 2020 over 4,500 Chinese medicine practitioners were registered under the AHPRA national registration and accreditation scheme[5]. TCM has expanded rapidly in recent years to the point where Chinese medicines now account for 3.2% of the total use of complementary medicines in Australia (Li G 2003).

(B) The purposes for which a substance is to be used and the extent of use of that substance

Amygdalin is only present in traditional Chinese medicines as a natural component of herbal substances. Some examples of these ingredients follow, showing their titles in the Chinese Pharmacopoeia (CP), with their CP indications (noting that references from the CP often use terms that are familiar to TCM practitioners but not in use in Western medicine). The TGA's 'listing' system will limit indications / claims to those that do not require health professional advice and for which the sponsor holds traditional and / or scientific evidence of efficacy.

- Armeniacae Semen Amarum
  (苦杏仁，Kuxingren)
  Bitter Apricot Seed

[4] 2016 Census: Multicultural: https://www.abs.gov.au/ausstats/abs@.nsf/lookup/Media%20Release3

[5] Chinese Medical Board of Australia, registration data table March 2020: https://www.chinesemedicineboard.gov.au/About/Statistics.aspx

- CP indications: Cough and wheezing, chest fullness, profuse sputum, and constipation caused by intestinal dryness.

- **Persicae Semen**
  (桃仁，Taoren)
  Peach Seed

- CP indications: Amenorrhea, dysmenorrhea, masses, stuffiness, lung abscess, intestinal abscess, traumatic injuries, constipation caused by intestinal dryness, cough and wheezing.

The extent of use of these substances in medicines in Australia is not known but probably very low considering the current Schedule 10 prohibition for medicines that contain any amount of amygdalin. As ingredients in the Chinese Pharmacopeia with a long history of use in traditional Chinese medicines, Kuxingren, Taoren and similar herbal substances that contain amygdalin are widely used in Chinese communities throughout the world.

(C) Toxicity and Safety of the Substance

The toxicity of oral exposure to amygdalin is due to the release of cyanide after hydrolysis in the gut by β-glucosidase. Thus the acute toxic effects of amygdalin are those of cyanide.

In humans, depending on the dose, the symptoms of acute amygdalin/cyanide toxicity are nausea, vomiting, diarrhoea, dizziness, tachypnoea, progressing to cyanosis, seizures, coma, and eventually respiratory arrest and death. There is evidence supporting chronic exposure of cyanogenic glycosides resulting in neuropathy, myelopathy, and/or goitre, but this is complicated by other factors, including malnutrition, making causality unclear.

In adults, oral amounts of 1 to 1.5 g of amygdalin per day show little evidence of toxicity, with toxicity evident at doses over 2 g per day, although fatalities have occurred at doses of 0.5 to 2.5 g, particularly in children. The severity of toxicity varies with a number of factors including the preparation of the amygdalin source, status of gut flora, nutritional status and concomitant administration of other nutrients such as vitamins.

On the basis of animal studies, and as assessed by a wide range of regulatory and expert committees, oral intake of 5 to 20 μg/kg/d cyanide is considered to present no appreciable risk, equivalent to 300 to 1200 μg/d for a 60 kg adult and 100 to 400 μg/d for a 20 kg child. Assuming 100% hydrolysis of amygdalin to hydrogen cyanide (the worst case scenario), this is equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult and 1.7 to 6.8 mg/d for a 20 kg child.

As detailed in Part 2.1B above, by way of comparison 100 g of confectionary could legally contain more than 8 times the proposed maximum adult daily dose of 5 mg amygdalin in

unscheduled traditional Chinese medicines and one standard drink of red wine could legally contain more than 4 times the proposed daily limit.

Reports by independent toxicologist Dr Susan James (Part 3) and an independent expert engaged by the TGA agreed that "on the basis of animal studies, and as assessed by a wide range of regulatory and expert committees, oral intake of 5 to 20 µg/kg/d cyanide (equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult) is considered to present no appreciable risk to consumers".

(D) Dosage, Formulation, labelling, packaging and presentation of a Substance

TCM products containing ingredients that have amygdalin as a natural component can be presented in many different oral dose forms (e.g. tablet, capsule, pill), usually in combination with other herbs.

In terms of packaging TCM medicines are often labelled with Chinese characters in addition to the required label statements in English. Child resistant closures would be required if the medicine contained ingredients that are specified in Part 2 of Schedule 1 to *Therapeutic Goods Order No. 95 - Child-resistant packaging requirements for medicines 2017* (TGO 95). However, none of the ingredients in question are specified in the Order.

(E) Potential for Misuse/Abuse of the Substance

Single ingredient products containing amygdalin at high dose (as 'laetrile') have had a history of misuse for cancer treatment. These products will remain in Schedule 10.

We are not aware of any reports of overdose, misuse or abuse of traditional Chinese medicines containing low doses of amygdalin as a component of ingredients in traditional Chinese medicines.

(F) Any Other Matter that May be Relevant to the Scheduling of a Substance

We are not aware of any other matters that would be relevant to the Delegate's decision.

PART 2.2 – Criteria which must be addressed – proposals to change Parts 1-3 or Part 5 of the Poisons Standard

This application does not propose any change to Parts 1-3 or Part 5 of the Poisons Standard.

Conclusion

This application proposes excluding amygdalin from Schedule 10 when included as a natural component in traditional Chinese medicines for oral use in adults with a maximum daily dose not exceeding 5 mg. An associated change to exclude hydrocyanic acid from Schedule 4 when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults with a maximum daily dose not exceeding 0.3 mg of hydrocyanic acid is also proposed.

It addresses concerns from the November 2020 meeting of the ACMS and a subsequent interim decision by the scheduling delegate in relation to the potential for illicit use in cancer therapy (both medically prescribed and by consumers), accidental poisoning (especially in children) or deliberate self-poisonings and chronic overuse of products containing amygdalin.

Reports by independent toxicologist Dr Susan James (Part 3) and an independent expert engaged by the TGA both concluded that "on the basis of animal studies, and as assessed by a wide range of regulatory and expert committees, oral intake of 5 to 20 µg/kg bw/d cyanide (equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult) is considered to present no appreciable risk to consumers".

We submit that there is substantial public health benefit, and no appreciable risk, from making traditional Chinese medicines containing low doses of amygdalin available to adult Australian consumers under the proposed conditions.

Part 3 – Supporting Data

3.1 Supporting data summary

Much of the information in the Overview and in the body of the application is taken directly from relevant parts of a Scientific Review prepared by toxicologist Dr Susan James based on a comprehensive literature search on the oral toxicity of amygdalin and hydrocyanic acid. The review is included in its entirety in Part 3.2 below and should be read as a stand-alone document. A declaration from Dr James indicating any competing interests or conflict of interests in providing this report together with a statement regarding her relationship with the applicant is also included. Details of the literature search are included in Part 3.3.

3.2 Toxicity review: Amygdalin and Hydrogen Cyanide

Toxicity review:
amygdalin and hydrogen cyanide

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Executive summary

Amygdalin (D-mandelonitrile-β-D-glucoside-6-β-glucoside) is a cyanogenic glycoside found naturally in plants including seeds of the *Prunus* genus. It is metabolised in mammalian gut by enzymes in the gut wall and gut flora to hydrogen cyanide. Amygdalin is currently prohibited from use in therapeutic goods in Australia even at very low levels.

Studies have found the oral single dose that is lethal to 50% of animals (LD_{50}) is in the range 522 to 880 mg/kg for amydgdalin and 3 to 22 mg cyanide ion/kg for cyanide in rats. In mice the single dose lethal to 10% of animals (LD_{10}) is approximately 450 mg/kg for orally administered amygdalin, and 4.2 mg/kg in intraperitoneally administered cyanide.

In longer term studies (13 weeks) no observable toxic effects were observed after oral exposure to 4.5 mg/kg/d cyanide in rats and 26 mg/kg/d in mice. After 12 months on a diet containing 50% cassava (containing a different cyanogenic glycoside to amygdalin and resulting in exposure to approximately 0.102 mg cyanide per day) rats displayed impaired motor coordination and cellular changes in liver and pancreas. Amygdalin and cyanide are not observed to be carcinogenic in animal studies. Amygdalin has been shown to be genotoxic in some but not all test systems. Cyanide has been found to be negative in genotoxicity tests systems at non-cytotoxic doses.

Amygdalin has been shown to produce foetal abnormalities at close to materno-toxic doses in hamsters when administered in a single dose. The effects of amygdalin from ground apricot kernels on reproduction in rats is unclear. In rabbits cyanide at 5 g/100 g in the diet produced impaired fertility. A diet of raw cassava resulted in impairments in fertility and some reproductive and developmental parameters at materno-toxic doses, but no effects when the cassava content in the diet was 45% or less.

Animal studies have demonstrated that the toxicity of oral amygdalin or cyanide is increased when administered in combination with β-glucosidase or ascorbic acid, and is decreased when administered with hydroxycobalamin and some herbal preparations. Administration of cysteine is able to ameliorate the ascorbic acid-increased toxicity of cyanide.

Case reports and clinical studies indicate that oral doses of amygdalin of 0.5 to 1.5 g/d have not resulted in toxicity. However, the lethal dose of amygdalin in adults is reported to be in the range 9 to 60 mg/kg (540 to 3600 mg for a 60 kg adult). The average lethal dose of cyanide is reported to be in the range 0.5 to 3.5 mg/kg (30 to 210 mg for a 60 kg adult).

Regulatory authorities have concluded that oral intake of 5 to 20 μg/kg/d of cyanide is not of toxicological concern over the long term, and Food Standards Australia New Zealand have established an acute reference dose for cyanide of 0.8 mg/kg for short term intake. Assuming complete hydrolysis of amygdalin to cyanide, the amount of amygdalin producing 5 to 20 μg hydrogen cyanide is 84 to 338 μg.

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Abbreviations

ArfD	Acute reference dose
ATSDR	Agency for Toxic Substances and Disease Registry
AUC_{0-t}	Area under the concentration time curve
bw	Body weight
C_{max}	Maximum concentration (in serum, plasma or blood
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
d	day
EPA	Environment Protection Agency
F0	Foundation generation
FSANZ	Food Standards Australia New Zealand (previously ANZFA)
HCN	Hydrogen cyanide
HPC/DNA	Hepatocyte primary culture DNA repair test
i.m.	Intramuscular
i.p.	Intraperitoneal
IV	Intravenous
KCN	Potassium cyanide
LD_{10}	Lethal Dose killing 10% of test animals
LD_{50}	Lethal Dose killing 50% of test animals
LOAEL	Lowest observable adverse effect level
MRL	Minimum Risk Level
NaCN	Sodium cyanide
NOAEL	No observable adverse effect level
NTP	National Toxicology Program
RPO	Red palm oil
TCM	Traditional Chinese Medicine
TDMI	Temporary Daily Maximum Intake
WHO	World Health Organisation

1. Introduction

Amygdalin (D-mandelonitrile-β-D-glucoside-6-β-glucoside; mandelonitrile-β-gentiobioside) is a cyanogenic glycoside found naturally in bitter almonds, apricot kernels and seeds of other plants in the *Prunus* genus. The structure of amygdalin is displayed in Figure 1 below.

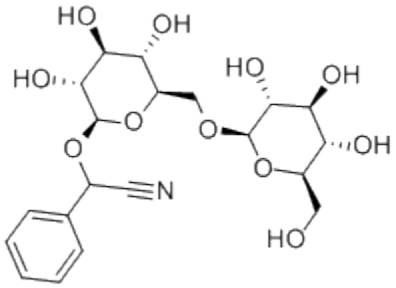


Figure 1: Chemical structure of amygdalin

Amygdalin is also referred to as Vitamin B17, although it is not a vitamin, and often as laetrile, although laetrile and amygdalin are not identical, since laetrile is actually a semi-synthetic form of amygdalin, with the chemical composition D -mandelonitrile- β-glucuronide.

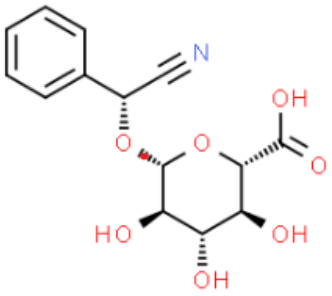


Figure 2: Chemical structure of laetrile

However, some products marketed as laetrile contain amygdalin instead, and many studies do not distinguish between laetrile and amygdalin, and both products are converted to hydrogen cyanide (HCN) *in vivo*, so in this review toxicity information from studies claiming to use amygdalin or laetrile will be used interchangeably.

Hydrogen cyanide (hydrocyanic acid, formonitrile, Prussic acid) is a colourless to blue liquid, which exists as a gas at temperatures above approximately 26°C. HCN is a simple molecule with the following structure:

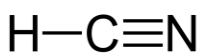


Figure 3: Chemical structure of hydrogen cyanide

HCN has a range of industrial uses, particularly as a fumigant, and in the production of industrial chemicals. The principal natural sources of HCN are cyanogenic glycosides (including amygdalin) found in many plants including cassava, sorghum, lima beans and members of the *Prunus* species (Speijers 1993). The mechanism of toxicity of hydrogen cyanide has been well studied and is by inhibition of mitochondrial cytochrome oxidase, which results in inhibition of oxygen consumption (Cooper et al 2008).

Amygdalin for therapeutic use is currently included in the Standard for the Uniform Scheduling of Medicines and Poisons in Schedule 10 (substances of such danger to health as to warrant prohibition of sale, supply and use).

Hydrogen cyanide for therapeutic use is included in Schedule 4 of the SUSMP, with non-therapeutic use included in Schedule 7.

Amygdalin is present in some traditional Chinese herbal medicine (TCM) products that contain parts of *Prunus* species. Currently such products are not permitted for sale in Australia. A review of the oral toxicity of amygdalin and HCN has been requested to determine whether there are appropriate limits below which amygdalin in products for therapeutic use can be removed from Schedule 10, and HCN in products for therapeutic use can be removed from Schedule 4.

The theoretical concentration of cyanide in amygdalin is 59.1 mg HCN/g amygdalin, based on molecular weight (Holzbecher et al 1984). The amount of cyanide in apricot kernels and bitter almonds[1] (seeds from *Prunus* species), both of which have been the subject of toxicity reports and fatalities, varies from <0.05 mg/kg to >2000 mg/kg according to the UK Committee on Toxicology (COT, 2006), depending on a variety of factors including cultivar and climatic conditions.

The toxicity of HCN and other cyanides has been the subject of review by many international expert bodies including the World Health Organisation (WHO) (Simeonova et al 2004), the United States Environment Protection Authority (EPA 2010), the Agency for Toxic Substances and Disease Registry (ATSDR 1993), and Food Standards Australia New Zealand (FSANZ) at various times (FSANZ 2004, 2008, 2015, 2016). The toxicity of the cyanogenic glycosides, including amygdalin, has also been the subject of expert review, including as part of the WHO Food Additives series (Speijers 1993, WHO 2012), as well as by the Committee on Toxicity (COT, 2006).

In addition to the expert reviews, data for this toxicity summary has been sourced from a systematic literature search for preclinical and clinical toxicity data on amygdalin and hydrogen cyanide.

[1] Bitter almonds and sweet almonds differ in that bitter almonds contain measurable quantities of cyanogenic glycosides, as well as the enzyme β-glucosidase. Sweet almonds (the usual eating almonds) contain β-glucosidase but only trace amounts of cyanogenic glycosides. Almond and peach seeds are also sometimes referred to as bitter almonds.

2. Pharmacokinetics

The pharmacokinetics of orally administered amygdalin have been well studied, although the location, source and role of some of the enzymes involved in the metabolic processes are still unclear. Blaheta et al (2016) and Cressey et al (2019) have reviewed the metabolism of amygdalin and other cyanogenic glycosides. The main pathway of amygdalin metabolism involves the cleaving of the terminal glucose by β(1-6)-glucosidase activity in the gut wall of the small intestine, producing prunasin (D-mandelonitrile β-D-glucoside). Prunasin is in turn metabolised to mandelonitrile by β-glucosidase in gut bacteria in the large intestine or colon. Mandelonitrile subsequently dissociates to cyanide and benzaldehyde. β-glucosidase is present in plant seeds and kernels containing amygdalin as well as in the human gut wall and gut bacteria. This metabolic pathway is illustration in Figure 4 below.

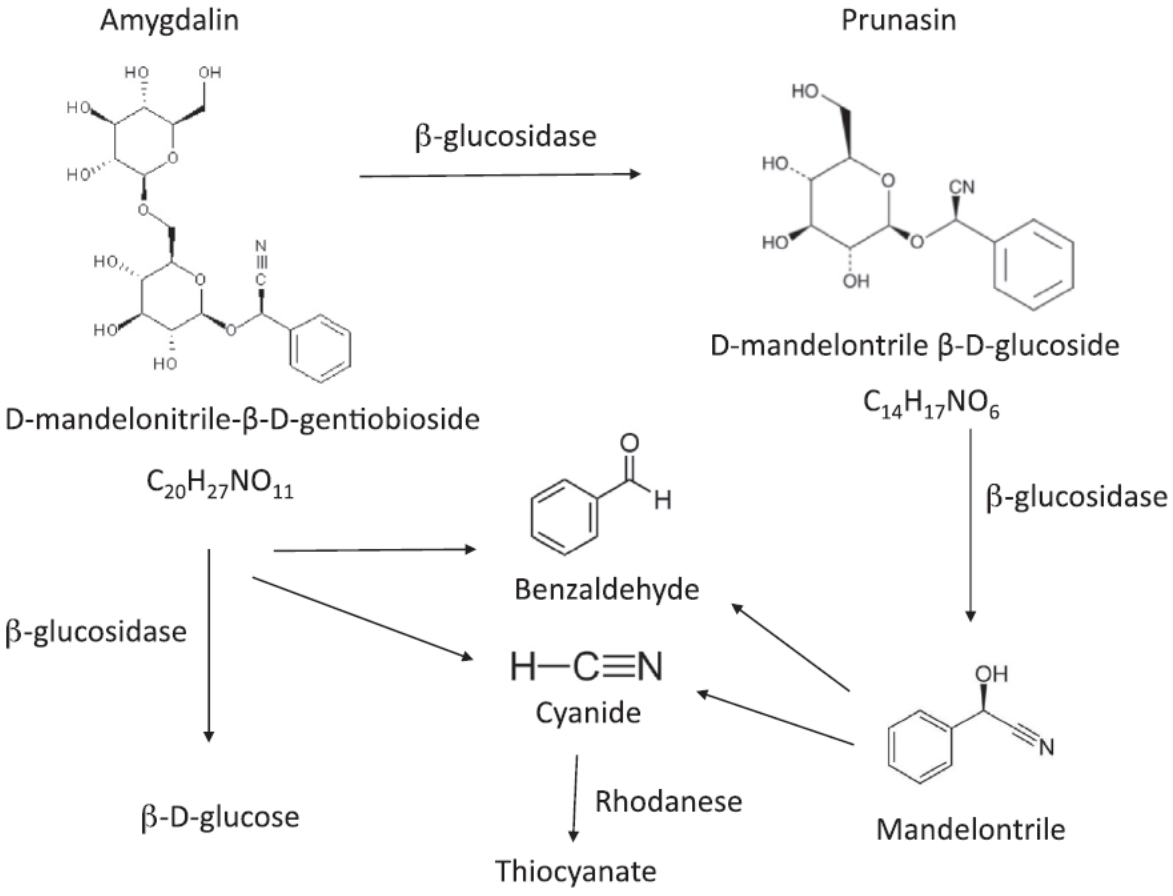


Figure 4: Metabolic pathway of amygdalin (source: Fig 1, Blaheta et al 2016)

The primary route of detoxification of cyanide in humans is via trans-sulfuration to form thiocyanate, which then undergoes renal clearance. The conversion of cyanide to thiocyanate is principally catalysed by rhodanese, although β-mercaptopyruvate-cyanide

sulfurtransferase is also thought to catalyse this reaction. Irrespective of the enzymes involved, the conversion requires the presence of a sulfur source such as thiosulfate. Thus the toxicity of cyanide is increased in situations in which the activity of the enzymes catalysing the trans-sulfuration is reduced, or there is a reduction in the available sulfur sources such as cysteine or methionine. The elimination half-life of thiocyanate is approximately 2.7 days in normal renal function (Curry et al 2015).

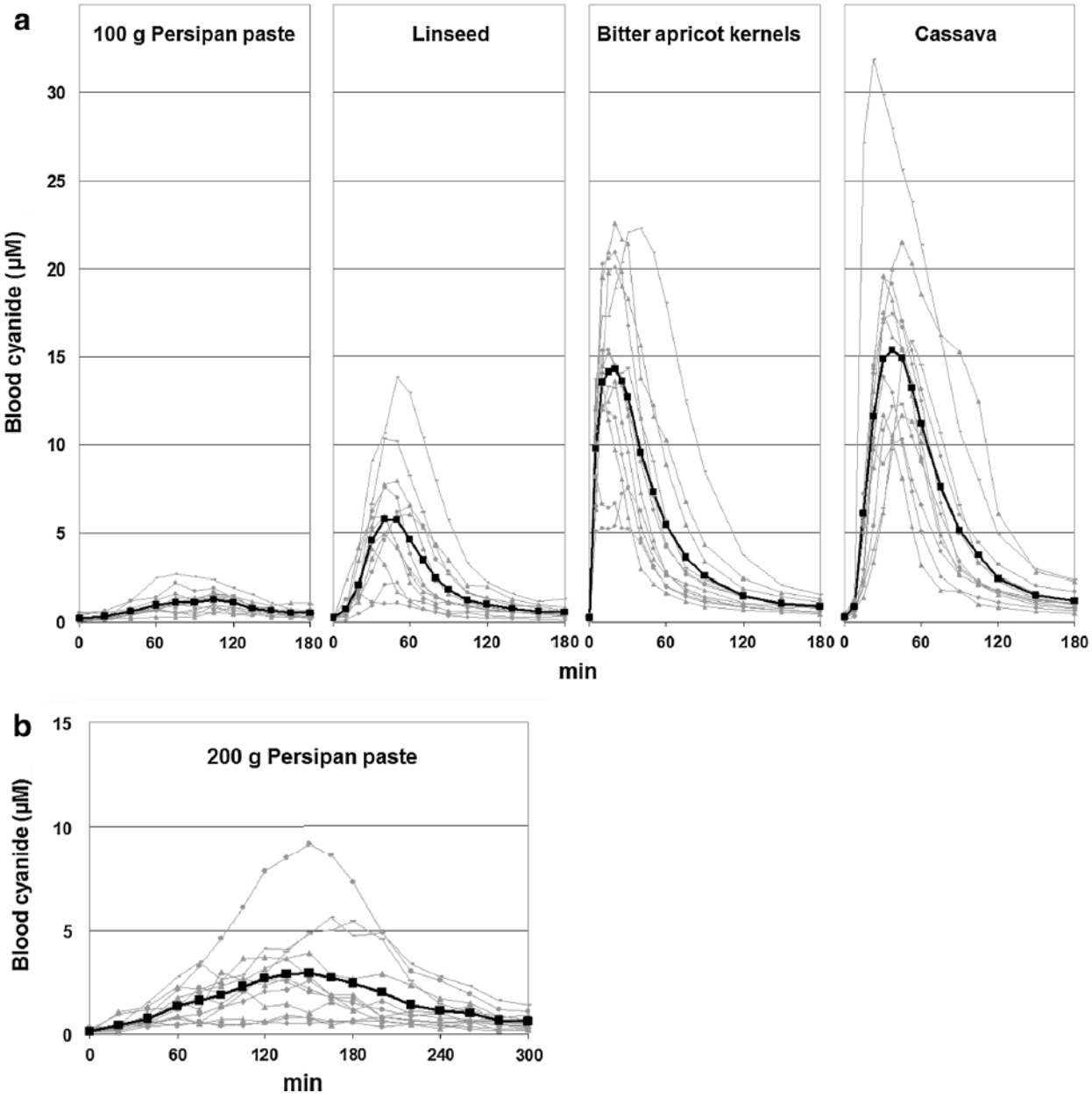
Cyanide can also be detoxified by reaction with hydroxycobalamin (Vitamin B12) to form cyanocobalamin (Kulig et al 1991).

The presence and activity of β-glucosidase has significant impact on the toxicity of amygdalin and other cyanogenic glycosides after absorption, since amygdalin toxicity is the result of release of cyanide. For instance, amygdalin is less toxic when administered intravenously than orally, since β-glucosidase is not present intracellularly in humans, and thus little cyanide is produced since IV administration bypasses the gut β-glucosidase enzymes.

The proportion of amygdalin metabolised to cyanide varies depending on a range of factors. If amygdalin is ingested along with sources of β-glucosidase (such as in apricot kernels) the proportion of cyanide produced can be increased. If gut flora is reduced, such as by antibiotic treatment, conversion of prunasin to mandelonitrile (and hence production of cyanide) is reduced.

To illustrate this point, the bioavailability of cyanide after consumption of different foods containing cyanogenic glycosides has been studied in human volunteers (Abraham et al 2014). The foods investigated were persipan paste, bitter almond kernels, linseed and cassava. The total cyanide content (free cyanide + cyanide released from cyanogenic glycosides and cyanohydrins following complete hydrolysis) of each of the foods was determined using a validated method. In a 5 way crossover study, 12 healthy adults consumed an amount of each food equivalent to 6.8 mg total cyanide (100 g persipan, about 2.1 g bitter apricot kernels, about 30.9 g ground linseed grains, and about 64 g cassava) and 200 g persipan (13.6 g total cyanide) in random order under fasting conditions, and blood samples were taken for whole blood cyanide content at various times until 180 minutes post-consumption. The peak cyanide levels and concentration time curves for the different foods were very different despite all foods containing the same theoretical amount of cyanide. Peak whole blood cyanide levels were 1.44 ± 0.60 μM for 100 g persipan, 3.40 ± 02.38 μM for 200 g persipan, 6.40 ± 3.34 μM for linseed, 15.46± 5.12 μM for bitter apricot kernels and 16.95 ± 5.96 μM for cassava. Interestingly, when the peak blood cyanide levels were compared between the 5 females and 7 males in the group, there was no significant difference between males and females for persipan paste in either amount, but the males had significantly lower peak cyanide levels than the females for the other three foods. The concentration time curves for the foods are displayed in Figure 5 below.

Figure 5: Concentration time curves in whole blood after consumption of persipan, bitter almond, linseed or cassava (source Abraham et al 2014 Figure 2)



The differences in the rate of absorption of cyanide between the different foods was attributed to the different amounts of β-glucosidase in the foods and their rates of reaction. Despite blood cyanide levels reaching ≥20 µM (approximately 0.5 mg/L, the level at which flushing or tachycardia have been reported [ATSDR 2006]) in several subjects after consumption of bitter almond kernels or cassava, no clinical symptoms of cyanide toxicity were observed.

In addition, the severity of cyanide toxicity from ingestion of bitter almonds or apricot kernels varies depending on the amygdalin content of the kernels, as well as on whether

the kernels are ingested whole, chewed, or otherwise processed prior to ingestion. Chewing and some other forms of processing can release the β-glucosidase in the kernels, increasing the conversion to cyanide, and increasing the toxicity. Conversely, some processing methods, or administration in combination with other ingredients, can reduce the conversion of amygdalin to HCN, reducing the toxicity (see under section 3.6 below).

The role and location of β-glucosidase in the metabolism and toxicity of amygdalin has been examined in a number of studies.

- An *in vitro* study used release of glucose from amygdalin and prunasin as a marker of β-glucosidase activity (Newmark et al 1981). The release of glucose was determined in various tissues removed from germ-free rats as well as neoplastic and non-neoplastic tissues removed from human cancer patients, and samples of non-neoplastic human small intestine. Glucose release from amygdalin and prunasin was highest in the rat kidney, small intestine and intestinal contents, but practically absent in the stomach and large intestine in the germ-free rat tissues. The lack of activity in the large intestine of the germ-free rats is consistent with the activity in the large intestine of normal rats being due to gut bacteria. Non-neoplastic human small intestine also demonstrated release of glucose from amygdalin and prunasin, but there was practically no activity from any of the neoplastic tissues.

- Newton et al (1981) used measurement of cyanide release from amygdalin as a measure of β-glucosidase activity from various segments of the gastrointestinal tract of rats, finding practically no hydrolysis in the stomach, and maximum hydrolysis in the caecum, followed by the ilium, colon and duodenum This group noted several human faecal bacteria were also capable of hydrolysing amygdalin to cyanide, with *Bacteroides fragilis* being several orders of magnitude more active in producing cyanide than *Clostridium perfringens*, *Streptococcus faecalis* or *Enterobacter aerogenes*.

- An *in vitro* study in mice examining the location in the gut from which most cyanide was detected also found little cyanide in the stomach and upper intestine, but increased amounts in the lower intestine and faeces (Hill et al 1980).

- The metabolism of amygdalin to cyanide in the rat was further characterised in an *in vitro* study using isolated perfused rat small intestine, homogenates of rat small intestine and purified rat small intestine enzymes and caecal contents(Strugala et al 1985). Assay of amygdalin and prunasin after incubation of amygdalin with various samples demonstrated that amygdalin was converted to prunasin by lysosomal β-glucosidase in the intestinal wall. Conversion of prunasin to mandelonitrile subsequently occurred via activity of gut flora.

Amygdalin has been demonstrated not to induce cytochrome P450 enzymes in a study in rats (Yamada et al 1998) when administered in drinking water for 4 days at a concentration of 2.5 mg/mL. Amygdalin did not produce any significant change in body weight gain, liver weight or testosterone metabolising activity. However, a statistically

significant decrease in hepatic P450 content on a nmol/mg of microsomal protein basis was reported. The study used small sample sizes (3 rats per treatment) and the study authors did not comment on the reduction in P450 content after treatment with amygdalin.

In a study investigating the excretion of amygdalin after oral and intravenous administration of 50 mg amygdalin to rats and 500 mg to dogs approximately 70% of the dose was found in the urine as amygdalin after IV administration and approximately 1% after oral administration in both species (Rauws et al 1982). An unknown compound, subsequently identified as prunasin, was also excreted in the urine in both rats and dogs after oral administration (equivalent to approximately 39% of the amygdalin dose in rats and 21% in dogs). This compound was also detected after IV administration in rats (at equivalent to approximately 6% of the amygdalin dose) but not in dogs.

In a study in which 50 mg/kg bw amygdalin in aqueous solution was administered by gavage to conventional and germ-free Sprague Dawley rats recovery of amygdalin from the urine of the germ-free rats was higher than that in the conventional rats, and amygdalin was also recovered in the faeces of the germ-free rats and not the conventional rats (Carter et al 1979).

Cyanide concentrations in animals

A study in conventional and germ-free Sprague Dawley rats reported blood cyanide levels after administration of 600 mg/kg bw amygdalin as an aqueous solution by gavage in the conventional rats were 2.6 to 4.5 µg/mL while those in the germ-free rats were < 0.4 µg/mL, the same as un-dosed rats (Carter et al 1979). Blood thiocyanate levels were also significantly higher in the treated conventional rats.

A study in CD2F1 mice compared blood cyanide concentrations after administration of amygdalin by gavage, or potassium cyanide (KCN) by i.p. injection at non-lethal doses of approximately 80% of the LD_{10} dose (4.2 mg/kg bw i.p. for potassium cyanide and 450 mg/kg bw orally for amygdalin) (Hill et al 1980). Peak blood cyanide concentrations were in the range of 0.3 to 1.5 µg/mL after oral amygdalin and 1.1 to 2.6 µg/mL after i.p KCN. Peak cyanide levels were reached between 2 and 20 minutes after KCN administration and 90 to 120 minutes after amygdalin administration.

A study on the kinetics of amygdalin in rats found cyanide levels in blood ranging from 64.8 to 425 µg/dL (0.648 to 4.25 µg/mL) in 57 animals who died during an acute oral toxicity study at doses between approximately 400 to 1100 mg/kg amygdalin (Newton et al 1981). This study found no linear correlation between the blood cyanide level and the amount of amygdalin administered.

A subacute study in Fischer 344 rats examined the toxicity of amygdalin administered intraperitoneally daily for 5 days (Khandekar and Edelman 1979). Serum cyanide levels were measured in 2 animals given 250 mg/kg bw/d and 3 animals given 750 mg/kg/d; all 5 animals died, apparently from cyanide toxicity. Mean cyanide serum concentrations were 366 µg/dL and 390 µg/dL respectively.

3. Preclinical toxicity

3.1. Acute toxicity

Acute toxicity studies have been conducted on amygdalin in rats and dogs, and on various cyanide salts in rats, rabbits and mice. The results of the acute toxicity studies are included in Table 4 in Attachment 1, and briefly summarised below.

Amygdalin

Acute oral toxicity studies in animals have reported LD_{50} values for amygdalin of between 522 mg/kg and 880 mg/kg in rats (Newton et al 1981; Song et al 2014; WHO 2012).

Adewusi and Oke (1985) undertook an acute toxicity study in Wistar rats in which the LD_{50} value of amygdalin administered by gavage was found to be 880 mg/kg bw administered in distilled water, with death occurring within 2 to 4 hours of administration. However, 600 mg/kg bw amygdalin resulted in 100% mortality when the amygdalin was followed by 10 units of β-glucosidase.

Carter and co-workers administered single doses of aqueous solutions of amygdalin by gavage to conventional and germ-free Sprague Dawley rats as part of a study on the role of gastrointestinal flora on amygdalin toxicity (Carter et al 1979). After a dose of 600 mg/kg bw amygdalin, lethargy, respiratory difficulty and convulsions were observed in the conventional rats, who usually died within 2 to 5 hours of administration. The same dose administered to the germ free rats did not produce any visible signs of toxicity and no deaths.

Schmidt and co-workers examined the toxicity of "laetrile" tablets and liquid (confirmed as containing 338 mg amygdalin per tablet and 2.0 g amygdalin per vial of liquid by assay) in mongrel dogs in combination with sweet almonds (which contain the enzymes required to hydrolyse amygdalin, but not amygdalin itself) (Schmidt et al 1978). The doses of amygdalin ranged from 0.334 g to 4.056 g amygdalin, 1 to 5 times the human equivalent dose typically used for laetrile in humans for cancer treatment at the time (0.50 to 2.50 g/d). Between 7 and 40 sweet almonds were administered – no effects were observed after administration of 20 sweet almonds alone. Eleven dogs were studied, with several dogs dosed a second time after full recovery from the first dose. Six of the dogs died as a result of cyanide poisoning, at doses ≥1.00 g laetrile and ≥20 sweet almonds. The clinical changes in the animals after dosing consisted of respiratory problems (leading to respiratory arrest in the animals that died), motor ataxia and grand mal seizures, disorientation, sinus arrythmia or tachycardia, and bradycardia. These symptoms are similar to those experienced in humans by poisoning with amygdalin or cyanide.

A study investigating the excretion of amygdalin after single oral and intravenous administration of 50 mg amygdalin to Wistar rats and 500 mg to Beagle dogs found no evidence of cyanide toxicity with either the oral or IV doses in either species (Rauws et al 1982).

A study in CD2F1 mice comparing blood cyanide levels after administration of amygdalin by gavage, or potassium cyanide by i.p. injection involved a preliminary dose-finding phase (Hill et al 1980). LD_{10} doses of potassium cyanide and amygdalin were estimated to be 4.2 mg/kg bw i.p. for potassium cyanide and 450 mg/kg bw orally for amygdalin on the basis of preliminary studies.

Cyanide

The ATSDR (2006) reported on oral LD_{50} values after administration of various cyanide salts. Calculated as mg CN^-/kg, the oral LD_{50} values ranged from 3 to22 mg CN^-/kg in rats and approximately 2.5 mg CN^-/kg in rabbits. The LD_{50} values varied depending on the cyanide salt administered and the administration details.

3.2. Sub-acute and sub-chronic toxicity

Sub-acute studies have been conducted on amygdalin in rats, guinea pigs and rabbits with dosing periods of between 5 and 24 days. Sub-chronic toxicity studies on cyanide have been conducted in rats and mice for 13 weeks. The results of the sub-acute and sub-chronic toxicity studies are included in Table 5 in Attachment 1, and briefly summarised below.

Amygdalin

A subacute study in Fischer 344 and Sprague Dawley rats examined the toxicity of amygdalin administered intraperitoneally daily for 5 days (Khandekar and Edelman 1979). At doses of 100, 250, 500 and 750 mg/kg bw/d mortality was 4.7%, 30.8%, 44.1% and 56.6% respectively, with the majority of the deaths occurring in the first 3 days of treatment. The difference in mortality between the 250, 500 and 750 mg/kg doses were not statistically significantly different. There was no difference in mortality between the Fischer 344 and Sprague Dawley rats.

Basu and co-workers studied the effects of ascorbate on the metabolism of laetrile and toxicity of potassium cyanide in guinea pigs (Basu et al 1983). Daily oral doses of 10 mg laetrile with or without 100 mg ascorbic acid for 24 days had no obvious toxic effects. A single dose of potassium cyanide at 8 mg/kg bw produced mild tremor in 3 of 8 animals. However, the same dose administered after pre-treatment with 300 mg/d ascorbate for 3 consecutive days resulted in signs of severe toxicity, with tremor, ataxia and paralysis followed by convulsions in all 8 animals. When 10 mg cysteine was administered with the ascorbate, the toxic effect was reduced, with no obvious effects in 3 of 9 animals, mild tremor in one animal, and the same signs of severe toxicity as occurred without the cysteine in the remaining 5 animals. The metabolism of ascorbic acid requires cysteine, and laetrile also requires cysteine for detoxification of cyanide to thiocyanate. It is proposed that competition for cysteine between ascorbic acid and laetrile decreases the detoxification of laetrile.

A subacute study by Oyewole and Olayinka (2009) was conducted using amygdalin. Male Wistar rats were orally administered 20 mg/kg bw amygdalin daily for 14 days, with or without hydroxycobalamin (25 mg/kg bw or 50 g/kg bw) One animal in the amygdalin-

alone group died, and parenchymal necrosis, portal inflammation and fibrosis were observed in the livers of rats who survived to the end of the treatment period. No deaths or liver effects were observed in the rats treated with both amygdalin and hydroxycobalamin.

A recent study examined the toxicity of both free amygdalin and crushed apricot seeds in P91 Californian rabbits (Kovacikova et al 2019). Groups of 12 rabbits were administered either 0.6 or 3.0 mg/kg bw amygdalin intramuscularly daily for 14 days, or 60 or 300 mg/kg bw crushed apricot seeds in food daily for 14 days. The doses of amygdalin were stated to be equivalent to 0.035 and 0.18 mg/kg bw cyanide respectively and the doses of crushed apricot seeds were stated to be equivalent to 3.12 mg/kg bw amygdalin (0.18 mg/kg bw cyanide) and 15.6 mg/kg bw amygdalin (0.92 mg/kg bw cyanide) respectively. A fifth group of 12 rabbits received no amygdalin and acted as a control. These doses had little effect on the health of the rabbits, with no deaths and no clinically significant changes in biochemical or haematological parameters.

Cyanide

The pivotal toxicity study upon which many of the regulatory guidelines for cyanide are based is a study conducted by the USA National Toxicology Program in 1993 (cited in Simeonova 2004; ATSDR 2006; and others), in which groups of 10 F344/N rats and B6C3F1 mice were administered sodium cyanide in drinking water at concentrations of 0, 3, 10, 30, 100 and 300 ppm for 13 weeks (equivalent to up to 12.5 mg/kg bw/d in rats and 26 mg/kg bw/d in mice. In this study there were no treatment-related deaths and no biologically relevant biochemical changes in any dose group or either species. No clinical signs or histopathological effects in the central nervous system were noted at any doses. However, male rats exhibited effects on testicular sperm count, epididymal sperm motility and testicular and epididymal weights at the highest dose (12.5 mg/kg bw/d) and this was considered the Lowest observable adverse event level (LOAEL), with 4.5 mg/kg bw/d as the No observable adverse events level (NOAEL) for regulatory purposes.

3.3. Carcinogenicity

Amygdalin

No long term or carcinogenicity studies of amygdalin have been identified. However, a 1 year study in which Wistar rats were fed a diet of normal rat chow, 50% fresh cassava and 50% normal rat chow, or 75% fresh cassava and 25% normal rat chow, was cited in a WHO report (2012). An average cyanide concentration of 10 mg/kg in the cassava, resulting in average exposures of 0, 0.075 or 0.102 mg cyanide per animal per day. No carcinogenic effects were reported in the study, but decreased body weights from 3 months until the end of the study were reported in animals fed both the cassava diets. Motor coordination was significantly decreased in both cassava diet groups from 5 months. Histopathology conducted at the 12 month time point showed signs of toxic hepatitis with hyperplasia and microvascular changes in hepatocytes, and mild atrophy of pancreatic acini with minimal focal dilatation of ducts, in both cassava diet groups also.

Cyanide

A 2 year long term study on cyanide in which rats were administered up to 10.8 mg/kg cyanide in the diet, found no treatment-related effects on survival, growth, signs of toxicity or histopathological changes in organs (Simeonova et al, 2004). Cyanide exposure has not been correlated with carcinogenicity in humans or animals (ATSDR 2006)

3.4. Genotoxicity

Amygdalin

The mutagenicity of amygdalin as well as mandelonitrile glucuronide was tested in *Salmonella typhimurium* strains TA98 and TA100. Amygdalin was found to be mutagenic in mouse host-mediated assays after a single oral dose of 250 mg/kg bw amygdalin. Urine collected from mice dosed with either 125 mg/kg bw or 250 mg/kg bw amygdalin was also mutagenic, with mutagenicity increased in the presence of β-glucuronidase and arylsulfatase (Fenselau et al 1977). However, a study found no mutagenic activity from amygdalin at concentrations up to 100 µg/mL in a test measuring spontaneous convertants and revertants in a diploid strain of *Saccharomyces cerevisiae* (Todorova et al 2017).

Williams (1984) reviewed the use of the hepatocyte primary culture DNA repair test (HPC/DNA repair test). In Williams' report amygdalin is stated to be negative in the HPC/DNA repair test and its carcinogenic status is stated as "uncertain". The source of the data in the review by Williams is not stated.

Cyanide

Cyanide salts (KCN, NaCN) have been found negative in a majority of bacterial mutagenicity tests in *Salmonella typhimurium* and *Escherichia coli*, and negative for chromosomal aberration and DNA repair. Cyanide induced DNA damage in some studies, but only at cytotoxic doses (Simeonova et al 2004, ATSDR 2006).

3.5. Fertility and Reproduction

Amygdalin

A reproductive and developmental study with amygdalin was reviewed by WHO (2012). In this study, pregnant hamsters were treated with a single oral dose of amygdalin (200 to 275 g/kg) on gestational day 8 (Willhite 1982). Maternal toxicity was noted at doses of 250 mg/kg and above, and dose-related foetal abnormalities were observed from doses of 200 mg/kg and above. The whole blood cyanide concentration was 4.0 ± 1.1 nmol/mL 2.5 hours after the oral administration of 275 mg/kg amygdalin. A single IV dose of 275 mg/kg amygdalin on gestational day 8 did not produce maternal or foetal effects, and resulted in a whole blood cyanide concentration of 0.06 ± 0.03 nmol/mL. A single oral dose of 275 g/kg amygdalin resulted in no foetal abnormalities when administered with an initial i.p. injection of 300 mg/kg sodium thiosulfate followed by additional sodium thiosulfate i.p. injections administered every 120 minutes for 10 hours after the amygdalin

dose. It is unclear whether the foetal effects seen in the oral dose study were due to maternal toxicity.

The effect of ground apricot kernels (10% in the diet) on reproduction in Sprague Dawley rats was examined by Miller and co-workers in two studies (Miller et al 1981). In the first study three groups of young breeding -age male and female rats were fed ground kernels containing low (<50 mg/100 g), medium (100 to 200 mg/100 g) or high (>200 mg/100g) levels of cyanide for 5 weeks. In a second experiment the rats were fed kernels containing either the low or high cyanide levels for 15 weeks and then bred with rats of the opposite sex on the same diet. Rats fed no ground apricot kernels were used as controls in both experiments.

Rats in the first study showed no significant changes in blood chemistry between groups. In female but not male rats liver rhodanese activity and thiocyanate levels increased with increasing apricot kernel levels in the food. Urinary excretion of thiocyanate was higher in the two high dose groups than the control or low dose groups. In the second study the parturition index was similar between the low dose and high dose group, but 3 day survival index, lactation index and weaning weight were significantly lower in the high dose group than the low dose group. However, the control group had a lower parturition index, 3 day survival index and weaning weight than the low dose group. Birth weights were not different between groups.

Cassava based diets containing 0, 15, 30 or 45% cassava root meal were fed to female New Zealand White rabbits to examine their effect on reproduction and growth (Eshiett et al 1980). The female rabbits were fed the diets for 42 days and then bred to untreated males. The offspring from this breeding were given the same cassava-based diet as the dams for 8 weeks. The F0 females were then bred a further 2 times. There were no significant differences between the groups in number of pups per litter, number of surviving pups, pup weights at birth, 14, 28 and 35 days postpartum, pup growth during the cassava diet, pup organ weights at the end of the feeding study, and urine and serum thiocyanate concentrations in the dams or the pups.

Cyanide

A fertility study was conducted in which female rats (n=10) were treated for 2 weeks with 5 or 10 g potassium cyanide/100 g diet (equivalent to approximately 1000 or 2000 mg cyanide /kg bw/d)(Olusi et al 1979). The female rats were then mated with untreated male rats; no pregnancies resulted at either dose level. The female rats exhibited dose dependent decreases in body weight gain, blood haemoglobin (18% and 23%) and serum T_4 concentration (54% and 74%). In the same study, when female rats were fed raw cassava, they exhibited similar changes in body weight gain, blood haemoglobin and serum T_4 concentrations as the high dose potassium cyanide-fed group, however, upon mating with untreated males 4 of 10 rats became pregnant (compared with 9 of 10 in a control group).there was also a significant reduction in average litter size and individual birth weight and an increase in neonatal deaths. The surviving pups showed poor development and reduced brain weight.

3.6. Toxicity in combination with herbal or other ingredients

A recent study examined the toxicity of the individual and combined components of a Traditional Chinese herbal medicine compose of the dried ripe seeds of *Prunus armenica* (containing amygdalin, and known as *Xingren* in Chinese) and the dried herbaceous stems of *Ephedra sinica Stapf*,(containing ephedrine and pseudoephedrine and known as *Mahuang* in Chinese (Song et al 2016). An acute oral toxicity study was conducted in Kunming mice, to determine the LD_{50} of *Mahuang* (M), *Xingren* (X), and combinations of the two ingredients in the ratios MX(4:1), MX(2:1), MX(1:1), MX(1:2) and MX(1:4). Table 1: shows the LD_{50} results for the individual ingredients and the combinations. *Xingren* alone is more toxic than *Mahuang* or the combinations but even a combination of MX(1:4) is markedly less toxic than *Xingren* alone.

Table 1:Toxicity of Mahuang and Xingren combinations in mice.

Treatment	$LD_{50\ g/kg}$ bw)		Concentration of amygdalin (mg/g)
	Median	95% CI	Mean ± SD
Mahuang	93.2	85.2 – 102.0	-
Xingren	29.9	25.3 – 35.3	11.77 ± 0.72
MX(4:1)	87.9	81.7 – 94.5	12.83 ± 0.70
MX(2:1)	81.6	77.9 – 85.3	12.84 ± 1.52
MX(1:1)	81.4	75.5 – 87.9	14.16 ± 0.98
MX(1:2)	64.6	62.9 – 66.3	11.38 ± 1.20
MX(1:2)	59.3	52.6 – 66.9	10.19 ± 0.94

The concentration of amygdalin (L-amygdalin + D-amygdalin) was similar in all combinations to that of *Xingren* alone, but this was a consequence of a reduction in L-amygdalin and an increase in D-amygdalin in combination with *Mahuang*.

A study by Tang et al (2017) also studied the effects of the combination of amygdalin and Ephedra alkaloids in rats. In this study groups of Sprague Dawley rats were treated orally with 20 mg each of ephedrine, pseudoephedrine and methylephedrine in combination with either cinnamic acid (3.03 mg/kg), amygdalin (56.97 mg/kg), glycyrrhizic acid (12.42 mg/kg) and liquiritin (3.79 mg/kg) or a combination of all four compounds. The concentration of the Ephedra alkaloids in rat plasma were measured at various times from 5 to 360 minutes after dosing. Compared to the combination of Ephedra alkaloids with no other treatment, the addition of amygdalin significantly increased the C_{max} and AUC_{0-t} of ephedrine and pseudoephedrine, reduced the mean residence time of all three Ephedra alkaloids, and decreased the AUC_{0-t} of methylephedrine. Cinnamic acid, glycyrrhizic acid and liquiritin also produced significant changes to the pharmacokinetics of the Ephedra alkaloids. The Traditional Chinese herbal medicine Ephedra decoction contains the Ephedra alkaloids as well as the other 4 compounds and the study authors suggest that the pharmacokinetic changes in the Ephedra alkaloids by the other components of the decoction may be of relevance to the clinical use of Ephedra in Traditional Chinese medicine.

Iheioha (2002) examined the effect of traditional processing methods in the production of gari (toasted cassava granules), on the cyanogen content and toxicity of the gari. Traditionally gari is enriched with red palm oil (RPO, which consists primarily of fatty acids) during production. The toxic component of cassava is prunasin, which is converted to hydrogen cyanide. Two samples of gari were produced, one with 15 mg/kg RPO mixed in prior to fermentation and one without. Otherwise the preparation of the two samples was identical. Total cyanogen, acetone cyanohydrin and free cyanide contents were determined in both samples and there were no significant differences between the two samples in the content of any of these compounds or in crude protein content. The two different samples of gari were then fed to groups of Sprague Dawley rats for 10 weeks, while a control group received normal rat chow. Both groups fed gari exhibited similar loss of appetite and

reduced weight gain from the start of the second week to the end of the study compared to the controls group. Both groups fed gari also exhibited hair loss and change in hair colour from white to brown. From about the 5th week of treatment, the rats fed gari developed decreased sensitivity to sound and weakness, wasting of the hind limbs, and from the 7th week, death. However, these effect were more severe and present in significantly greater numbers in the rats fed gari without RPO. For instance, 75% of the rats fed gari without RPO died by the tenth week of the study, while only 8.3% of rats fed gari with RPO died, with similar results for the other clinical effects. Gross necropsy recorded generalised atrophy of body tissues and organs and wasting of body fat in all animals fed gari, with or without RPO. More than half the animals in both groups also exhibited vacuolar degeneration of hepatocytes. However, degeneration necrosis in the brain and renal tubules were observed in significantly more animals in the group fed gari without RPO than in those fed gari with RPO. These results suggest that RPO did not decrease the toxicity of gari by reducing the content of cyanogens, but perhaps by inhibiting the metabolically mediated release of free cyanide upon consumption, or increasing the detoxification processes.

Go et al (2018) examined the amygdalin concentration and toxicity of two different forms of syrups made from Maesil (*Prunus mume*, also known as Korean green plums, Chinese green plums or Japanese ume), known to contain amygdalin. The syrup was prepared using 1:1 Maesil and sucrose which was matured for 3 months. To prepare "Maesil syrup without Maesils" the Maesils were then removed and the syrup matured for a further 9 months, while "Maesil syrup with Maesils" was allowed to mature for a further 9 months without removal of Maesils. The content of amygdalin in the syrup without Maesils was significantly higher than in the syrup with Maesils (166.82 ± 4.16 μg/mL vs 134.98 ± 5.96 μg/mL). Content of prunasin was also higher in the syrup without Maesils (31.57± 0.16 μg/mL vs 26.06± 0.15 μg/mL). When administered to female rats at a dose of 10 mL/kg bw/d by gavage for 14 days (equivalent to 1.34 or 1.66 mg amygdalin/kg bw/d) no changes in weight gain, food or water consumption, relative organ weights, haematological or biochemical indices were found and no histopathological abnormalities were observed.

Lui et al (2017) investigated the inhibitory effects of various Chinese herbal extracts on the activity of β-glucosidase derived from almonds, and then examined the toxicity of a Chinese herbal medicine containing amygdalin (*Persicae Semen* ethanol extract) in mice when combined with β-glucosidase inhibitory herb extracts. Of 30 herbs assessed for β-glucosidase inhibitory effects, water extracts of 5 herbs, and ethanol extracts of 7 herbs, were found to have inhibitory activity against β-glucosidase. Of all the inhibitory herbal extracts, the ethanol and water extracts of *Lycii Cortex* had the smallest IC_{50} results (1.35 mg/mL for water extract and 0.56 mg/mL for ethanol extract). Further study found that *Lycii Cortex* inhibition of β-glucosidase was non-competitive in nature. By comparing decomposition rates of amygdalin at different concentrations with the inhibitory rate of the *Lycii Cortex* ethanol extract at different concentrations, a ratio of 7.19 *Persicae semen* ethanol extract to 9.18 *Lycii Cortex* ethanol extract was determined to be theoretically optimal. The *in vivo* oral toxicity of the *Persicae semen* ethanol extract alone and in the theoretically determined optimal ratio with *Lycii Cortex* ethanol extract was investigated by examining the relative LD_{50} values in Kunming mice using the up-down method. The LD_{50}

of the *Persicae semen* extract alone was 1750 mg/kg bw, while the LD50 when combined with *Lycii Cortex* extract was 4100 mg/kg bw, demonstrating that the toxicity of *Persicae semen* extract is decreased 2.43 times when administered in combination with *Lycii Cortex* extract.

Jaswal et al (2018) reviewed the effect of different gut bacterial compositions on the metabolism of amygdaline and noted studies in which some probiotics and foods were able to alter the gut microbiome and hence the β-glucosidase activity of the gut. In theory this should alter the cyanide production from amygdalin, although this has not been demonstrated in *in vivo* studies.

Tanwar et al (2018) reported a HCN content in wild apricot kernels of 136.85 ± 2.67 mg/100 g raw kernels. It is reported in this study that the range of HCN in wild apricot kernels is between 148 and 480 mg/100 g, and the HCN content in bitter almonds ranges from 106 to 250 mg/100 g. Detoxification of wild apricot kernels is possible by appropriate processing. Tanwar and co-workers found that 100% of the hydrogen cyanide content of ground apricot kernels was removed by immersing the flour in 25% sodium chloride solution for 12 hours and then rinsing under running water, repeating this process, and then drying the flour for 36 hours at 45^{o}C.

4. Clinical toxicity

4.1. Symptoms

The initial symptoms of acute cyanide poisoning (also the symptoms of amygdalin poisoning) include nausea, vomiting, diarrhoea and epigastric pain. These may be followed by neurological symptoms including dizziness, headaches, disorientation, irritability, lethargy, weakness, and stupor, as well as coma and seizures. Initial tachypnoea and dyspnoea may be followed by respiratory depression, cyanosis and eventual respiratory arrest (Hazardous Substances Database (HSDB) 2017). Hypotension and shock may also occur.

Chronic cyanide poisoning after chronic consumption of cyanogenic plants results in neuropathy and myelopathy, including Konzo, a specific tropical myelopathy observed in populations with a high intake of cassava, which contains linamarin, a cyanogenic glycoside metabolised to prunasin and then to HCN (HSDB 2017, COT 2006). Goitre is also associated with chronic consumption of cyanogenic plants, since thiocyanate interferes with iodine uptake in the thyroid (Speijers 1993). However, these populations with high intake of cyanogenic glycoside-containing plants also exhibit a high incidence of malnutrition, and it is considered that nutritional deficiency, particularly of methionine and riboflavin, or iodine, in combination with chronic cyanide exposure, is involved in the aetiology of neuropathy, myelopathy and goitre (Speijers 1993).

No reports of hepatotoxicity associated with acute or chronic exposure to amygdalin or other cyanogenic glycosides have been identified. Hepatotoxicity has been reported in some rabbit studies after oral exposure to sodium or potassium cyanide at doses of 15 to

20 mg/kg/d cyanide ion, but no consistent evidence of hepatotoxicity has been associated with cyanide exposure in other animals or humans (ATSDR 2006).

4.2. Case reports and clinical studies

There are a number of case reports of human toxicity or fatalities from oral amygdalin. These are summarised in Table 6 in Attachment 2.

In addition to the case reports in Table 6, Akyildiz and co-workers (2010) reported on 13 paediatric patients admitted to a hospital in Turkey with cyanide toxicity from ingestion of apricot seeds between 2005 and 2009. The mean (range) age of the patients was 5.7 years (3 to 9 years). The mean (range) time to onset of symptoms was 1 hour (20 minutes to 3 hours) and the median (range) number of apricot seeds was 8 (5 to 21). Twelve of the children had a history of eating the apricot seeds, Five patients swallowed the seeds whole while the remainder chewed the seeds. There was no statistical relationship between the number of seeds consumed and the severity of symptoms. Headache, vomiting, irritability, and abdominal pain were the most common symptoms, experienced in 9, 11, 5 and 5 patients respectively. Metabolic acidosis was recorded in 9 patients, as was hyperglycaemia. Poisoning was severe in 9 patients, resulting in mechanical ventilation, hypotension, coma or convulsions. Poisoning was considered mild in the other 4 patients. Patients were treated with one or more of hydroxycobalamin, sodium bicarbonate, cyanide treatment kit (sodium nitrite and sodium thiosulfate) and insulin. All patients recovered after 2 to 6 days.

Amygdalin has been the subject of clinical studies, after it was promoted as a "natural cancer cure". Early clinical trials were summarised by Blaheta et al (2016) as having administered various doses to humans, including:

- 1 g IV, for 4–43 weeks (mean 17.5 weeks, mean 2 injections/week);
- 0.1–0.5 g (IV and oral);
- 1–10 g IV daily, followed by 1 g daily oral administration;
- 0.1–1 g oral daily;
- 0.1–1 g/day, IV or i.m. administration; or
- 0.5 – 2 g orally per day for up to 43 weeks.

Details of the methodology and exact nature of the treatments are unavailable.

Two clinical studies were sponsored by the National Cancer Institute in the USA. A preliminary study by Moertel et al (1981) treated 6 patients with advanced cancer with DL amygdalin (4.5 g/m^2/day IV for 21 days) then D amygdalin (0.5 g orally 3 times daily) and "metabolic therapy" (Vitamins A, C, E, B-complex and pancreatin) for 5 to 15 weeks. Additional details of the study were also published by Ames et al (1981). No adverse effects were observed after IV doses. Whole blood levels of cyanide where essentially undetectable after IV dosing. No clinical or laboratory evidence of toxicity was observed after oral administration either. However, blood cyanide levels were detectable, with peak levels increasing over the first 2 to 5 days of treatment before plateauing at up to 2.05 µg/mL. The addition of 1 ounce (approximately 28 g) of raw almonds to the oral amygdalin dose

produced nausea, vomiting, headache, light-headedness in one patient, but no symptomatic toxicity was reported in the other patients (Ames et al 1981).

A larger study was subsequently conducted, enrolling 179 patients with cancer for which there was no known standard treatment (Moertel et al 1982). 165 patients (including the 6 from the 1981 study) were treated with DL amygdalin (4.5 g/m^2/day IV for 21 days) then D amygdalin (0.5 g orally 3 times daily) and "metabolic therapy" (Vitamins A, C, E, B-complex and pancreatin). Fourteen patients were treated with a "high dose" regimen of DL amygdalin (7 g/m^2/day IV for 21 days) then D amygdalin (0.5 g orally 4 times daily) and "metabolic therapy" (Vitamins A, C, E, B-complex and pancreatin, 1 – 4 times the amount given to the remaining patients). Adverse reactions encountered during the study and thought to be related to amygdalin were reported (see Table 2).

Table 2: Adverse reactions to IV and oral amygdalin treatment (Moertel et al 1982)

Reaction	IV treatment (%) (n=178)	Oral treatment (%) (n=132)
Nausea	31	30
Vomiting	25	17
Headache	7	8
Dizziness	7	10
Mental obtundation	4	5
Dermatitis	2	2

"A few" patients had a syndrome of headache, dizziness, mental obtundation nausea and vomiting, that subsided when oral amygdalin was discontinued. One patient on a high dose regimen had bouts of tachycardia and dyspnea 2 hours after her morning oral dose. Symptoms stopped when the dose was discontinued and did not reappear when the dose was recommenced at 3 times per day.

Toxicity was sometimes but not always associated with high blood cyanide levels. Blood cyanide levels were measured at the end of IV amygdalin treatment and 2 hours after the first morning dose of oral amygdalin 2 to 5 days and 2, 7, and 14 weeks after commencement of oral amygdalin treatment. Maximum cyanide levels for each patient were reported (see Table 3).

Table 3: Maximum blood cyanide levels reported in each patient (Moertel et al 1982)

Maximum blood cyanide level (µg/mL)	Standard dose regimen (n)	High dose regimen (n)
0.00 – 0.99	65	4
1.00 – 1.99	24	3
2.00 – 2.99	5	1
≥3.00	3	-

An open label pharmacokinetic, safety and tolerability study was conducted on single and multiple IV doses of the traditional Chinese medicine *Huoxue-Tongluo* lyophilised powder for injection, formulated from *Persicae semen* and *Paeoniae Radix Rubra* (Li et al 2016). For pharmacokinetic analysis amygdalin (as a bioactive component of *Persicae semen*, and paeoniflorin (as a bioactive component of *Paeoniae Radix Rubra*) were measured. Healthy Chinese male and female volunteers (n=12 in the single dose study and n=9 in the multiple dose study) were administered either a 6 g IV infusion (containing 25.3 mg amygdalin and 35.8 mg paeoniflorin) of *Huoxue-Tongluo* once daily for 7 days, or a single 3 g IV infusion followed 7 days later by a single 9 g IV infusion. Blood samples were collected for amygdalin and paeoniflorin analysis up to 20 hours post dose in the single dose studies and 24 hours post dose on day 1 and day 7 of the multiple dose study. *Huoxue-Tongluo* was well tolerated with no serious adverse events reported, and no clinically significant changes in vital signs or serum biochemistry except for 1 patient with raised serum alanine aminotransferase at the end of the multiple dose study, which returned to normal without intervention within 2 weeks. Amygdalin is less toxic when administered intravenously than orally, since IV administration bypasses the gut where much of the amygdalin conversion to cyanide occurs. Mean C_{max} and AUC_{0-24} for amygdalin from the highest dose (9 g) were 824.0 ± 118.0 ng/mL and 3981 ± 546 g/h/mL respectively. Pharmacokinetics were dose proportional over the tested dose range. In the multiple dose study steady state was reached by day 4 and no significant accumulation of amygdalin was observed over the treatment period.

Estimated or demonstrated toxic doses

Solomonson (1981; quoted in Speijer 1993) reported that the lethal oral dose in adults is 0.02 to 0.13 mmol/kg amygdalin (9 to 60 mg/kg), but Oke (1979, quoted in Speijer 1993) reported that 1 g or more of amygdalin has been ingested by well-nourished individuals without producing side effects.

An average fatal dose of cyanide of 1.52 mg/kg (range 0.5 to 3.5 mg/kg) in adults has been estimated by the USA EPA from case reports of intentional or accidental poisonings (ATSDR, COT, 2006). The lowest published lethal dose of HCN is reported to be 0.57 mg/kg but this was reported in 1938 and has not been confirmed (WHO 2012). Assuming 59.1 mg cyanide is released from 1000 mg amygdalin, this would equate to a fatal dose of amygdalin of 25.7 mg/kg (range 8.5 to 59.2 mg/kg). This could be considered a worst case situation, as it assumes the release in the gut of the total theoretical amount of cyanide from amygdalin, and it is unclear what proportion of the total possible cyanide would be released from amygdalin. The estimated range of 8.5 to 59.2 mg/kg is, however, consistent with the lethal oral dose range of 9 to 60 mg/kg quoted in Speijers (1993).

It is apparent that there is significant inter-individual variability in the toxic response to amygdalin ingestion. This is likely to be due to variability in both the conversion of amygdalin to cyanide in the gut (depending on activity of β-glucosidase) as well as variability in the activity in detoxication processes, which require the availability of various amino acids and are reduced in malnourished individuals.

Cyanide concentrations in humans

Cyanide can be measured in plasma, whole blood or red blood cells (RBCs). Concentrations in whole blood or red cells are higher as cyanide is preferentially distributed to RBCs. Cyanide is produced endogenously, including in neurons and leukocytes (Cipollone and Visca 2007) and may also be present in humans from exposure to environmental sources of cyanide in otherwise unexposed people.

Healthy subjects

Curry et al (2015) summarised studies measuring cyanide concentrations in RBCs and stated that concentrations of <29 µg/L (1 µmol/L) are typically found in healthy adults.

Cooper et al (2008) indicates that endogenous levels of HCN in human blood have been measured at levels from 0.3 to 2 µmol/L (8.7 to 58 µg/L).

Plasma levels of HCN are lower than those in RBCs, and are more difficult to measure accurately. However, plasma concentrations of 4 µg/L and 6 µg/L in healthy adult non-smokers and smokers respectively have been reported (Wilson and Matthews 1966 as cited in Curry et al 2015).

Whole blood concentrations of cyanide are difficult to measure accurately, and false high concentrations can occur in situations when the actual circulating cyanide levels are much lower than the reported levels. This may explain the wide range of reported "normal" levels of cyanide in whole blood (0.05 to 0.5 mg/L) (Curry et al 2015).

Toxic concentrations

Curry et al (2015) reported that RBC concentrations of cyanide of 5 mg/L are associated with obvious signs of toxicity, but early toxicity (i.e. mild metabolic acidosis) may occur at concentrations of 1 mg/L.

Cooper et al (2008) indicated that toxic levels of cyanide in human blood are between 20 and 50 µmol/L (580 to 1450 µg/L).

ATSDR (2006) reports that any blood levels >0.02 mg/100 mL (>0.2 mg/L) are toxic and death occurs at >0.3 mg/100 mL. (>3 mg/L) but toxic effects such as flushing and tachycardia can be observed from 0.05 to 0.1 mg/100 mL (0.5 to 1 mg/L).

Borron et al (1996) states that whole blood cyanide ≥40 µmol/L (≥1160 µg/L) is toxic and ≥100 µmol/L (≥2900 µg/L) is potentially lethal.

Plasma levels of HCN are lower than those in RBCs, and are more difficult to measure accurately. However, mild toxicity has been reported at plasma concentrations of 30 to 35 µg/L, and the minimum lethal concentration in plasma is reported as 243 µg/L.

Speijers (2015, as reported in Blaheta et al 2016) states that 500 µg HCN/dL (5 mg/L) in blood is lethal, while Sauer et al (2015, also as reported in Blaheta et al 2016) states that

20 µg HCN/dL (200 µg HCN/L) in serum is toxic and 300 µg HCN/dL (3 mg/L) in serum is lethal.

5. Regulatory limits

No regulatory limits for exposure to amygdalin or cyanogenic glycosides in general have been set. However, an acute reference dose for cyanide of 5 µg/kg bw/d has been suggested by the UK Committee on Toxicity (COT 2006), and this is similar to the tolerable daily intake of 12 µg/kg bw/d in drinking water set by the WHO (2003) and 20 µg/kg bw/d set by the Council of Europe (2000). The European Food Safety Authority (EFSA, 2004) concluded that there was insufficient data to establish a tolerable daily intake for cyanide, but considered that an intake of 3 to 6 µg cyanide per kg bw/d from food was not of concern.

The USA ATSDR set an intermediate oral minimum risk level (MRL) of 0.05 mg/kg/d for cyanide based on a study by the USA NTP in 1993 (cited in Simeonova 2004; ATSDR 2006; and others) where a NOAEL of 4.5 mg/kg/d was found in a 13 week rat study (ATSDR 2006) This is equivalent to approximately 3 mg/d cyanide in a 60 kg adult or 1 mg/d in a 20 kg child. The European Committee of Experts on Flavourings of the Council of Europe (CoE, 2005) set a temporary maximum daily intake (TMDI) of 0.023 mg/kg bw/d based on the same study using a different safety factor.

Food Standards Australia New Zealand (FSANZ) have reviewed the toxicity of cyanogenic glycosides and hydrogen cyanide on several occasions, particularly in relation to the safety of cassava, bamboo and apricot kernels. In 2008 FSANZ established an acute reference dose (ARfD)[2] equivalent to 0.08 mg HCN/kg bw on the basis of a possible NOAEL of 70 mg/kg linmarin (the main cyanogenic glycoside in cassava) in a single dose study in hamsters (Frakes et al 1985).

FSANZ have set a limit of 10 mg HCN/kg in ready-to-eat cassava chips (FSANZ 2008, 2016). Limits of HCN in other foods and drinks (FSANZ 2015) include:

- 25 mg/kg in confectionery
- 5 mg/kg in stone fruit juices
- 50 mg/kg in marzipan
- 1 mg/kg per 1% alcohol in alcoholic beverages.

FSANZ recognises that unprocessed cassava and bamboo shoots, which contain cyanogenic glycosides at potentially toxic levels, can be safely consumed if processed appropriately, since this reduces the concentration of hydrogen cyanide released to safe levels. Peeling and cooking cassava (baking frying, boiling or roasting), and peeling, slicing and boiling bamboo shoots, are recommended by FSANZ as suitable processing methods to render these products safe for consumption (FSANZ 2004)

[2] The ARfD of a chemical is defined an estimate of a substance in food or drinking water, expressed on body weight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer on the basis of all known facts at the time of evaluation“ (FAO/WHO, 1998).

Assuming complete hydrolysis of amygdalin to cyanide, the amount of amygdalin producing 5 to 20 μg of cyanide is 84 to 338 μg.

6. Conclusion

The toxicity of oral exposure to the cyanogenic glycoside amygdalin is due to the release of cyanide after hydrolysis in the gut by β-glucosidase. Thus the acute toxic effects of amygdalin are those of cyanide.

In humans, depending on the dose, the symptoms of acute amygdalin/cyanide toxicity are nausea, vomiting, diarrhoea, dizziness, tachypnoea, progressing to cyanosis, seizures, coma, and eventually respiratory arrest and death.

There is evidence supporting chronic exposure of cyanogenic glycosides resulting in neuropathy, myelopathy, and/or goitre, but this is complicated by other factors including, malnutrition making causality unclear.

In adults, oral amounts of 1 to 1.5 g of amygdalin per day show little evidence of toxicity, with toxicity evident at doses over 2 g per day, although fatalities have occurred at doses of 0.5 to 2.5 g, particularly in children. The severity of toxicity varies with a number of factors including the preparation of the amygdalin source, status of gut flora, nutritional status and concomitant administration of other nutrients such as vitamins.

On the basis of animal studies, and as assessed by a wide range of regulatory and expert committees, oral intake of 5 to 20 μg/kg/d cyanide is considered to present no appreciable risk, equivalent to 300 to 1200 μg/d for a 60 kg adult and 100 to 400 μg/d for a 20 kg child. Assuming 100% hydrolysis of amygdalin to hydrogen cyanide, this is equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult and 1.7 to 6.8 mg/d for a 20 kg child.

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Attachment 1: Summary of preclinical toxicity

Table 4: Summary of preclinical toxicity of amygdalin and HCN – single dose studies

Reference	Species (strain)	Dose (administration)	Result	Comment
Single dose				
Adewusi and Oke 1985	Rat (Wistar)	880 mg/kg amygdalin (gavage) 600 mg/kg amygdalin followed by 10 U β-glucosidase	LD_{50} 880 mg/kg 100% mortality	Death occurred within 2 to 4 hours
Carter et al 1979	Rat (Sprague Dawley) Rat (Sprague Dawley germ -free)	600 mg/kg amygdalin (aqueous solution, gavage) 600 mg/kg amygdalin (aqueous solution, gavage)	Lethargy, respiratory difficulty, convulsions, died within 2 to 5 hours No visible signs of toxicity	
Newton et al 1981	Rat (Fischer 344)	Approx. 400 to 1100 mg/kg amygdalin (gavage)	LD_{50} 522 mg/kg	Ataxia, cyanotic extremities, laboured respiration, coma, death
WHO 2004	Rat (Sherman) Rat Rabbit	KCN (gavage, oral) HCN, (oral) NaCN, (oral) KCN (oral) HCN, (oral) KCN, (oral) NaCN (oral)	LD_{50} 10 mg/kg LD_{50} 0.156 mmol/kg LD_{50} 0.117 mmol/kg LD_{50} 0.115 mmol/kg LD_{50} 0.092 mmol/kg LD_{50} 0.104 mmol/kg LD_{50} 0.090 mmol/kg	LD_{50} 3 to 4 mg cyanide/kg for all salts in rats
Rauws et al 1982	Rat (Wistar)	50 mg amygdalin/animal (oral or IV)	No evidence of cyanide intoxication.	
Hill et al 1980	Mouse (CD2F1)	Amygdalin 400 to 2220 mg/kg (oral gavage) KCN 3 to 6 mg/kg (i.p.)	LD_{10} approx 450 mg/kg LD_{10} approx 4.2 mg/kg	LD_{50} appears to be between 500 and 750 mg/kg
Rauws et al 1982	Dog (Beagle)	500 mg amygdalin/animal (oral or IV)	No evidence of cyanide intoxication.	

Reference	Species (strain)	Dose (administration)	Result	Comment
Schmidt et al 1978	Dog (mongrel)	0.334 to 2.000 g laetrile (liquid form, gavage) + 7 to 40 crushed sweet almonds OR 0.338 to 4.056 g laetrile (tablet form, orally) + 10 to 40 crushed sweet almonds	6 of 12 dogs dosed with ≥1.00 g laetrile and ≥20 sweet almonds died within 4 hours	Symptoms included respiratory problems motor ataxia, grand mal seizures, disorientation, sinus arrythmia, tachycardia, bradycardia.

Table 5: Summary of preclinical toxicity of amygdalin and HCN – repeat dose studies

Reference	Species (strain)	Dose (administration)	Result	Comment
Repeat dose				
Khander and Edelman 1979	Rat (Fischer 344)	100, 250, 500 or 750 mg/kg/d amygdalin for 5 days (i.p.)	Mortality 4.7%, 30.8%, 44.1% and 56.6% respectively.	
Oyewole and Olayinka 2009	Rat (Wistar)	20 mg/kg/d amygdalin for 14 days (orally) +/- hydroxycobalamin (25 or 50 mg/kg/d)	Amygdalin alone: 1 death, surviving animals showed parenchymal necrosis, portal inflammation and fibrosis in liver. Amygdalin + hydroxycobalamin (either dose) No deaths or liver effects.	
Kovacikova et al 2019	Rabbit (California P19)	0.6 or 3.0 mg/kg/d amygdalin (i.m.) or 60 or 300 mg/kg crushed apricot seeds (in food, orally)	No deaths, no toxic signs, no clinically significant biochemical or haematological changes at any dose.	
Basu et al 1983	Guinea pig	10 mg laetrile +/- 100 mg ascorbic acid for 24 days (oral) 8 mg/kg KCN (single dose, oral) +/- 300 mg/day ascorbate (3 days oral) +/- 10 mg cysteine (3 days oral)	No observable toxic effects KCN alone: mild tremor in 3/8 animals. KCN + ascorbic acid: severe toxicity as tremor, ataxia and paralysis followed by convulsions in 8/8 animals. KCN + ascorbic acid + cysteine: no effect in 3/9 animals, mild tremor in 1/9 and severe toxicity in 5/9	
NTP 1993 (cited in Simeonova 2004; ATSDR 2006; and others)	Rat (F344/N)	0, 3, 10, 30, 100 or 300 ppm sodium cyanide in drinking water for 13 weeks)	Effects on testicular sperm count, epididymal sperm motility and testicular and epididymal weights in male rats at 300 ppm in drinking water (equivalent to 12.5 mg/kg/d, LOAEL). NOAEL 100 ppm in drinking water (equivalent to 4.5 mg/kg/d)	
NTP 1993 (cited in Simeonova 2004; ATSDR 2006; and others)	Mouse (B6C3F1)	0, 3, 10, 30, 100 or 300 ppm sodium cyanide in drinking water for 13 weeks)	No toxic effects. NOAEL 300 ppm in drinking water (equivalent to 26 mg/kg/d)	
WHO 2004	Rat	0, 4.3 or 10.8 mg/kg/d HCN (in diet fumigated with HCN, oral) for 2 years	No treatment related effects. NOAEL 10.8 mg/kg cyanide.	From 1955 study

Attachment 2: Summary of case reports

Table 6: Case reports of amygdalin or HCN exposure

Source	Patient	Exposure	Clinical data	Treatment	Outcome
Beamer et al 1983	22 yr old male	12 to 18 tablets of laetrile.	Initially comatose, unresponsive to pain, muscle rigidity, intermittent tonic clonic seizures, severe metabolic acidosis, almond odour on breath. Lungs, heart, blood glucose normal. Methaemoglobin peaked at 10.5%.	Amyl nitrite 15 to 30 seconds per minute for 3 mins, 100% O_2 ventilation, sodium nitrite 300 mg IV twice, sodium thiosulfate 12.5 g IV, sodium bicarbonate 88 m Eq IV twice .Also gastric lavage, urinary catheterisation and neuromuscular blockade	Full recovery
Bromley et al 2005	68 yr old female with cancer	3 g amygdalin[1]. Also 4800 mg/d Vitamin C, Warfarin 5 mg/d, multivitamins, ubiquinone 150 mg/d, herbal essence, shark cartilage 500 mg/d	Dizziness, feeling unwell, tonic clonic seizures, reduced GCS (minimum 5), metabolic acidosis	Ventilated with 100% oxygen, activated charcoal, hydroxycobalamin 5 g IV infusion	Full recovery.
Chan 2006	28 yr old male, vegetarian	Mixed Chinese herbal prescription[2] drunk as a concoction twice daily	3 week history of gradual onset weakness in 4 limbs. Numbness of toes for 5 months and fingers for 3 months. Mixed sensorimotor axonal neuropathy low serum Vitamin B12.	Lost to follow-up before treatment	
Hall et al 1986	4 yr old boy, Downs syndrome and seizure disorder	12 tablets laetrile (6 g total)[3]	Unresponsive, multiple seizures, areflexic, hypoventilation, slow pulse and BP unobtainable, metabolic acidosis. Whole blood cyanide peaked at 16.3 µg/mL	5 mg diazepam, ventilated with 100% oxygen, amyl nitrite perles by intermittent inhalation, 45 mEq sodium bicarbonate. 5 mL 3% sodium nitrite and 25 mL 25% sodium, thiosulfate by IV infusion	Full recovery

Source	Patient	Exposure	Clinical data	Treatment	Outcome
Kalyanaraman et al 1983	67 yr old female with lymphoma	3 tablets/d laetrile[4]. Previous treatment for lymphoma including vincristine previously ceased.	Progressive paraesthesia of extremities, difficulty standing and walking for 4-6 months. Nerve conduction studies showed partial denervation, conduction velocities unobtainable. Blood cyanide, thiocyanate and cobalamin levels elevated.	Cessation of laetrile	Telephone follow-up reported improvement in walking.
Lam et al 2012	63 yr old female, past metastatic cancer of lung and recent pulmonary embolism	Novodalin (amygdaline extract 500 mg apricot powder) for 5 months	Dyspnoea, cough, tachycardia, hyperventilation, lactic acidosis, normal hepatic and renal function.	IV sodium thiocyanate, fluids, antibiotics, corticosteroids. Blood cyanide concentration 0.14 mg/L on 5th day of admission.	Became haemodynamically stable but oxygen requirements remained high.
Leor et al 1986	65 yr old female with advanced hepatocellular carcinoma and cirrhosis	3 ampoules of 3 g amygdalin over 2 days (Total 9 g).	Coma, apnoeic, low blood pressure, acidosis. Blood cyanide level 0.23 µg/mL 2 hours after hospital admission.	Ventilation with 100% O_2, sodium nitrite (0.6 g), sodium thiosulfate.	Patient regained full consciousness but liver function worsened and oliguria developed over the following days. The patient died 11 days after admission.
Moss et al 1981	32 yr old female with Hippel-Lindau's disease. Patient had undergone hemangioblastoma resection, right nephrectomy and partial hepatectomy.	Single dose of 9 g of laetrile after previous daily use of laetrile and enzyme preparation for 4 years.	Serum cyanide levels were 385 µg/dL on admission and 35 µg/dL 24 hours later.	Stomach lavage, amyl nitrite by inhalation, 50 mg sodium thiosulfate IV and 50 mg by nasogastric tube.	Uncomplicated medical course.
O'Brien et al 2005	32 yr old female with breast cancer and liver metastases	6 amygdalin tablets	Progression from gait disturbance to writing on the ground with decreased consciousness. GCS score between 6 and 11. Rapid pulse, low body temperature, systolic BP and respiration rate, marked metabolic acidosis	Phenytoin (1 g), 6 mg desmopressin, 20 µg/min adrenaline and noradrenaline 7 hours after admission. Broad spectrum antibiotics	Symptomatic recovery.

Source	Patient	Exposure	Clinical data	Treatment	Outcome
Pentore et al 1996	56 yr old female	Approx 300 g choke cherries steeped in alcohol (cyanide levels 4.7 to 15 mg/kg in cherries and 43 to 45 mg/kg in alcohol)[5]	Severe headache, nausea, vomiting, respiratory difficulties, sleepiness. Upon admission, anguished, confused dyspnoic followed by coma and diffusely hypotonic. Atrial fibrillation and bradycardia alternating with supraventricular tachycardia. Severe metabolic acidosis. Normal CT scan. Confused and disorientated for 14 days. 27 days after admission blurred vision and distal paraesthesia of lower limbs, reduction in visual acuity with bilateral disk atrophy. Bradykinesia, proximal rigidity.	Artificial respiration. Pacemaker inserted for 4 days 1 week after admission.	Regained sense of orientation and heart rhythm after 3 weeks. After 14 months Parkinson-like symptoms: masked face, mild rigidity of limbs, shuffling gait, increased salivation. Dysprosodic and dysphonic speech, impaired visual acuity but no clinical signs of sensory-motor neuropathy.
Peterson et al 1979	41 yr old pregnant female with history of verrucous carcinoma of gingiva.	Daily IM injections of "20 mg laetrile" for 10 days starting early 3rd trimester, then daily IM injections of "10 mg laetrile" until delivery	Infant had APGAR of 8 at 1 min, 9 at 5 mins. Appropriate birth weight with mild acrocyanosis. No abnormalities. Maternal and cord blood cyanide levels normal. Mild to moderate jitteriness on Day 2.	No treatment	Some persistent jitteriness at 3 weeks but otherwise normal.
Sauer et al 2015	4 yr old male with history of malignant brain disease	Oral Novodalin "vitamin B17" 4 x 500 mg/d, oral apricot kernel powder (5 to 10/day) Vitamins A, B, D, E and selenium and sulfur powder.	Collapsed after session of CAM treatment. Agitated, unresponsive and encephalopathic, GCS of 3 at hospital arrival. Severe metabolic acidosis. Serum cyanide level 515 µg/L 2 hours after last administration of vitamin B17.	Fluid resuscitation and oxygen administration initially. 2 g sodium thiosulfate administration	Rapid improvement within 2 hrs of sodium thiosulfate administration. Full clinical recovery.

Source	Patient	Exposure	Clinical data	Treatment	Outcome
Shragg et al 1982	67 yr old female with carcinoma of large bowel.	2 months of laetrile injections then 6 months of oral laetrile[6] (one every second day approximately). 12 ground bitter almonds[6]	Crampy abdominal pain followed by collapse. Upon hospital arrival, unresponsive, incontinent of stool, rapid pulse, slow respiration. Initial blood cyanide levels approx. 200 µg/dL. Peak methaemoglobin levels >10%.	Initially oxygen administered by mask and 1 ampoule of amyl nitrite. 300 mg sodium nitrite and 12.5 g sodium thiosulfate IV. Mechanical ventilation, Stomach lavaged. 48 g sodium biphsophate, 18 g sodium phosphate and 30 g activated charcoal via gastric tube.	Alert 20 minutes after sodium nitrite/ sodium thiosulfate.
Smith et al 1977	48 yr old female with lymphoma	6 mg laetrile IV/week and 1.5 mg orally per day	Fever, malaise, headache, severe abdominal cramps, elevated temperature, erythematous rash, lymphadenopathy and hepatosplenomegaly	Laetrile, discontinued, symptoms disappeared in 2 days. Symptoms reappeared 15 days after restarting laetrile with blood cyanide level 1 mg/dL, and again resolved 2 days after discontinuing laetrile.	Symptoms disappeared when laetrile discontinued
	46 yr old male with metastatic large cell anaplastic carcinoma of the lung	Laetrile 500 mg/d orally for 6 months	Progressive neuromuscular weakness of upper and lower extremities and bilateral ptosis.	Laetrile discontinued and symptoms resolved	Symptoms disappeared when laetrile discontinued
Vlad et al 2015	39 yr old female	¼ teaspoon of ground apricot kernels with cyanide content >3000 mg/kg	Unconscious, status epilepticus. Hypothermia, tachycardia, normotensive, sever lactic acidosis, hyperglycaemia, EEG, head CT, MRI and lumbar puncture normal.	Midazolam, supportive treatment.	Recovered.
Grass 2016	28 yr old female	Bitter almonds (amount not clear but possibly 80 g)	Nausea, shortness of breath followed by unconsciousness, GCS score 4 to 5, bradycardia and unrecordable BP, but weak pulse, metabolic acidosis	Naloxone, flumazenil. Intubation, “crystalloid infusions”, phenylephrine. 5 mg hydroxycobalamin IV x 2, 15 g IV sodium thiosulfate.	GCS score 15 the following day, and extubation without complication. No further details.

Source	Patient	Exposure	Clinical data	Treatment	Outcome
Liegner et al 1981	61 yr old female with past history of breast cancer	500 mg laetrile tablet twice daily for 5 years. Recent exposure to flurazepam HCl, phenolphthalein laxative, chlorothiazide, meprobamate, secobarbital and amobarbital, oxycodone and methocarbamol	Sudden onset rigors with fever. No sign of infection site, chest x-ray, urinalysis, urine throat and blood cultures normal. Diagnosed granulocytic maturation arrest on the basis of bone marrow aspirate.	Placed in isolation, laetrile withheld. Fever resolved in 3 days, white blood cell count normal in 9 days. Laetrile restarted at 500 mg twice daily and developed chills, aches, malaise within 7 days, followed by paronychia of finger, sores on tongue, fever and headache. Agranulocytosis again recorded. Placed in isolation, treated with IV cefamandole naftate 8 g/day.	Full recovery, remained well and avoided use of laetrile.
Roberts et al 2011	66 yr old female	80 – 100 apple seeds, chewed and swallowed[7]	Slight anxiety, blood CN level < 20 ng/mL	50 g activated charcoal with sorbitol given 4 hours post-ingestion. No other treatment	After 4 hours observation, left in good condition. No subsequent adverse events on follow-up
Rubino et al 1979	49 yr old female with history of nodular lymphoma	20 to 40 apricot pits containing 409 mg cyanide/100 g moist seeds..	Headache, weakness, disorientation, nausea within 30 minutes of ingesting apricot pits. Vomited substantial quantity of pits. Methaemoglobin level 5% (normal <3%) and blood cyanide level 3.2 mg/L (>1 mg/L considered toxic) after treatment	Inhalation of amyl nitrite, IV administration of 10 mL of 3% sodium nitrite and 50 mL of 25% sodium thiosulfate	Symptoms resolved, discharged after 3 days.
Humbert et al 1977	11 month old female	1 to 5 500 mg amygdalin tablets	Lethargy, vomiting, irregular breathing, shock, acidosis, coma. Cyanide blood concentration 29 µg/dL. Respiratory arrest 14 hours after ingestion.	Bicarbonate, plasma expanders, sodium nitrite and sodium thiosulfate (doses not stated)	Died 3 days after administration

Source	Patient	Exposure	Clinical data	Treatment	Outcome
Ortega and Creek 1978 from Blaheta	2 year old	Amygdalin 500 mg orally + 3.5 g IV daily. Parenteral dose then administered as enema	Vomiting, diarrhoea, lethargy, tachypnoea, cyanosis after second enema		
Sadoff et al 1978 (from Blaheta	Adult	12 g amygdalin	Dizziness, convulsions, tetanic contractures of the hands, coma		Died 1 day after administration
Maxwell 1978 (from Blaheta)	Adult	2 times "normal" dose of amygdalin resulting in blood level of 600 µg HCN/dL	No signs of toxicity		
Speijers (1993)	17 yr old female	2.6 g oral amygdalin,			Died 24 hours after ingestions despite regularly taking 4 g amygdalin IV with no adverse effects.
Suchard et al 1998)	41 yr old female	30 apricot kernels (approx 15 g) chewed and swallowed	Weakness and numbness, progressing to dyspnoea, difficulty swallowing, unresponsiveness, hypotonia, metabolic acidosis. Whole blood cyanide 43.1 µmol/L 5 hours after ingestion. Maximum methaemoglobinaemia 10.5%	S.C. adrenaline, IV saline, methylprednisolone, dextrose, naloxone and diphenhydramine with no response. Amyl nitrate by inhalation, 300 mg sodium nitrite and 12.5 g sodium thiosulfate by IV infusion. Activated charcoal 50 g. Further 150 mg sodium nitrite and 12.5 g sodium thiosulfate by IV infusion, followed by sodium thiosulfate at 2 g/h for 24 hours.	Hospital discharge in stable condition after 2 days.

1. Potentially producing up 10 180 mg cyanide. Toxicity potentially exacerbated by high doses of Vitamin C.
2. Herbal mix included "baizhu" (Astractylodes macrocephala) 56.25 g, ''beiwuweizi'' (Schisandra chinensis) 150 g, ''chuanxiong'' (Ligusticum chuangxiong) 15 g, ''danggui'' (Angelica sinensis) 75 g, ''digupi'' (Lycium chinense) 37.5 g, ''fuling'' (Poria cocos) 75 g, ''huangbai'' (Phellodendron chinense) 37.5 g, ''huangqi'' (Astragalus membranaceus) 37.5 g, ''jingjie'' (Schizonepeta tenuifolia) 3 g, ''longdan'' (Gentiana manshurica) 37.5 g, ''qinghao'' (Artemisia annua) 15 g, ''sharen'' (Amomum villosum) 37.5 g, ''renshen'' (Panax ginseng) 75 g, ''taoren'' (Prunus persica) 30 g, and

‘‘wangbuliuxing’’ (Vaccaria segetails) 15 g. Chronic cyanide toxicity from Prunus persica component of herbal mix exacerbated by Vitamin B12 deficiency presumed to be cause of neuropathy.

3. Potentially producing between n 30 and 309 mg hydrogen cyanide.
4. Potentially producing 25-75 mg cyanide.
5. Approximately 10 to 20 mg cyanide.
6. Laetrile tablets averaged 11.5 mg amygdalin (average 6% cyanide); Average cyanide content 6.2 mg per bitter almond.
7. Sample of apple seeds yielded 0.410 mg/g cyanide, suggesting total dose of cyanide was 1.4 to 1.8 mg cyanide.

DR SUSAN JAMES
Ph. D. Pharmacology (Toxicology)
REGULATORY AFFAIRS CONSULTANT

In relation to toxicity report for amygdaline/HCN:

I, the undersigned, declare that I have:

- Made an objective and impartial assessment of the data in the light of current scientific knowledge;
- Have no competing interests or conflict of interests in providing this report.

I further declare that the expert report represents my own view.

Further, I declare the following to be the full extent of the professional relationship between myself and the applicant: subcontracted consultant for preparation of this report.

Name of expert: Susan James

Signature: 

Date: 15 June 2020

Address: 14 Selwood Court, VIC 3178

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3.3 Expert review commissioned by TGA

Scheduling Evaluation Report

Application to amend the Poisons Standard with respect to amygdalin and hydrocyanic acid for human therapeutic use

Chinese Medicine Industry Council of Australia Ltd (CMIC)

Evaluator: [redacted]

Delegate: [redacted]

Date: 23/10/2020

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1. EXECUTIVE SUMMARY

The Chinese Medicine Industry Council requests:

a) A rescheduling of amygdalin from Schedule 10 to Schedule 4 except when included in or expressly excluded from Schedule 4;

b) A new Schedule 4 entry for amygdalin when included as a natural component in traditional Chinese medicines for oral use in adults with an exclusion to 'unscheduled' when the maximum recommended daily dose is equivalent to no greater than 5 mg of amygdalin; and

c) A change to the Schedule 4 entry for hydrocyanic acid with an exclusion when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults.

Amygdalin (D-mandelonitrile-β-D-glucoside-6-β-glucoside) is a cyanogenic glycoside found naturally in plants including seeds of the Prunus genus. It is metabolised in mammalian gut by enzymes in the gut wall and gut flora to hydrogen cyanide. Amygdalin is currently prohibited from use in therapeutic goods in Australia even at very low levels.

Studies have found the oral single dose that is lethal to 50% of animals (LD_{50}) is in the range 522 to 880 mg/kg for amygdalin and 3 to 22 mg cyanide ion/kg for cyanide in rats. In mice the single dose lethal to 10% of animals (LD_{10}) is approximately 450 mg/kg for orally administered amygdalin, and 4.2 mg/kg in intraperitoneally administered cyanide.

In longer term studies (13 weeks) no observable toxic effects were observed after oral exposure to 4.5 mg/kg/d cyanide in rats and 26 mg/kg/d in mice. After 12 months on a diet containing 50% cassava (containing a different cyanogenic glycoside to amygdalin and resulting in exposure to approximately 0.102 mg cyanide per day) rats displayed impaired motor coordination and cellular changes in liver and pancreas. Amygdalin and cyanide are not observed to be carcinogenic in animal studies. Amygdalin has been shown to be genotoxic in some but not all test systems. Cyanide has been found to be negative in genotoxicity tests systems at non-cytotoxic doses.

Amygdalin has been shown to produce foetal abnormalities at close to materno-toxic doses in hamsters when administered in a single dose. The effects of amygdalin from ground apricot kernels on reproduction in rats is unclear. In rabbits cyanide at 5 g/100 g in the diet produced impaired fertility. A diet of raw cassava resulted in impairments in fertility and some reproductive and developmental parameters at materno-toxic doses, but no effects when the cassava content in the diet was 45% or less.

Case reports suggest that toxicity in adults can occur with oral amygdalin/laetrile in single doses ranging from 3 g to 10.5 g (but this could be as low as 0.6g) and daily

doses from 0.42 g to 1.5 g, with fatality at doses of 3g and 10.5g in adults and 0.5-2.5 g in infants. Toxicity in adults has been reported after ingestion of single doses of apricot or peach kernels containing the equivalent of 25 mg to 1384 mg amygdalin or after ingestion of other seed containing preparations (bitter almonds plus laetrile tablets, apple seeds, or chokecherries) with a total estimated amygdalin content ranging from 60 mg to 4 g. However, little evidence of toxicity has been observed in clinical studies using a combination of IV amygdalin treatment plus oral amygdalin in doses of 1.5 g or 2g daily. Based on the average lethal dose of cyanide, which is reported to be in the range 0.5 to 3.5 mg/kg, the lethal dose of amygdalin in adults is estimated to be 9 to 60 mg/kg (540 to 3600 mg for a 60 kg adult).

This suggests that there is significant variability in the toxic response to amygdalin ingestion. The severity of cyanide toxicity is known to be influenced by a range of factors which affect the metabolism and detoxification of amygdalin to cyanide, including the amygdalin content of the herbal ingredient, which may vary depending on varietal differences, seasonal effects on growth, freshness, and processing; the β-glucosidase content of the herbal ingredient, which aids the conversion of amygdalin to cyanide; the route of administration, e.g. oral administration results in higher cyanide levels compared to IV administration, which bypasses the gut β-glucosidase enzymes; chewing or processing (e.g. grinding) of the herbal ingredient, which can release the β-glucosidase in the herbal ingredient, increasing the conversion to cyanide; co-administration with other substances (e.g. other herbal ingredients) that may influence either the metabolism of amygdalin to cyanide or the detoxification of cyanide; and inter-individual variability with respect to gut microbial flora and nutritional status.

On the basis of animal studies, regulatory authorities have concluded that oral intake of 5 to 20 µg/kg/d of cyanide is not of toxicological concern over the long term, and Food Standards Australia New Zealand have established an acute reference dose for cyanide of 0.8 mg/kg bw for short term intake. Assuming complete hydrolysis of amygdalin to cyanide, the amount of amygdalin producing 5 to 20 µg hydrogen cyanide is 84 to 338 µg. Thus, a daily oral intake of 5.1 to 20.3 mg amygdalin for a 60 Kg adult and 1.7 to 6.8 mg for a 20 kg child is considered to present no appreciable risk. A dose of 5 mg amygdalin is also lower than the permitted quantity in some foods and drinks.

However, there is less evidence for the safety of higher doses of amygdalin, especially considering the wide variability on cyanide toxicity observed following oral administration of amygdalin-containing substances.

The safety data may support the exclusion from Schedule 10 for medicines containing a maximum daily dose of less than 5 mg amygdalin but do not support the proposed exclusion from Schedule 10 when included as a natural component in traditional Chinese medicines for oral use in adults and inclusion in Schedule 4 at a maximum daily adult dose of more than 5 mg).

2. PURPOSE OF APPLICATION

Regulatory background issues

The Submission included information provided by the Medicines Scheduling Secretariat Team (23 November 2017) relating to the available scheduling history of amygdalin, which is summarised as follows:

Date	Amygdalin Scheduling	Reason for decision
November 1974	A new entry for '*amygdalin including defatted kernels of bitter almonds, apricots and peaches containing amygdalin*' was created in the prohibited list of the Uniform Poisons Standard	On the basis of its supply as a new drug for the treatment of cancer (Laetrile)
May 1975	No apparent action regarding the scheduling of amygdalin	Evidence provided by the Australian Drug Evaluation Committee which indicated that there was no evidence that amygdalin had any effect against cancer and no evidence of its safety
November 1977	The PSSC considered a proposal to amend the scheduling of amygdalin to Schedule 7 and recommended that the production of amygdalin in Australia under proper supervision, and its distribution under strict controls, as proposed in Victoria, free of charge, should be investigated as a matter of urgency.	To allow compassionate use in Victoria in certain cancer patients, to eliminate the exploitation of cancer patients. Although new toxicity data were considered adequate, in making this statement the PSSC in no way implies the admission of efficacy or any therapeutic value of amygdalin.
August 1986	The DPSC noted that amygdalin was still being imported on an individual patient usage basis despite the opinion that there is no evidence of its efficacy in the treatment of advanced cancer. The scheduling of amygdalin at this time was noted to be Schedule 7 and it is assumed that this recommendation occurred in November 1977.	No information is available regarding the wording of the Schedule 7 nor reasons for its inclusion
August 1992	Included amygdalin for therapeutic use in Appendix C of the SUSDP (now Schedule 10)	Due to concerns about its serious toxicity profile and lack of efficacy data

November 1999	NDPSC clarified that the SUSDP entry for amygdalin acid does not apply to sweet almond oil	
February 2000	NDPSC recommended to the NZ Minister Of Health that amygdalin be moved into Part 1 of the Medicines Regulations (Prescription medicines)	This recommendation relates to the harmonisation of scheduling of 'medicines banned from human therapeutic use' in Australia (listed in Appendix C to the SUSDP) and New Zealand. It appears that no new efficacy or safety data were considered by the NDPSC. At the time, amygdalin was not scheduled in NZ2005. The NZ MCC agreed that amygdalin should be classified as a prescription medicine at all strengths to harmonise with the Australian Appendix C scheduling. [1]
February 2005	When considering the availability of certain substances for therapeutic use listed in Appendix C, the NDPSC agreed that no action should be taken at the time to limit availability of amygdalin	Amygdalin for the treatment of terminal cancers appeared to be the Appendix C substance most often accessed through the Special Access Scheme (SAS) (under Category A notification for "life threatening conditions"). The committee did express concern however over the apparent contradiction that certain substances which had been included in Appendix C on the grounds that they present such danger to health as to warrant prohibition should be made available for therapeutic use under special circumstances.

This information indicates that in 1974, amygdalin was included in the prohibited list of the Uniform Poisons Standard on the basis of its supply as a new drug for the treatment of cancer (Laetrile). At a later date (presumably in November 1977), the scheduling of amygdalin was amended to Schedule 7 of the SUSDP to allow compassionate use in Victoria in certain cancer patients, despite the lack of efficacy data for this use but taking into account the adequacy of the toxicity data. The scheduling of amygdalin was last amended in August 1992 to include amygdalin for therapeutic use in Appendix C of the SUSDP (now Schedule 10), due to concerns about its serious toxicity profile and lack of efficacy data. As part of the harmonisation of the scheduling of Appendix C medicines, the NDPSC recommended

[1] https://medsafe.govt.nz/profs/class/Agendas/agen htm

to the NZ Minister Of Health in 2000 that amygdalin be moved into Part 1 of the Medicines Regulations (Prescription medicines), which ensures that the regulatory process will prevent their being granted consent to market. In order to prevent their use in even very low concentrations, the New Zealand schedule includes the words "at all strengths".

The scheduling of amygdalin was not considered again until 2005, when the NDPSC agreed that no action should be taken at the time to limit its availability for therapeutic use, despite concerns that substances of such danger to health as to warrant prohibition of sale, supply and use but expressed concern over the apparent contradiction that certain substances which had been included in Appendix C on the grounds that they present such danger to health as to warrant prohibition should be made available for therapeutic use under special circumstances.

Current entries in SUSMP

AMYGDALIN for therapeutic use is included in Schedule 10 (substances of such danger to health as to warrant prohibition of sale, supply and use).

HYDROCYANIC ACID is included in Schedules 4 and 7 and in Appendices F, G and J, as follows:

- HYDROCYANIC ACID for therapeutic use is included in Schedule 4
- HYDROCYANIC ACID is included in Schedule 7 **except**:
  a) when included in Schedule 4; or
  b) its salts and derivatives other than cyanides separately specified in this Schedule.
- HYDROCYANIC ACID, when included in Schedule 7, is required to be labelled with the following Appendix F Warning Statements and Safety Directions:
  - Warning Statement 13: 'May be fatal if inhaled, swallowed or absorbed through skin'.
  - Safety Directions 4: 'Avoid contact with skin' and 8: 'Avoid breathing dust (or) vapour (or) spray mist'.
- Appendix G (Dilute preparations): The requirements of this Standard do not apply to HYDROCYANIC ACID at a concentration not more than 1 microgram per litre or kilogram.
- Appendix J (Schedule 7 poisons requiring additional controls on availability and use): HYDROCYANIC ACID AND CYANIDES: Poisons marked with 'p' have been identified as representing a significant risk to public health. Additional restrictions on their possession and use must be applied through an authorisation or licensing process which includes a case by case assessment of risks to public health.

Proposed changes

The Chinese Medicine Industry Council requests:

d) A rescheduling of amygdalin from Schedule 10 to Schedule 4 except when included in or expressly excluded from Schedule 4;

e) A new Schedule 4 entry for amygdalin when included as a natural component in traditional Chinese medicines for oral use in adults with an exclusion to 'unscheduled' when the maximum recommended daily dose is equivalent to no greater than 5 mg of amygdalin; and

f) A change to the Schedule 4 entry for hydrocyanic acid with an exclusion when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults.

The suggested amended scheduling is as follows (changes underlined):

Schedule 10

AMYGDALIN for therapeutic use except when included in or expressly excluded from Schedule 4.

Schedule 4

AMYGDALIN when included as a natural component in traditional Chinese medicines for oral use in adults **except** when the maximum recommended daily dose is equivalent to no greater than 5 mg of amygdalin.

HYDROCYANIC ACID for therapeutic use except when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults.

Schedule 7

HYDROCYANIC ACID **except**:

a) when included in Schedule 4; or

b) its salts and derivatives other than cyanides separately specified in this Schedule.

No changes to the Appendix F, G or J entries are proposed.

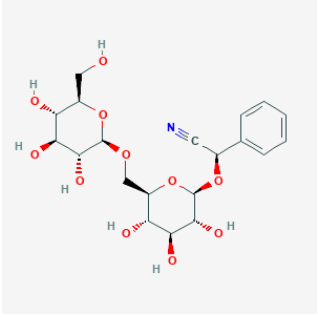
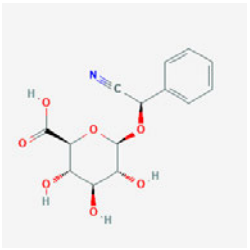
3. SUBSTANCE

Description of the substance

Amygdalin is a cyanogenic glycoside found naturally in bitter almonds, apricot kernels and seeds of other plants in the *Prunus* genus. It is also referred to as Vitamin B17, although it is not a vitamin, and often as laetrile, although laetrile and amygdalin are not identical (see comparison of the nomenclature and structure in

the table below; Source: Pub Chem; ChemID; Chemical Book; Merck Index). Laetrile is a semi-synthetic compound that is synthesised from amygdalin by hydrolysis of one of the β-D-glucopyranosyl groups.

The toxicity of oral exposure to these cyanogenic glycosides is due to the release of cyanide after hydrolysis of the nitrile group in the gut by β-glucosidase.

International non-proprietary name (INN):	**Amygdalin***	**Laetrile**	**Hydrogen cyanide (AAN)**
Synonyms:	(R)-Amygdalin; (R)-Laenitrile; Amygdaloside; Vitamin B17; D-mandelonitrile-β-D-glucoside-6-β-glucoside; Mandelonitrile-β-gentiobioside; (R)-α-((6-o-β-D-Glucopyranosyl-β-D-glucopyranosyl)oxy)benzeneacetonitrile	(R)-Laetrile; Vitamin B(sub17); D-mandelonitrile-β-glucuronide; l-Mandelonitrile-β-glucuronoside; β-D-Glucopyrano siduronic acid, α-cyanobenzyl	Hydrocyanic acid*; Prussic acid
IUPAC Name	(2*R*)-2-phenyl-2-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-[[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]oxymethyl]oxan-2-yl] oxyacetonitrile	(2*S*,3*S*,4*S*,5*R*,6*R*)-6-[(*R*)-cyano(phenyl)methoxy] -3,4,5-trihydroxyoxane-2-carboxylic acid	Formonitrile
CAS Number:	29883-15-6	1332-94-1	74-90-8
Structural formula (Pub Chem)			H—C≡N
Molecular formula	$C_{20}H_{27}NO_{11}$	$C_{14}H_{15}NO_7$	HCN
Molecular weight	457.4 g/mol	309.27 g/mol	27.03 g/mol

* TGA Herbal Component Name.

Amygdalin is available for use as an Equivalent Ingredient in: Export Only, Listed Medicines.

Hydrocyanic acid is not available as an Active Ingredient in any application; Not available as an Excipient Ingredient in any application; Available for use as an Equivalent Ingredient in: Export Only, Listed Medicines.

Hydrogen cyanide is Available for use as an Active Ingredient in: Biologicals, Export Only, Listed Medicines, Over the Counter, Prescription Medicines; Available for use in Listed Medicines as a Homoeopathic Ingredient only; Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines; Not available as an Equivalent Ingredient in any application.

None of these substances is the subject of a pharmacopoeial monograph.

Monographs for Bitter Apricot Seed and Apricot Kernel are included in Pharmacopeia of the People's Republic of China and the Japanese Pharmacopoeia, respectively.

Pharmacology

PHARMACODYNAMIC PROPERTIES

Mechanism of action

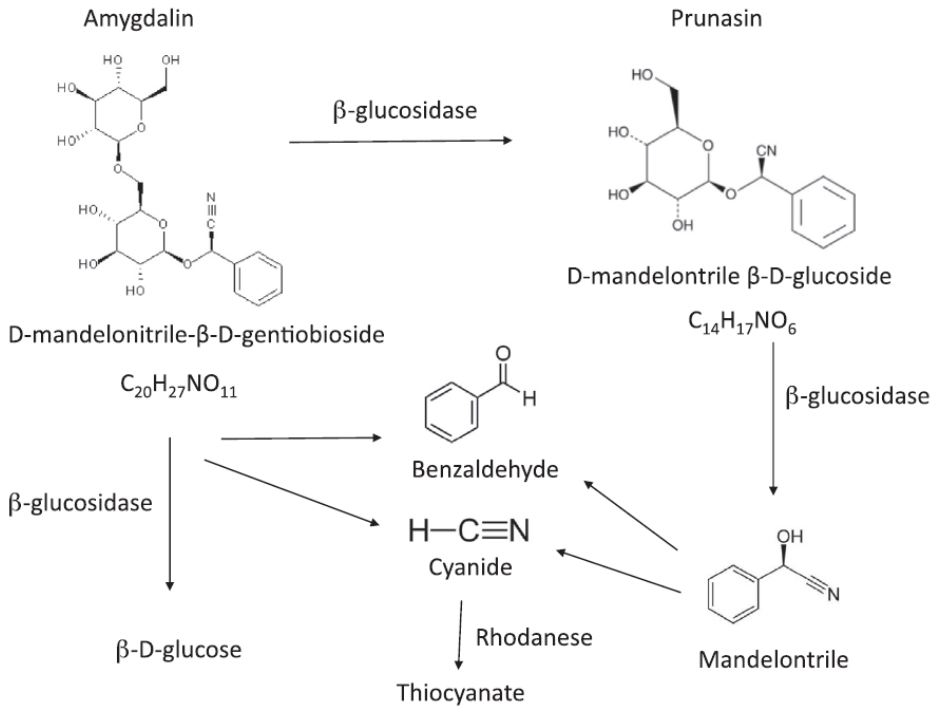
Amygdalin (D-mandelonitrile-β-D-glucoside-6-β-glucoside; mandelonitrile-β-gentiobioside) is a cyanogenic glycoside. It is metabolised in mammalian gut by β-glucosidase in the gut wall and gut flora to hydrogen cyanide. Thus, the acute toxic effects of amygdalin are those of cyanide, which halts cellular respiration by acting as a non-competitive inhibitor for the mitochondrial enzyme, cytochrome c oxidase.

Pharmacokinetics

The pharmacokinetics of orally administered amygdalin have been well studied, although the location, source and role of some of the enzymes involved in the metabolic processes are still unclear.

Metabolism

The metabolic pathway of amygdalin (Blaheta 2016) is shown below:



The main pathway of amygdalin metabolism involves the cleaving of the terminal glucose by β(1-6)-glucosidase activity in the gut wall of the small intestine, producing prunasin (D-mandelonitrile β-D-glucoside). Prunasin is in turn metabolised to mandelonitrile by β-glucosidase in gut bacteria in the large intestine or colon. Mandelonitrile subsequently dissociates to cyanide and benzaldehyde.

The proportion of amygdalin metabolised to cyanide varies depending on a range of factors, including co-ingestion of sources of β-glucosidase (such as in plant seeds and apricot kernels), which will increase production, and reductions in the gut flora responsible for conversion of prunasin to mandelonitrile, which may reduce production of cyanide (Toxicity review: amygdalin and hydrogen cyanide).

Absorption

Following ingestion of different foods containing 6.8 mg total cyanide, peak blood cyanide levels ranged from 1.44 to 16.95 µM with t_{max} ranging from ~25 to 150 min (Abraham 2016). The peak blood cyanide level after ingestion of about 2.1 g bitter apricot kernels was 15.46± 5.12 µM (t_{max} ~ 25 min). The differences in the rate of absorption of cyanide between the different foods was attributed to the different amounts of β-glucosidase in the foods and their rates of reaction. Despite blood cyanide levels reaching ≥20 µM (approximately 0.5 mg/L, the level at which flushing or tachycardia have been reported (ATSDR 2006) in several subjects after consumption of bitter almond kernels or cassava, no clinical symptoms of cyanide toxicity were observed.

The severity of cyanide toxicity from ingestion of bitter almonds or apricot kernels is influenced by a number of factors, including the amygdalin content of the kernels, whether the kernels are chewed or processed prior to ingestion, and the

combination with other ingredients. Chewing and some processing releases β-glucosidase in the kernels, thereby increasing toxicity, whereas other forms of processing or combination with herbs such as Mahuang (ephedra) that reduce levels of prunasin may reduce toxicity.

Distribution

Once cyanide is absorbed, it is rapidly distributed by the blood throughout the body.

Excretion

In humans, cyanide is detoxified primarily via trans-sulfuration to form thiocyanate but can also be detoxified by reaction with hydroxycobalamin (Vitamin B12) to form cyanocobalamin.

Thiocyanate undergoes renal clearance with an elimination half-life of approximately 2.7 days in normal renal function.

PRECLINICAL SAFETY DATA

A review of the non-clinical toxicity literature relating to amygdalina and hydrogen cyanide was carried out by the applicant (see Toxicity Review). A search of the Embase, Medline, Dart (for hydrogen cyanide) and ToxNet databases identified animal studies relating to acute, sub-acute and sub-chronic toxicity, carcinogenicity, mutagenicity/genotoxicity, reproductive and developmental toxicity, and toxicity in combination with herbal or other ingredients.

Acute toxicity

Acute oral toxicity studies in animals have reported LD_{50} values for amygdalin of between 522 mg/kg and 880 mg/kg in rats (Newton 1981; Song 2014; WHO 2012; Adewusi 1985; Carter 1979) and an LD_{10} value of 450 mg/kg bs in mice (Hill 1980). In dogs, cyanide poisoning resulting in death occurred at doses ≥1.00 g laetrile when administered with ≥20 sweet almonds, which contain the enzymes required to hydrolyse amygdalin, but not amygdalin itself. Single oral and IV doses of 50 mg amygdalin to Wistar rats and 500 mg to Beagle dogs found no evidence of cyanide toxicity (Rauws 1982).

The ATSDR (2006) reported oral LD_{50} values for cyanide of 3 to22 mg /kg in rats and approximately 2.5 mg/kg in rabbits.

Sub-acute and sub-chronic toxicity

In rats, amygdalin doses of 100, 250, 500 and 750 mg/kg bw/d for 5 days resulted in mortality of 4.7%, 30.8%, 44.1% and 56.6% respectively, with the majority of the deaths occurring in the first 3 days of treatment (Khandekar 1979). In guinea-pigs, pretreatment with ascorbate was found to enhance the toxicity of a single dose of potassium cyanide at 8 mg/kg bw but administration with cysteine reduced the toxic effects (Basu 1983). When oral amygdalin was administered to 32 rats (4 per group), at a dose of 20 mg/kg bw daily for 14 days, with or without hydroxycobalamin (25 mg/kg bw or 50 mg/kg bw), one of the rats who received

amygdalin without the antidote died of cyanide poisoning before the end of the experimental period while no mortality was recorded in rats who received the antidote (Oyewole 2009). In rabbits, IM amygdalin at a dose of 0.6 or 3.0 mg/kg bw (equivalent to 0.035 and 0.18 mg/kg bw cyanide) daily for 14 days, or 60 or 300 mg/kg bw crushed apricot seeds (equivalent to 3.12 mg/kg bw amygdalin or 0.18 mg/kg bw cyanide and 15.6 mg/kg bw amygdalin or 0.92 mg/kg bw cyanide, respectively) in food daily for 14 days had little effect on the health of the rabbits, with no deaths and no clinically significant changes in biochemical or haematological parameters (Kovacikova 2019).

A pivotal toxicity study conducted by the USA National Toxicology Program in 1993 found no treatment-related deaths, biologically relevant biochemical changes, clinical signs or histopathological effects in the central nervous system when rats and mice were administered sodium cyanide in drinking water at concentrations of 0, 3, 10, 30, 100 and 300 ppm for 13 weeks (equivalent to up to 12.5 mg/kg bw/d in rats and 26 mg/kg bw/d in mice). However, male rats exhibited effects on testicular sperm count, epididymal sperm motility and testicular and epididymal weights at the highest dose (12.5 mg/kg bw/d) and this was considered the Lowest observable adverse event level (LOAEL), with 4.5 mg/kg bw/d as the No observable adverse events level (NOAEL) for regulatory purposes.

Carcinogenicity

No long term or carcinogenicity studies of amygdalin have been identified but a one-year study found no carcinogenic effects in rats fed a diet of normal rat chow, 50% fresh cassava and 50% normal rat chow, or 75% fresh cassava and 25% normal rat chow (WHO report 2012). The average cyanide concentration in the cassava was 10 mg/kg, resulting in average exposures of 0, 0.075 or 0.102 mg cyanide per animal per day. Decreased body weights from 3 months until the end of the study were reported in animals fed both the cassava diets. Motor coordination was significantly decreased in both cassava diet groups from 5 months. Histopathology conducted at the 12 month time point showed signs of toxic hepatitis with hyperplasia and microvascular changes in hepatocytes, and mild atrophy of pancreatic acini with minimal focal dilatation of ducts, in both cassava diet groups also.

A 2-year, long-term study in which rats were administered up to 10.8 mg/kg cyanide in the diet, found no treatment-related effects on survival, growth, signs of toxicity or histopathological changes in organs (Simeonova 2004). Cyanide exposure has not been correlated with carcinogenicity in humans or animals (ATSDR 2006).

Genotoxicity

The mutagenicity of amygdalin as well as mandelonitrile glucuronide was tested in *Salmonella typhimurium* strains TA98 and TA100. Amygdalin was found to be mutagenic in mouse host-mediated assays after a single oral dose of 250 mg/kg bw amygdalin. Urine collected from mice dosed with either 125 mg/kg bw or 250 mg/kg bw amygdalin was also mutagenic, with mutagenicity increased in the presence of β-glucuronidase and arylsulfatase (Fenselau 1977). However, a study

found no mutagenic activity from amygdalin at concentrations up to 100 µg/mL in a test measuring spontaneous convertants and revertants in a diploid strain of *Saccharomyces cerevisiae* (Todorova 2017).

In a review of the use of the hepatocyte primary culture DNA repair test (HPC/DNA repair test), amygdalin is stated to be negative in the HPC/DNA repair test and its carcinogenic status is stated as "uncertain" (Williams 1984).

Cyanide salts (KCN, NaCN) have been found negative in a majority of bacterial mutagenicity tests in *Salmonella typhimurium* and *Escherichia coli*, and negative for chromosomal aberration and DNA repair. Cyanide induced DNA damage in some studies, but only at cytotoxic doses (Simeonova et al 2004, ATSDR 2006).

Fertility and Reproduction

A reproductive and developmental study with amygdalin in pregnant hamsters treated with a single oral dose of amygdalin (200 to 275 g/kg) on gestational day 8 (Willhite 1982; WHO 2012) found evidence of maternal toxicity at doses of 250 mg/kg and above, and dose-related foetal abnormalities at doses of 200 mg/kg and above. The whole blood cyanide concentration was 4.0 ± 1.1 nmol/mL 2.5 hours after the oral administration of 275 mg/kg amygdalin. A single IV dose of 275 mg/kg amygdalin on gestational day 8 did not produce maternal or foetal effects, and resulted in a whole blood cyanide concentration of 0.06 ± 0.03 nmol/mL. A single oral dose of 275 g/kg amygdalin resulted in no foetal abnormalities when administered with an initial i.p. injection of 300 mg/kg sodium thiosulfate followed by additional sodium thiosulfate i.p. injections administered every 120 minutes for 10 hours after the amygdalin dose. It is unclear whether the foetal effects seen in the oral dose study were due to maternal toxicity.

The effect of ground apricot kernels (10% in the diet) on reproduction in Sprague Dawley rats was examined in two studies (Miller 1981). Rats fed ground kernels containing low (<50 mg/100 g), medium (100 to 200 mg/100 g) or high (>200 mg/100g) levels of cyanide for 5 weeks showed no significant changes in blood chemistry between groups. In female but not male rats liver rhodanese activity and thiocyanate levels increased with increasing apricot kernel levels in the food. Urinary excretion of thiocyanate was higher in the two high dose groups than the control or low dose groups. Rats fed kernels containing either the low or high cyanide levels for 15 weeks and then bred with rats of the opposite sex on the same diet had a similar parturition index but 3 day survival index, lactation index and weaning weight were significantly lower in the high dose group than the low dose group, although the control group had a lower parturition index, 3 day survival index and weaning weight than the low dose group. Birth weights were not different between groups.

In a fertility study (Olusi 1979), female rats treated for 2 weeks with 5 or 10 g potassium cyanide/100 g diet (equivalent to approximately 1000 or 2000 mg cyanide /kg bw/d) failed to conceive and exhibited dose dependent decreases in body weight gain, blood haemoglobin (18% and 23%) and serum T4 concentration

(54% and 74%). Female rats fed raw cassava exhibited similar changes in body weight gain, blood haemoglobin and serum T4 concentrations as the high dose potassium cyanide-fed group, but 40% conceived compared to 90% in controls. Significant reductions in average litter size and individual birth weight and an increase in neonatal deaths and poor development and reduced brain weight in surviving pups.

However, a cassava based diet containing 0, 15, 30 or 45% cassava root meal had no effects in reproduction and growth in female rabbits or their offspring (Eshiett 1980).

These results suggest that high dose cyanide diets may have some effects on fertility and reproduction.

Toxicity in combination with herbal or other ingredients

A recent study (Song 2016) examined the toxicity of the individual and combined components of a Traditional Chinese herbal medicine composed of the dried ripe seeds of *Prunus armenica* (containing amygdalin, and known as *Xingren* in Chinese) and the dried herbaceous stems of *Ephedra sinica Stapf* (containing ephedrine and pseudoephedrine and known as *Mahuang* in Chinese). An acute oral toxicity study in Kunming mice, the LD_{50} of *Mahuang* (M), *Xingren* (X), and combinations of the two ingredients in the ratios MX(4:1), MX(2:1), MX(1:1), MX(1:2) and MX(1:4) were 93.2, 29.9, 87.9, 81.6, 81.4, 64.6, and 59.3 g/kg bw, respectively, demonstrating that *Xingren* alone is more toxic than *Mahuang* or the combinations but even a combination of MX(1:4) is markedly less toxic than *Xingren* alone. The concentration of amygdalin (L-amygdalin + D-amygdalin) was similar in all combinations to that of *Xingren* alone, but this was a consequence of a reduction in L-amygdalin and an increase in D-amygdalin in combination with *Mahuang*. It was suggested that the stereoselective metabolism of amygdalin facilitated by Mahuang acts to enhance and control the effects of Xingren in the MX combination.

A study in rats (Tang et al 2017) found that cinnamic acid (3.03 mg/kg), amygdalin (56.97 mg/kg), glycyrrhizic acid (12.42 mg/kg) and liquiritin (3.79 mg/kg), or a combination of all four compounds, significantly altered the pharmacokinetics of a combination of Ephedra alkaloids (20 mg each of ephedrine, pseudoephedrine and methylephedrine, administered orally). The addition of amygdalin significantly increased the Cmax and $AUC_{0\text{-}t}$ of ephedrine and pseudoephedrine, reduced the mean residence time of all three Ephedra alkaloids, and decreased the $AUC_{0\text{-}t}$ of methylephedrine. The Traditional Chinese herbal medicine Ephedra decoction contains the Ephedra alkaloids as well as the other 4 compounds and the study authors suggest that the pharmacokinetic changes in the Ephedra alkaloids by the other components of the decoction may be of relevance to the clinical use of ephedra in Traditional Chinese medicine.

Ihedioha (2002) examined the effect of traditional processing methods in the production of gari (toasted cassava granules), on the cyanogen content and toxicity of the gari. Traditionally gari is enriched with red palm oil (RPO, which consists

primarily of fatty acids) during production. The toxic component of cassava is prunasin, which is converted to hydrogen cyanide. Two samples of gari were produced, one with 15 mg/kg RPO mixed in prior to fermentation and one without. Otherwise the preparation of the two samples was identical. Total cyanogen, acetone cyanohydrin and free cyanide contents were determined in both samples and there were no significant differences between the two samples in the content of any of these compounds or in crude protein content. The two different samples of gari were then fed to groups of Sprague Dawley rats for 10 weeks, while a control group received normal rat chow. Total cyanogen, acetone cyanohydrin, free cyanogen, and crude protein contents were not found to be significantly ($p > 0.05$) different between the two. The samples were fed exclusively to two different groups of Sprague-Dawley rats for a ten week experimental period during which clinical observations were recorded daily. At the end, vital body organs were examined grossly and microscopically. There was a significant ($p < 0.05$) reduction in severity and percentage of animals exhibiting clinical abnormalities and lesions of chronic cyanide poisoning in the group fed gari produced with RPO. This result implies an association between the enrichment of cassava mash with RPO during gari production and the reduction of severity and percentage of animals affected by chronic cyanide poisoning.

Go et al (2018) examined the amygdalin concentration and toxicity of two different forms of syrups made from Maesil (*Prunus mume*, also known as Korean green plums, Chinese green plums or Japanese ume), known to contain amygdalin. Maesil syrup from which the plums were removed early in maturation process had significantly higher content of amygdalin (166.82 ± 4.16 μg/mL vs 134.98 ± 5.96 μg/mL) and prunasin (31.57± 0.16 μg/mL vs 26.06± 0.15 μg/mL) but lower polyphenols and a longer half-life in the bloodstream than the syrup matured with plums. This suggests that the complex Maesil syrup components have a role in preventing amygdalin degradation.

Lui et al (2017) investigated the inhibitory effects of various Chinese herbal extracts on the activity of β-glucosidase derived from almonds, and then examined the toxicity of a Chinese herbal medicine containing amygdalin (*Persicae Semen* ethanol extract) in mice when combined with β-glucosidase inhibitory herb extracts. Of 30 herbs assessed for β- glucosidase inhibitory effects, water extracts of 5 herbs, and ethanol extracts of 7 herbs, were found to have inhibitory activity against β-glucosidase. Of all the inhibitory herbal extracts, the ethanol and water extracts of *Lycii Cortex* had the smallest IC_{50} results (1.35 mg/mL for water extract and 0.56 mg/mL for ethanol extract). Further study found that *Lycii Cortex* inhibition of β-glucosidase was non-competitive in nature. By comparing decomposition rates of amygdalin at different concentrations with the inhibitory rate of the *Lycii Cortex* ethanol extract at different concentrations, a ratio of 7.19 *Persicae semen* ethanol extract to 9.18 *Lycii Cortex* ethanol extract was determined to be theoretically optimal. The *in vivo* oral toxicity of the *Persicae semen* ethanol extract alone and in the theoretically determined optimal ratio with *Lycii Cortex* ethanol extract was investigated by examining the relative LD_{50} values in Kunming mice using the up-

down method. The LD_{50} of the *Persicae semen* extract alone was 1750 mg/kg bw, while the LD_{50} when combined with *Lycii Cortex* extract was 4100 mg/kg bw, demonstrating that the toxicity of *Persicae semen* extract is decreased 2.43 times when administered in combination with *Lycii Cortex* extract.

Jaswal (2018) reviewed the effect of different gut bacterial compositions on the metabolism of amygdaline and noted studies in which some probiotics and foods were able to alter the gut microbiome and hence the β-glucosidase activity of the gut. In theory this should alter the cyanide production from amygdalin, although this has not been demonstrated in *in vivo* studies.

Tanwar (2018) reported a HCN content in wild apricot kernels of 136.85 ± 2.67 mg/100 g raw kernels. It is reported in this study that the range of HCN in wild apricot kernels is between 148 and 480 mg/100 g, and the HCN content in bitter almonds ranges from 106 to 250 mg/100 g. Detoxification of wild apricot kernels is possible by appropriate processing. Tanwar found that 100% of the hydrogen cyanide content of ground apricot kernels was removed by immersing the flour in 25% sodium chloride solution for 12 hours and then rinsing under running water, repeating this process, and then drying the flour for 36 hours at 45°C.

These studies suggest that the toxicity of amygdalin in herbal substances can be influenced by combination with other ingredients or the method of processing.

CLINICAL TOXICITY

Symptoms

The initial symptoms of acute cyanide poisoning (also the symptoms of amygdalin poisoning) include nausea, vomiting, diarrhoea and epigastric pain. These may be followed by neurological symptoms including dizziness, headaches, disorientation, irritability, lethargy, weakness, and stupor, as well as coma and seizures. Initial tachypnoea and dyspnoea may be followed by respiratory depression, cyanosis and eventual respiratory arrest (Hazardous Substances Database (HSDB) 2017). Hypotension and shock may also occur.

Chronic cyanide poisoning after chronic consumption of cyanogenic plants results in neuropathy and myelopathy, including Konzo, a specific tropical myelopathy observed in populations with a high intake of cassava, which contains linamarin, a cyanogenic glycoside metabolised to prunasin and then to HCN (HSDB 2017, COT 2006). Goitre is also associated with chronic consumption of cyanogenic plants, since thiocyanate interferes with iodine uptake in the thyroid (Speijers 1993). However, these populations with high intake of cyanogenic glycoside-containing plants also exhibit a high incidence of malnutrition, and it is considered that nutritional deficiency, particularly of methionine and riboflavin, or iodine, in combination with chronic cyanide exposure, is involved in the aetiology of neuropathy, myelopathy and goitre (Speijers 1993).

No reports of hepatotoxicity associated with acute or chronic exposure to amygdalin or other cyanogenic glycosides have been identified. Hepatotoxicity has been

reported in some rabbit studies after oral exposure to sodium or potassium cyanide at doses of 15 to 20 mg/kg/d cyanide ion, but no consistent evidence of hepatotoxicity has been associated with cyanide exposure in other animals or humans (ATSDR 2006).

Case reports and clinical studies

A review of the clinical toxicity literature was carried out by the applicant (see Toxicity Review). A search of the Embase, Medline and ToxNet databases identified a number of cases reports and clinical studies relating to amygdalin or HCN exposure.

These case reports included:

- 6 reports of toxicity in adults with single oral amygdalin/laetrile at the following doses:
  - 6 tablets (0.6 or 3g[#]) (O'Brien 2005)
  - 18 tablets (1.2 or 9g[#]) (Beamer 1983)
  - 6 tablets (3g) (Bromley 2005)
  - 1 ampoule (3g) (Leor 1986)
  - 3 ampoules (9g) (Moss 1981)
  - 3.5 ampoules (10.5g) (Sadoff 1978)[*]
- 5 reports of toxicity in adults with daily oral amygdalin/laetrile at the following doses:
  - 3 tablets (equivalent to 25-75mg cyanide or 0.42 -1.27g amygdalin) (Kalyanaraman 1983),
  - 1 tablet/capsule (0.5g) (Lam 2012),
  - 1 tablet (0.5g) (Smith 1977),
  - 2 tablets (1.0g) (Liegner 1981), and
  - 3 tablets (1.5g) (Smith 1977).

[#] dose reported as number of tablets of unknown content; tablets appear to be available in100mg and 500mg strengths.

[*] The review of the literature carried out by the applicant (see Toxicity Review: Attachment 2: Summary of case reports) reported the dose of amygdalin in the Sadoff 1978 report (which had been incorrectly reported by Blaheta 2016) as '12 g amygdalin'. When the original Sadoff 1978 reference was sourced, it was apparent that this case report related to a 17 year old female who had ingested 3.5 ampoules, each containing 3g amygdalin, equivalent to a dose of 10.5g, instead of 12 g. It is noted that the Sadoff 1978 case report was correctly cited in a review by Speijers 1993; however, the summary table in the Expert Report, when referring to the Speijers 1993 review, incorrectly reported the amygdalin dose as '2.6 g oral amygdalin' when it should have been 10.5 g.

- Fatalities were reported with single oral doses of 3g (Leor 1986) and 10.5g (Sadoff 1978).
- Four cases of toxicity were reported in adults after ingestion of apricot or peach kernel at the following doses:
  - 0.5g (1/4 teaspoon ground apricot kernels with cyanide content >3000mg/kg, *equivalent to >1.5 mg cyanide or >25 mg amygdalin*) (Vlad 2015);
  - 15g (30 apricot kernels, *equivalent to 450 mg amygdalin*) (Suchard 1998);
  - 10-20g (20-40 kernels, *equivalent to 692-1384 mg amygdalin, based on cyanide content of 409mg/100 seeds*) (Rubino 1979);
  - a daily dose of 60g peach kernels (in mixed Chinese herbal prescription containing 30g/dose, *equivalent to 600 mg amygdalin/dose, based on an amygdalin content of NLT 2.0%*) (Chan 2006).
- One case was reported after a combination of 12 bitter almonds (~6g, *equivalent to 74.4 mg amygdalin, based on average amygdalin content of 6.2mg/almond*) plus one laetrile tablet (11.5 mg) (Shragg 1982).
- Toxicity was also reported in adults after ingestion of:
  - bitter almonds (~80g, *equivalent to 2.4-4g amygdalin*)(Grass 2016);
  - apple seeds (80-100, *equivalent to 60-300 mg amygdalin, based on an amygdalin content of 0.1-0.4%*) (Roberts 2011);
  - alcohol macerated chokecherries (~300g, with an estimated cyanide content of 10-20mg, *equivalent to 169-338 mg amygdalin*) (Pentore 1996).
- In children, four cases of severe poisoning were reported following administration of amygdalin at the following doses:
  - 12 tablets (6g)(Hall 1986);
  - a combination of apricot kernels (5-10 per day, equivalent to 75-150 mg amygdalin) plus oral amygdalin (2g per day) in a 4 year old (Sauer 2015);
  - a combination of oral amygdalin (0.5g per day), I.V. amygdalin (3.5g per day) plus amygdalin enema in a 2 year old (Ortega 1978); and
  - 1-5 amygdalin tablets (0.5-2.5g) in a 11 month old infant, which was fatal (Humbert 1977).
- Poisoning was also reported in 13 children (severe in 9 children) aged 3-9 years following ingestion of between 5 and 21 (median 8) apricot seeds (estimated amygdalin content of 75-315mg (median 120mg)) (Akyildiz 2010).

Clinical studies (Mortel 1981; Ames 1981) reported no adverse effects and no clinical or laboratory evidence of toxicity (blood cyanide levels of up to 2.05 microgram/mL) when treating 6 cancer patients with DL amygdalin (4.5 g/m^2/day IV for 21 days) then D amygdalin (0.5 g orally 3 times daily) and "metabolic therapy" (Vitamins A, C, E, B-complex and pancreatin) for 5 to 15 weeks. In a similar but larger study in 165 patients (Moertel 1982), 5- 30% experienced adverse reactions

such as nausea, vomiting, headache, dizziness and mental obtundation, and one of the 14 patients on a high dose regimen (DL amygdalin 7 g/m^2/day IV for 21 days then D amygdalin 0.5 g orally 4 times daily) had bouts of tachycardia and dyspnoea; however, toxicity was sometimes but not always associated with high blood cyanide levels.

An open label pharmacokinetic, safety and tolerability study (Li 2016) reported no serious adverse events and no clinically significant changes in vital signs or serum biochemistry (except for 1 patient with raised serum alanine aminotransferase) with single or multiple IV doses of the traditional Chinese medicine Huoxue-Tongluo lyophilised powder for injection, formulated from Persicae semen and Paeoniae Radix Rubra.

Substance characteristics in relation to the Scheduling Factors[2]

This application proposes amendments to Schedules 10 and 4 of the Poisons Standard. The factors for these schedules and for 'unscheduled' are addressed below.

Factor	Applicant's response	Evaluation
Schedule 10		
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.	In general, Schedule 10 is appropriate for amygdalin (including 'laetrile') as a stand-alone ingredient in medicines for therapeutic use.	The doses of amygdalin (including 'laetrile') used as a stand-alone ingredient in medicines for therapeutic use (100-500mg/dose) appear to be in the same range as those used in Chinese medicine (100-300 mg/dose). Due to the high degree of variability in the toxic effects of cyanide following consumption of herbal preparations containing amygdalin, these preparations may be associated with higher risk so that its sale, supply and/or use require very strict control, with access generally being prohibited. The potential health risk

[2]Scheduling Policy Framework https://www.tga.gov.au/publication/scheduling-handbook-guidance-amending-poisons-standard

		does not include potential for abuse, diversion into illicit products or other factors which would warrant inclusion in Schedule 9.
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.		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, with the exception of products containing a maximum daily dose of less than 5 mg amygdalin.
The Secretary may establish a cut-off from Schedule 10 where the substance no longer meets the factors for inclusion in this Schedule or in any other Schedule in the Poisons Standard.	This application proposes an exclusion from Schedule 10 for medicines that are included in Schedule 4 (see below).	Exclusion from Schedule 10 for medicines containing a maximum daily dose of less than 5 mg amygdalin may be appropriate.
Schedule 4		
The ailments or symptoms that the substance is used for require medical, veterinary or dental intervention Diagnosis, management or monitoring of the medical condition is such that it requires medical, veterinary or dental intervention before the substance is used.	The proposed inclusion in Schedule 4 relates solely to amygdalin when included as a natural component in traditional Chinese medicines for oral use in adults. Other medicines that include amygdalin (or 'laetrile') will remain in Schedule 10. The proposed entry will allow appropriate management of the public health risk associated with amygdalin while enabling its inclusion as a natural component of traditional Chinese medicines in 'prescription only medicines' (e.g. as a	Diagnosis, management or monitoring of the medical condition is such that it requires medical intervention before the substance is used.

	registered complementary medicine or via TGA's Special Access Scheme) with a cut-off at very low doses for sale as 'unscheduled medicines'. The selected cut-off of 5 mg per maximum daily dose is based on animal studies and assessment by a wide range of regulatory and expert committees that an oral intake of 5 to 20 µg/kg/d cyanide (equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult) is considered to present no appreciable risk. It is substantially less than the legal limit in many foods for human consumption in Australia and New Zealand.	
The use of the substance requires adjunctive therapy or evaluation or specialised handling for administration. Adjunctive therapy could include other medicines, non-pharmacological measures, or specialised medicine delivery devices. Evaluation could include laboratory tests or additional clinical assessments. For human medicines, a requirement for administration by injection will usually mean medical or dental supervision is required because of the additional risks and complexity of this route of administration.	No response from applicant	The use of the substance may require specialised handling for administration (e.g. preparation of decoction) but, under the terms proposed by the applicant, it is not expected that this would involve administration by injection.
The use of the substance at established therapeutic	The applicant is not aware of any reports of overdose,	Although the applicant is not aware of any reports of

dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use. Control of access and duration of therapy by a medical, veterinary or dental practitioner is required.	misuse or abuse of traditional Chinese medicines containing 'low doses' of amygdalin as a component of ingredients in traditional Chinese medicines. Single ingredient products containing amygdalin at high dose (as 'laetrile') have had a history of misuse for cancer treatment.	overdose, misuse or abuse of traditional Chinese medicines containing 'low doses' of amygdalin as a component of ingredients in traditional Chinese medicines, it is not clear if this also applies to Chinese medicines containing higher doses of amygdalin. There have been reports of poisoning from intentional ingestion of a large number of raw apricot kernels used as an alternative or complementary medicine, for cancer prevention or treatment, as a health tonic, or for suicide/deliberate self -poisoning. There have also been reports of toxicity from intentional ingestion of amygdalin in ampoules intended for parenteral administration and tablets.
The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical, veterinary or dental practitioner is required to minimise the risk of using the substance. **The margin of safety between the therapeutic and toxic dose of the substance is such that it requires medical, veterinary or dental intervention to minimise the risk of using the substance.**	No response from applicant	The adverse effects of amygdalin relate to cyanide toxicity, which is dose dependent and potentially lethal. The severity of cyanide toxicity following oral administration of amygdalin-containing substances exhibits wide variability, as it is affected by a range of factors which influence the metabolism and detoxification of amygdalin to cyanide (e.g. amygdalin and β-glucosidase content of the herbal ingredient, route of administration, processing, co-administration with other substances, and inter-individual variability with

		respect to gut microbial flora and nutritional status . This variability in the severity of cyanide toxicity following consumption of amygdalin-containing herbal ingredients means that it is difficult to predict a safe dose, even if the amygdalin content of herbal ingredients were standardised.
The seriousness or severity and frequency of the interactions of the substance (medicine-medicine, medicine-food, or medicine-disease) are such that monitoring or intervention is required by a medical, veterinary or dental practitioner.	No response from applicant	Co-administration of amygdalin with other substances or nutrients (e.g. Vitamins C and B12) has been found to affect the severity of toxicity and is potentially life-threatening.
The use of the substance has contributed to, or is likely to contribute to, communal harm. For example, the development of resistant strains of microorganisms. Appropriate use, and/or the decision to continue treatment, requires evaluation by a medical, veterinary or dental practitioner.	No response from applicant	The use of amygdalin has not been reported to contribute to communal harm. As it is not known to have any antimicrobial activity, it is not likely to result in the development of resistant strains of microorganisms.
The experience of the use of the substance under normal clinical conditions is limited. Unexpected effects of the substance may only become evident after widespread use. Close monitoring of the patient is required by a medical, veterinary or dental practitioner to	No response from applicant	The applicant asserts that the practice of TCM has developed from knowledge accumulated through clinical observation and treatment over several millennia. However, since no information has been provided to support this assertion, it is concluded that the experience of the

monitor for unanticipated effects.		use of the substance under normal clinical conditions is limited.
Unscheduled		
In accordance with the cascading principle, exemption of a particular medicinal preparation to allow supply from general sales outlets (such as supermarkets) means that it does not meet the factors for Schedules 2, 3, 4 or 8. Medicinal preparations exempted from scheduling must be determined to be able to be supplied, with reasonable safety, without any access to health professional advice.	Amygdalin as a natural component and in the low doses proposed for exclusion from Schedule 4 in traditional Chinese medicines for oral use in adults has no appreciable safety risk. It does not meet the factors for Schedules 2, 3, 4 or 8 and can be used with reasonable safety, without any access to health professional advice.	Amygdalin in the low doses proposed for exclusion from Scheduling (maximum daily dose not exceeding 5 mg) in traditional Chinese medicines for oral use in adults has no appreciable safety risk. It does not meet the factors for Schedules 2, 3, 4 or 8 and can be used with reasonable safety, without any access to health professional advice.
The term 'with reasonable safety' means: • The consumer is able to identify and self-manage the condition for which the medicine is intended without health professional input.	The classification of these medicines as 'unscheduled' will make them eligible for 'listing' on the Australian Register of Therapeutic Goods (ARTG) subject to TGA agreement to changes to the Therapeutic Goods (Permissible Ingredients) Determination. Controls within the listing system will ensure that only indications that do not require health professional input are available for use with these medicines. If the medicine cannot be listed it must be 'registered' and will be subject to full evaluation by TGA. Again, this will ensure that only indications that do not require health professional input are approved for use with these medicines	No information has been provided regarding the proposed conditions of use of these 'unscheduled' medicines. However, the evaluation of 'unscheduled' under the listing or registration system should ensure that only indications that do not require health professional input are approved for use with these medicines. Therefore, the consumer should be able to identify and self-manage the condition for which the medicine is intended without health professional input.

	(unless they have a specific exemption from TGA).	
• The risk of the consumer confusing their condition with more serious diseases or conditions is very small.	Controls within the listing / registration system will ensure that indications for more serious disease or for conditions that could be confused with more serious disease are not available / approved for use with these medicines.	Controls within the listing / registration system should ensure that indications for more serious disease or for conditions that could be confused with more serious disease are not available / approved for use with these medicines.
• The risks to health from the medicine are small and can be managed with packaging and labelling. Risks to be assessed include, but are not limited to, risks from adverse reactions, drug/food interactions and contraindications.	Controls within the listing / registration system will ensure that any risks from herbal ingredients that include amygdalin at very low dose are appropriately managed by packaging and labelling (e.g. by mandatory label warnings).	Controls within the listing / registration system should ensure that any risks from herbal ingredients that include amygdalin at a maximum daily dose not exceeding 5 mg are appropriately managed by packaging and labelling (e.g. by mandatory label warnings).
• The risk of inappropriate use and misuse is negligible.	The applicant is not aware of any reports of inappropriate use or misuse of traditional Chinese medicines.	The risk of inappropriate use and misuse of medicines containing a maximum daily dose of amygdalin not exceeding 5 mg is negligible.
• There is little need to take any special precautions in handling.	The applicant is not aware of any need to take special precautions in handling traditional Chinese medicines.	Since the risks relate to ingestion, there is little need to take any special precautions in handling.
• There is net public health benefit from wider availability for the consumer	The applicant submits that there is a substantial public health benefit from wider availability of a full range of traditional Chinese medicines for the consumer, including those that contain very low doses of amygdalin as a natural component of herbal substances used in those medicines.	Although exclusion from scheduling would allow wider availability for the consumer, it has not been established that wider availability would benefit the health of consumers.

The proposed Schedule 4 entries for amygdalin and hydrocyanic acid – AMYGDALIN when included as a natural component in traditional Chinese medicines for oral use in adults **except** when the maximum recommended daily dose is equivalent to no greater than 5 mg of amygdalin and HYDROCYANIC ACID for therapeutic use except when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults – are unusual in that they specify amygdalin when included as a 'natural component in traditional Chinese medicines'. Presumably, this was intended to exclude amygdalin extracted from herbal ingredients. However, there are no other schedule entries that apply specifically to Chinese medicines and based on the toxicity data, there does not appear to be any reason why this should not apply to all amygdalin preparations.

It is noted that the wording of some current entries in the Poisons Standard refers to 'preparations when labelled with a recommended daily dose not exceeding a specified quantity of the specified poison', and may also specify the maximum concentration and/or maximum dose (for undivided preparations) or maximum quantity per dosage unit (for divided preparations).

Subject to the provision of sufficient efficacy and safety data to support the inclusion of amygdalin in Schedule 4, suggested wording for a Schedule 4 entry for amygdalin could be – AMYGDALIN when included in preparations when labelled with a recommended daily dose not exceeding a specified quantity of the specified poison. Although the safety data support an exemption from scheduling for amygdalin in preparations labelled with a maximum recommended dose not exceeding 5 mg, there is insufficient evidence to support a Schedule 4 entry for amygdalin. Therefore, exclusion from Schedule 10 for preparations containing a maximum daily dose not exceeding 5 mg amygdalin may be appropriate, e.g. Schedule 10: AMYGDALIN for therapeutic use except when included preparations containing a maximum daily dose not exceeding 5 mg.

The proposed exclusion of hydrocyanic acid for therapeutic use from Schedule 4 when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults has not been justified. If amygdalin is excluded from scheduling at a maximum recommended daily dose not exceeding 5mg, a corresponding limit should be applied to the exclusion of hydrocyanic acid, e.g. at a dose not exceeding 0.3 mg hydrocyanic acid. Therefore, the Schedule 4 entry for could be worded as "HYDROCYANIC ACID for therapeutic use except when included in preparations labelled with a maximum recommended daily dose not exceeding 0.3 mg".

The NDPSC has previously expressed concern over the apparent contradiction that certain substances which had been included in Appendix C (now Schedule 10) on the grounds that they present such danger to health as to warrant prohibition should be made available for therapeutic use under special circumstances.

As an alternative to exclusion from scheduling, a lower schedule, e.g. S2, could be considered for preparations with a maximum daily dose of ≤ 5mg. This was not proposed by the applicant, possibly because one of the factors for pharmacy

medicines (Schedule 2) is that access to advice from a pharmacist should be available to maximise the safe use of the medicine.

It is noted that CMEC have made recommendations on maximum daily doses of active ingredients in Listed medicines.

4. EVALUATION

Considerations under section 52E of the Therapeutics Goods Act 1989

(a) the risks and benefits of the use of a substance

Risks

The primary risk associated with the use of amygdalin is the potential for severe acute cyanide poisoning, the symptoms of which are nausea, vomiting, diarrhoea, dizziness, and tachypnoea, progressing to cyanosis, seizures, coma, and eventually respiratory arrest and death. An additional risk would be the potential for adverse effects associated with chronic exposure of cyanogenic glycosides, such as neuropathy, myelopathy, and/or goitre.

These risks are exacerbated by the variability in the severity of cyanide toxicity resulting from the administration of amygdalin, which is influenced by a number of factors, which are discussed in detail in the section (c) the toxicity and safety of a substance. This variability in the severity of cyanide toxicity following consumption of amygdalin-containing herbal ingredients means that it is difficult to predict a safe dose, even if the amygdalin content of herbal ingredients were standardised.

Amygdalin for therapeutic use is currently included in Schedule 10 on the grounds that it presents such danger to health as to warrant prohibition of sale, supply and use.

This application proposes excluding amygdalin from Schedule 10 when included as a natural component in traditional Chinese medicines for oral use in adults and including it in Schedule 4 with a cut-off to unscheduled at a maximum daily adult dose of 5 mg or less.

The evidence provided in this application supports the view that an oral intake of 5 to 20 µg/kg bw/d cyanide (equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult), presents no appreciable risk to consumers, although it is noted that no evidence for efficacy of these doses was provided. Based on the absence of risk to consumers, it is considered that the proposed exclusion from scheduling of preparations containing a maximum daily dose of less than 5 mg amygdalin would be acceptable.

The evidence provided in this application is considered insufficient to support the efficacy and safety of amygdalin in doses above 5 mg per day. Therefore, it is

considered that the proposed scheduling of amygdalin (excluding it from Schedule 10 when included as a natural component in traditional Chinese medicines for oral use in adults and including it in Schedule 4 at a maximum daily adult dose of more than 5 mg) presents an appreciable risk to consumers due to the potential for cyanide toxicity.

Benefits

The applicant submits that there is substantial public health benefit, and very little risk, from removing the scheduling barrier from access to a full range of traditional Chinese medicines by medically qualified TCM practitioners and from access to TCM products at very low doses of amygdalin to Australian / Chinese consumers, as this would allow wider availability for the consumer.

The application provided little information about the efficacy of amygdalin in Chinese medicines at either very low or high doses. However, it is acknowledged that Traditional Chinese medicine (TCM) is a medical system based on theory, pathology, diagnosis, treatment and herbal pharmacology principles that differ from those of orthodox medicine or Western naturopathy and that the practice of TCM has developed from knowledge accumulated through clinical observation and treatment. TCM has an established history in Australia and has expanded rapidly in recent years, with Chinese medicines accounting for 3.2% of the total use of complementary medicines in Australia in 2003.

However, it cannot be concluded that wider availability would benefit the health of consumers.

(b) the purposes for which a substance is to be used and the extent of use of a substance

Amygdalin is a cyanogenic glycoside found naturally in many plants including cassava, sorghum, lima beans, linseed, apple seeds, bitter apricot seed (*Armeniacae Semen Amarum*), peach seed (*Persicae Semen*) and the seeds of other plants in the *Prunus* genus, including bitter almond (*Prunus amygdalus* var. *amara*), plum (*Prunus domestica*), and chokecherry (*Prunus virginiana*),.

Many traditional Chinese medicines are formulated to include one or more of these plant ingredients, mainly apricot kernels, usually in combination with other traditional Chinese herbs.

The submission states that amygdalin is only present in traditional Chinese medicines as a natural component of herbal substances (as opposed to single ingredient products containing amygdalin at a high dose). Examples of these substance include bitter apricot seed (*Armeniacae Semen Amarum*; Kuxingren CP), which is indicated in the Chinese Pharmacopoeia (CP) for *"cough and wheezing, chest fullness, profuse sputum, and constipation caused by intestinal dryness"*; and peach seed (*Persicae Semen*; Taoren CP), which is indicated for *"amenorrhea,*

dysmenorrhea, masses, stuffiness, lung abscess, intestinal abscess, traumatic injuries, constipation caused by intestinal dryness, cough and wheezing".

The submission did not include any other information about other herbal substances used in Chinese medicines that have amygdalin as a natural component.

The Pharmacopeia of the People's Republic of China (2015) includes the following information in the monographs for Bitter Apricot Seed and Peach Seed.

	Bitter Apricot Seed	Peach Seed
Names	Armeniacae Semen Amarum Kuxingren	Persicae Semen Taoren
Source	Dried ripe seed of *Prunus armeniaca* L. var. *ansu* Maxim. , *Prunus sibirica* L., *Prunus mandshurica* (Maxim.) Koehne or *Prunus armeniaca* L. (Fam. Rosaceae). The fruit is collected in summer and the seed is removed from the pulp and the shell, and dried in the sun.	Dried ripe seed of *Prunus persica* (L.) Batsch or *Prunus davidiana* (Carr.) Franch. (Fam. Rosaceae). The fruit is collected when ripe. The seed is removed from sarcocarp and shell (endocarp), and dried in the sun.
Description	Flattened-cordate, 1-1. 9 cm long, 0. 8-1. 5 cm wide, 0. 5-0. 8 cm thick. Externally yellowish-brown to deep brown, acute at one end, obtusely rounded plump and unsymmetrical at the other end. A short-line hilum situated at the acute end and a chalaza at the rounded end with numerous upwards deep-brown veins. Tests thin; cotyledons 2, milky-white, oily. Odour, slight; taste, bitter.	Seed of Prunus persica Prolate-ovate, 1. 2-1. 8 cm long, 0. 8-1. 2 cm wide, O. 2-0. 4 cm thick. Externally yellowish-brown to reddish-brown, with numerous granular protrudings. One end acute, expanded in the middle, the other end obtuse-rounded and slightly oblique, with relatively thin edge. A short linear hilum occurring by the acute end and a relatively distinct and slightly dark chalaza at the round end, with many longitudinal vascular bundles radiated from the chalaza. Tests thin, cotyledons 2, almost white and oily. Odour, slight; taste, slightly bitter.
Assay	It contains not less than 3.0 percent of amygdalin (C_{20} H_{27} NO_{11}) calculated with reference to the dried drug. (NLT 2.1% in dried slices)	It contains not less than 2.0 percent of amygdalin (C_{20} H_{27} NO_{11}) calculated with reference to the dried drug. (NLT 1.60% in dried slices)
Actions	To direct qi downward, suppress cough, relieve	To activate the blood to eliminate stasis, moisten the intestines, open

	wheezing, moisten the intestines and open the bowels.	the bowels, suppress cough, and relieve wheezing.
Indications	Cough and wheezing, chest fullness, profuse sputum, and constipation caused by intestinal dryness.	Amenorrhea, dysmenorrhea, masses, stuffiness, Lung abscess, intestinal abscess, traumatic injuries, constipation caused by intestinal dryness, cough, and wheezing.
Administration and dosage	5-10 g, unprocessed for decoction, added when the decoction is nearly done.	5-10 g.
Precautions and Warnings	Be care of overdosage for oral administration to avoid poisoning.	Used with caution during pregnancy.

The Pharmacopeia of the People's Republic of China does not include recommended maximum daily dosages of Bitter Apricot Seed or Peach Seed.

In Traditional Chinese Medicine, Bitter Apricot Kernel (xing ren) *Semen Armeniacae Amarum* can be used in combination with other ingredients such as Herba Ephedrae and Radix Glycyrrhizae (for treatment of cough due to exopathogenic wind-cold); Fructus Arctti, Folium Mori, Bulbus Fritillariae, Radix Platycodi, and Radix Glycyrrhizae (for treatment of cough due to exopathogenic wind-heat); Folium Mori, Bulbus Fritillariae, and Radix Adenophorae (for treatment of warm-dryness injury of lung, unproductive cough); Gypsum Fibrosum, Herba Ephedrae, and Radix Glycyrrhizae (for treatment of accumulation of pathogenic heat in the lung, pyrexia with acute asthma) and Radix Angelicae Sinensis, Radix Paeoniae Alba and Fructus Canabis (for treatment of constipation due to bowel dryness). (http://www.tcmtreatment.com/herbs/00-xingren.htm)

(c) the toxicity and safety of a substance

Amygdalin is a cyanogenic glycoside found naturally in many plants including cassava, sorghum, lima beans, bitter almonds, apricot kernels and seeds of other plants in the *Prunus* genus. Cyanogenic glycosides can convert to a type of cyanide when eaten. The mechanism of toxicity of hydrogen cyanide is by inhibition of mitochondrial cytochrome oxidase, which results in inhibition of oxygen consumption. Acute toxicity results in dyspnoea, weakness, dizziness, sweating, vomiting, disorientation, convulsions, paralysis, cyanosis, coma, and cardiovascular collapse.

The severity of cyanide toxicity is dependent upon a range of factors which influence the metabolism and detoxification of amygdalin to cyanide, including:

- The amygdalin content of the herbal ingredient, which may vary depending on varietal differences, seasonal effects on growth, freshness, and processing.
- The β-glucosidase content of the herbal ingredient, which aids the conversion of amygdalin to cyanide.
- The route of administration, e.g. oral administration results in higher cyanide levels compared to IV administration, which bypasses the gut β-glucosidase enzymes.
- Chewing or processing (e.g. grinding) of the herbal ingredient, which can release the β-glucosidase in the herbal ingredient, increasing the conversion to cyanide, and increasing the toxicity.
- Co-administration with other substances (e.g. other herbal ingredients) that may influence either the metabolism of amygdalin to cyanide or the detoxification of cyanide. An example of this is the reduced toxicity of Xingren when combined with Mahuang in Chinese medicine (Song 2016).
- Inter-individual variability with respect to gut microbial flora and nutritional status, which may affect the β-glucosidase dependent conversion of amygdalin to cyanide in the gut as well as the amino acid dependent detoxication processes.

Food Safety Australia New Zealand (FSANZ) has conducted a risk assessment on a number of foods containing cyanogenic glycosides and found only raw apricot kernels (both with and without skin) pose an acute public health and safety risk. Changes to the *Australia New Zealand Food Standards Code* to prohibit the sale of raw apricot kernels were made in 2015. FSANZ considers raw apricot kernels to be a food and does not address the issue of these foods being consumed for a therapeutic purpose or presented as a therapeutic good. FSANZ has set a limit of 10 mg HCN/kg in ready-to-eat cassava chips (FSANZ 2008, 2016). Limits of HCN in other foods and drinks (FSANZ 2015) include: 25 mg/kg in confectionery; 5 mg/kg in stone fruit juices; 50 mg/kg in marzipan; and 1 mg/kg per 1% alcohol in alcoholic beverages (e.g. apricot kernel derived products). ANZFSC Standard 4.5.1 has set a HCN limit of NMT 0.1 mg/L in wine, sparkling wine and fortified wine (ANZFSC Standard 4.5.1 – Wine production requirements (Australia only)).

By way of comparison, 100 g of confectionary could legally contain up to 2.5 mg of HCN. Assuming 100% conversion of amygdalin to cyanide (16.92 mg amygdalin is equivalent to 1 mg cyanide), this is equivalent to 42.5 mg of amygdalin, more than 8 times the proposed maximum adult daily dose of amygdalin in unscheduled traditional Chinese medicines. Similarly, one standard drink (~50 mL) of Amaretto Liqueur (28% alcohol) could legally contain up to1.4 mg cyanide, equivalent to 23.7 mg amygdalin, and one standard drink (100 mL) of wine could legally contain up to 1 mg HCN, equivalent to 16.9 mg of amygdalin, which are 3-4 times more than the proposed daily limit for unscheduled traditional Chinese medicines.

Surveys of currently available data by the FSANZ indicate there is considerable variability in levels of cyanogenic glycoside concentrations in apricot kernels. A

survey during the 2011 Queensland poisoning incident found levels of HCN in raw apricot kernels with skin (3 blended samples) ranged from 1,7000-2,3000 mg/kg. The ISFR* survey found levels of HCN in raw apricot kernels with skin (18 blended samples) ranged from 1,240-2,820 mg/kg; whereas those without skin (10 blended samples) ranged from 49 to 440 mg/kg. However, surveys with less samples reported higher levels in raw apricot kernels with skin (>3,000 mg/kg in 1 blended sample from 2014 WA incident and 4,090 mg/kg in a case study from poisoning incident). It is unlikely these surveys have identified the true range of cyanogenic glycosides in apricot kernels that are currently available for sale given the restricted number of studies and samples.

Based on a maximum HCN content in raw apricot kernels with skin of 2,820 mg/kg, a dosage of 3-10 g would contain 8.46-28.2 mg HCN. Assuming 100% conversion of amygdalin to HCN, this is equivalent to 143.8 to 479.4 mg amygdalin per dose (maximum amygdalin content of 47,705 mg/kg). This is consistent with the amygdalin content of 90-300mg per dose calculated based on an amygdalin content of NLT 3.0% (as specified in the Chinese Pharmacopoeia).

Solomonson (1981; quoted in Speijer 1993) reported that the lethal oral dose of amygdalin in adults is 0.02-0.13 mmol/kg bw (9 to 60 mg/kg). An average fatal dose of cyanide of 1.52 mg/kg (range 0.5 to 3.5 mg/kg) in adults has been estimated by the USA EPA from case reports of intentional or accidental poisonings (ATSDR, COT, 2006). Assuming 59.1 mg cyanide is released from 1000 mg amygdalin, this would equate to a fatal dose of amygdalin of 25.7 mg/kg (range 8.5 to 59.2 mg/kg). This could be considered a worst case situation, as it assumes the release in the gut of the total theoretical amount of cyanide from amygdalin, and it is unclear what proportion of the total possible cyanide would be released from amygdalin. The estimated range of 8.5 to 59.2 mg/kg is consistent with the lethal oral dose range of 9 to 60 mg/kg quoted in Speijers (1993).

Cyanide toxicity has been reported in humans at concentrations of 0.1 to 1.45 mg/L in blood, 1-5 mg/L in RBC, 0.2 mg/L in serum, and 0.03-0.035 mg/L in plasma. Lethal cyanide concentrations have been reported as 2.9-5 mg/L in blood, 3 mg/L in serum and 0.243 mg/L in plasma. This compares to cyanide levels of 8.7-58 microgram/L in blood, <29 microgram/L in RBC and 4-6 microgram/L in plasma that are typically found in healthy adults.

A review of the literature carried out by the applicant (see Toxicity Review) identified a number of cases reports and clinical studies relating to amygdalin or HCN exposure.

These case reports suggest that toxicity in adults can occur with oral amygdalin/laetrile in single doses ranging from 3 g to 10.5 g (but this could be as low as 0.6g) and daily doses from 0.42g to 1.5 g, with fatality at doses of 3g and 10.5g. Toxicity in adults was reported after ingestion of single doses of apricot or

* Implementation Subcommittee for Food Regulation

peach kernels containing the equivalent of 25 mg to 1384 mg amygdalin or after ingestion of other seed containing preparations (bitter almonds plus laetrile tablets, apple seeds, or chokecherries) with a total estimated amygdalin content ranging from 60 mg to 4 g. However, little evidence of toxicity has been observed in clinical studies using a combination of IV amygdalin treatment plus oral amygdalin in doses of 1.5 g or 2g daily. This suggests that there is significant variability in the toxic response to amygdalin ingestion.

The submission included little information about the doses of amygdalin used in Chinese herbal medicine. The Pharmacopeia of the People's Republic of China includes monographs for 'Bitter Apricot Seed' and 'Peach seed', which indicate that the standard dose of bitter apricot seed or peach seed is 5-10 g, which is equivalent to 150-300 mg amygdalin for bitter apricot seed and 100-200 mg for peach seed (based on the amygdalin content of NLT 3.0% in bitter almond seed and NLT 2.0% in peach seed, calculated with reference to the dried drug – Chinese Pharmacopoeia). However, it is possible that higher doses would be used, since the submission included one case report of toxicity with a daily dose of 60g peach kernels in a mixed Chinese herbal prescription containing 30g/dose, which would be equivalent to 600 mg amygdalin. The applicant could be requested to provide further information about the proposed use of amygdalin-containing herbal ingredients in Chinese herbal medicine, including the maximum single and daily doses of amygdalin likely to be prescribed.

On the basis of animal studies, and as assessed by a wide range of regulatory and expert committees, oral HCN intake of 5 to 20 microgram per kg body weight per day is considered to present no appreciable risk. This is equivalent to 300 to 1200 microgram/d of cyanide for a 60 kg adult and 100 to 400 microgram/d for a 20 kg child. Assuming 100% hydrolysis of amygdalin to hydrogen cyanide, on a molecular basis this is equivalent to 5.1 to 20.3 mg/d amygdalin for a 60 Kg adult and 1.7 to 6.8 mg/d for a 20 kg child.

A maximum adult daily dose of 5 mg amygdalin is at the low end of the range that is considered to present no appreciable risk (5.1 to 20.3 mg/d). This would provide some buffer to account for any variability in cyanide toxicity following ingestion of amygdalin-containing ingredients. A dose of 5 mg is also lower than the permitted quantity in some foods (e.g. 42.5 mg in 100 g of confectionary; 23.7 mg in one standard drink (~50 mL) of Amaretto Liqueur (28% alcohol); and 23.7 mg in one standard drink (100 mL) of wine.

However, there is less evidence for the safety of higher doses of amygdalin, especially considering the wide variability in cyanide toxicity observed following oral administration of amygdalin-containing substances. Further clarification of the maximum single and daily doses of amygdalin likely to be prescribed in Chinese medicine is required.

(d) the dosage, formulation, labelling, packaging and presentation of a substance

The submission did not include any information about the dosage, formulation, labelling, packaging or presentation of traditional Chinese medicines that include amygdalin as a natural component of herbal substances. However, it is noted that these aspects would be controlled under the registration or listing process. Labelling of such Chinese medicines is likely to include mandatory warning statements, although it is uncertain as to whether declaration of the amygdalin or HCN content would be required.

(e) the potential for abuse of a substance

Single ingredient products containing amygdalin at high dose (as 'laetrile') have had a history of misuse for cancer treatment. These products will remain in Schedule 10.

The applicant is not aware of any reports of overdose, misuse or abuse of traditional Chinese medicines containing 'low doses' of amygdalin as a component of ingredients in traditional Chinese medicines; however, it is not clear if this also applies to Chinese medicines containing high doses of amygdalin. Since this use is currently prohibited in Australia, reports would be from overseas.

There have been reports of poisoning in Australia and New Zealand from intentional ingestion of a large number of raw apricot kernels used as an alternative or complementary medicine, for cancer prevention or treatment, as a health tonic, or for suicide/deliberate self -poisoning (FSANZ).

Information from Poisons Information Centres in Australia has not been obtained. This could be requested.

A search of the Australian DAEN did not reveal any notifications of adverse events with Chinese herbal medicine, Kuxingren, amygdalin, laetrile, apricot kernels, which is expected, given the current restrictions on the use of these substances. A search of global databases (e.g. VigiBase, the WHO global database of individual case safety reports (ICSRs)) has not been undertaken.

Poisoning incidents following either accidental (children and adults) or intentional ingestion (by adults only) of raw apricot kernels in Australia and New Zealand have been reported to poison information centres (FSANZ). This includes the intentional ingestion of a large number of apricot kernels used as an alternative or complementary medicine, cancer treatment, health benefits/tonic or other reasons, suicide/deliberate self-poisoning.

There does not appear to be any potential for abuse resulting from addiction.

(f) any other matters considered necessary to protect public health

5. CONCLUSIONS

On the basis of animal studies, and as assessed by a wide range of regulatory and expert committees, oral intake of 5 to 20 µg/kg/d cyanide (equivalent to 5.1 to 20.3

mg/d amygdalin for a 60 Kg adult) is considered to present no appreciable risk to consumers.

This application proposes excluding amygdalin from Schedule 10 when included as a natural component in traditional Chinese medicines for oral use in adults and including it in Schedule 4 with a cut-off to unscheduled at a maximum daily adult dose of 5 mg or less. By way of comparison 100 g of confectionary could legally contain more than 8 times this proposed maximum daily dose. An associated change to exclude hydrocyanic acid from Schedule 4 when present as a natural component of amygdalin in traditional Chinese medicines for oral use in adults is also proposed.

The effect of these changes would be:

- To make TCM products containing very low doses of amygdalin available without prescription; and
- To allow medically qualified TCM practitioners to prescribe traditional Chinese medicines containing higher doses of amygdalin as Schedule 4 medicines (e.g. in registered complementary medicines or via the TGA's Special Access Scheme).

The applicant's submission that there is substantial public health benefit, and very little risk from access to TCM products at very low doses of amygdalin to Australian / Chinese consumers is accepted.

However, the applicant's submission that there is substantial public health benefit, and very little risk, from removing the scheduling barrier from access to a full range of traditional Chinese medicines by medically qualified TCM practitioners is not accepted, as there is less evidence for the safety of higher doses of amygdalin, especially considering the wide variability on cyanide toxicity observed following oral administration of amygdalin-containing substances.

It is suggested that access to TCM products at very low doses of amygdalin may be achieved through exclusion from Schedule 10 of preparations containing a maximum daily dose not exceeding 5 mg amygdalin and the exclusion from Schedule 4 of preparations containing a maximum daily dose not exceeding 0.3 mg hydrocyanic acid.

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PART 4 – Bibliography

- The 'Toxicity Review' in Part 3 of this application is a stand-alone document with its own reference list. For ease of access these references are duplicated below.

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