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Report on Appropriate Classification for Hydrocyanic acid

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Summary

An assessment has been made of safety considerations with respect to human usage of complementary medicine preparations containing the substance Hydrocyanic acid. This assessment includes a brief review of the bioavailability of hydrocyanic acid from cyanogenic glycosides found in various plants, and their known toxicity. This was related to determination of levels of Hydrocyanic acid intake known to be associated with adverse effects (and possible fatality) in humans.

The likely potency of known Hydrocyanic acid-containing preparations available in the marketplace in terms of producing 'cyanosis' or cyanide poisoning, was determined. Calculations were then made to derive suitable 'cut off points' below which a general sales classification is appropriate, and to recommend a maximum pack size of preparations containing stated levels of Hydrocyanic acid, with safety considerations being paramount.

Hydrocyanic acid

Hydrocyanic acid (prussic acid) is an aqueous colourless solution with a characteristic almond odour, and contains hydrogen cyanide (HCN) at a concentration of 2 to 4% w/w according to early editions of *Martindale*, although not specified in recent editions (1, 51). Hydrocyanic acid is listed also as a synonym for hydrogen cyanide (6), which is used as a gas for the eradication of pests and is intensely poisonous (1).

Very small levels of hydrocyanic acid are found in many plants, being

produced as a breakdown product from a type of secondary metabolite known as cyanogenic glycosides.

Monographs in older editions of the B.P.C. include:

Dilute Hydrocyanic Acid (B.P.C., 1954):

A solution containing 2% w/w of hydrogen cyanide (HCN).

Dose: 0.12 to 3ml.

Used in small doses for an alleged sedative action on the stomach.

Stronger Hydrocyanic Acid, (BPC 1934):

A solution containing 4% w/w of hydrogen cyanide (HCN).

Hydrocyanic acid toxicity

Hydrocyanic acid and its vapour are intensely poisonous, and signs and symptoms of toxicity are the same as those for cyanide (14).

Cyanide inhibits the mitochondrial respiratory chain enzyme cytochrome oxidase, an enzyme necessary for cellular oxygen transport. Poisoning by cyanides may occur from inhalation of the vapour, ingestion, or absorption through the skin. Poisoning may arise from cyanide pesticides, industrial accidental exposure, or the inhalation of fumes from some burning plastics. Poisoning may also occur from 'cyanide-containing' plants or fruits (1).

Signs of acute cyanide poisoning include headache, vertigo, agitation, confusion, coma, convulsions and death. When large doses of hydrocyanic acid are taken, unconsciousness occurs within a few seconds and death within a few minutes (1). Death through inhalation occurs in 1 hour at 100ppm, while 300ppm exposures prove fatal within several minutes.

The fatal dose of orally ingested hydrocyanic acid for adult humans is considered to be about 50mg, and of the K or Na cyanide salts, 200 – 500mg(6). The calculated lethal dose of KCN in children is 1.2-5mg/kg. In the U.K. the control exposure limit of hydrogen cyanide is 10ppm (short-term), and the recommended exposure limit of cyanides (as CN) is 5mg per m³ (long-term) (1,14).

The LD₅₀ of hydrogen cyanide is listed as being 0.5mg/kg (1, 6), meaning that a child weighing 10kg could be killed by a 5mg dose of hydrogen cyanide (61).

Cyanide is primarily considered as a neurotoxin, and various neurological conditions including ataxia, hypertonia, neuromyopathies and blindness as well as impaired thyroid function have been associated with chronic exposure (1,14).

With smaller toxic doses the symptoms, which occur within a few minutes, may include constriction of the throat, nausea, vomiting, giddiness, headache, palpitation, hyperpnoea then dyspnoea, bradycardia (initially tachycardia may occur), unconsciousness, and violent convulsions, followed by death. The

characteristic smell of bitter almonds may not be obvious. Cyanosis is not prominent. Similar but usually slower effects occur with cyanide salts.

Bioavailability of hydrocyanic acid in animals or humans is generally assessed through measuring plasma thiocyanate levels (7,12).

Cyanogenic glycosides:

Cyanogenic glycosides occur in at least 2,500 known plants (12), and many of these belong to the *Fabaceae*, *Rosaceae*, *Linaceae*, *Asteraceae* families. They are composed of an alpha-hydroxynitrile type aglycone and a sugar moiety (mostly D-glucose).

A large number of the most important human food plants contain cyanogenic glycosides, and these phytochemicals appear to have a natural function as chemoprotective agents against herbivores (2,3).

Cyanogenic glycoside containing plants widely used in phytotherapy include Wild Cherry bark (*Prunus serotina*), which contains prunasin, Elder (*Sambucus spp*) which contains sambunigrin, Linseed (*Linum spp*), which contains linustatin and neolinustatin (4), and various species of Clover (*Trifolium spp*) (5).

As is common in the plant kingdom, widespread variability in levels of these secondary metabolites is known to occur within different populations of the same species (5).

Pharmacokinetics and toxicity of cyanogenic glycosides

A major difficulty in determining the predisposition of cyanogenic glycoside-containing preparations to produce hydrocyanic acid-mediated adverse effects, is the lack of data on their measured hydrocyanic acid content. Furthermore, as hydrocyanic acid is produced largely *in vivo* following oral administration of these preparations, simple quantification of their hydrocyanic acid content prior to administration, has obvious limitations. Degrees of oral bioavailability of different compounds and their toxic aglycones, vary significantly from one glycoside to another (7). This variability in pharmacokinetic parameters probably accounts for much of the inter-species variability in terms of potential potency and toxicity.

The potential toxicity of most cyanogenic glycosides to humans however, appears to be limited due to generally slow release of hydrocyanic acid and its rapid detoxification following oral administration (3,7,8,9).

While dogs fed a diet of rice to which hydrocyanic acid was added developed hypothyroidism and goitre, those fed cassava, a food which contains large amounts of cyanogenic glycosides known to be a rich source of hydrocyanic acid, had a normal thyroid function after 14 weeks (10).

The production of hydrocyanic acid depends on both levels of cyanogenic glycosides and on the existence (or absence) of degrading enzymes. Generation of hydrocyanic acid from cyanogenic glycosides is a two step process involving a deglycosilation of the carbohydrate moiety by the enzyme beta-glucosidase to form cyanohydrins, followed by rapid cleavage of the molecule by alpha-hydroxynitrilase. The tissue level compartmentalisation of cyanogenic glycosides and their hydrolysing enzymes prevents large-scale hydrolysis in intact plant tissue (11,12).

Beta-glucosidases are present mainly in the human gastrointestinal tract but also in the liver, as well as in nuts, seeds, fruits, pits and vegetables. Conversion of cyanogenic glycosides to hydrocyanic acid appears to take place particularly in the human gut, as well as in the liver (13,14).

Potential toxicity of foods containing these substances is also usually avoided by careful pre-ingestion food processing. This can include sundrying (34), soaking in water for prolonged periods (33), cooking (4,15), or fermentation(16). An influence of dietary protein intake on potential toxicity of cyanogenic glycosides has been revealed by animal studies (17,18). Humans consuming an adequate protein diet generally have the physiological ability to detoxify these compounds satisfactorily (3, 36).

Most cyanogenic glycosides yield benzaldehyde on hydrolysis which accounts for the characteristic almond-like aroma of many cyanogenic glycoside containing plants.

Cyanide is normally exhaled through the lungs or metabolised to thiocyanates by the sulphur-dependent enzyme rhodanese (14,35), which are then eliminated by the kidneys.

Analytical procedures capable of quantifying levels of both cyanogenic glycosides and hydrocyanic acid, are well documented in the literature (19,12).

Toxicity of particular cyanogenic glycosides

Amygdalin (found in bitter almonds and peach kernels) and prunasin (found in Wild cherry bark and Cherry Laurel leaves, and a metabolite of amygdalin), are well known cyanogenic glycosides, and plants containing them are used widely both as foods as well as phytomedicines.

Two cases of cyanide poisoning after ingestion of bitter almonds, (45,46), and one following ingestion of choke cherries (47), have been reported.

Amygdalin & laetrile.

Considerable interest was generated in the 1970's and early 1980's in the use for cancer of oral and parenteral preparations of a semi-synthetic cyanogenic glycoside, mandelonitrile beta-glucuronide, patented as laetrile (20,28). Most of what was sold as laetrile however was in fact amygdalin, which probably had

similar properties on injection or ingestion (29). It was postulated that circulating amygdalin would be preferentially hydrolysed in cancer cells by beta-glucosidases to yield benzaldehyde and hydrogen cyanide in sufficient quantities to kill malignant cells. Amygdalin was subsequently shown to be ineffective as an anticancer agent either in animals or humans (24), possibly because the beta-glucosidase activity of cancer cells is quite low (30,31).

More than 37 poisonings and 17 deaths have been recorded as allegedly associated with laetrile, mostly from the ingestion of apricot or other fruit kernels (20,1). The terminally ill nature of many of these cases however, combined with the lack of documentation of relevant details in some cases, means that a proven link with laetrile ingestion remains unsubstantiated for many of these reports.

Available evidence indicates that amygdalin is not well absorbed from the gastrointestinal tract (1,20,21). Addition of 10% apricot kernels to the diet of rats for 18 weeks showed only moderate toxic effects (32). Oral administration of 500mg amygdalin three times a day to humans produced no toxic effects and only moderately raised blood cyanide levels (22). While ingestion of beta-glucosidase enzyme-containing raw fruits and vegetables with amygdalin has been alleged to produce cyanide poisoning (1), little evidence exists to substantiate this claim.

Studies on rats however, found that the mean lethal dose (LD50) of orally administered amygdalin (880mg/kg body weight) was reduced to below 600mg/kg body weight when this was administered with beta-glucosidase (13). Amygdalin has also recently been investigated as a prodrug, which when administered in conjunction with beta-glucosidase conjugated to a tumour-associated monoclonal antibody, showed significant cytotoxic activity on bladder cancer cells (23). Lack of such an effect by amygdalin alone however (24), reinforces the role of beta-glucosidases in cleaving cyanogenic glycosides to yield free cyanide.

Other adverse reactions reported with laetrile include hypotension, haemoglobinuria, gastro-intestinal haemorrhage, vomiting, headache, diarrhoea, fever, rash and muscular weakness (1,20).

Oral bioavailability of prunasin is somewhat greater, and it is absorbed essentially intact across the intestinal wall, without cleavage of the glycosidic bond and thus no formation of benzaldehyde or hydrocyanic acid during the mucosal passage (21, 57).

A German study in healthy volunteers and patients, found that bioavailability of hydrocyanic acid from very high dosages of linseed was poor, but that bitter almonds did raise plasma thiocyanate levels significantly (7).

In cattle, rates of dissociation of cyanohydrins are pH-dependent, with high rates of dissociation occurring at pH greater than 6 (27). This implicates a possible delay in the onset of symptoms of hydrocyanic acid poisoning due to

the time taken for glycosides to reach the alkaline environment of the small intestine.

Outbreaks of *Phalaris aquatica* “Sudden death” syndrome in Australian sheep, livestock in India and cattle in New Zealand, have been linked in some cases to potentially toxic levels of hydrocyanic acid (37,38,39).

Cassava

Cassava (Manihot esculenta), is a staple plant food for more than 500 million people in developing countries particularly in Africa, and the root contains a glucoside with a high content of the cyanogenic glycoside linamarin (also found in lima beans), as well as protein and other nutrients.

Orally ingested linamarin is relatively poorly bioavailable, about one-quarter being excreted unchanged and another quarter metabolized into an as yet unknown compound (25,26).

Excessive intake of *Cassava* which has not been properly processed to reduce hydrocyanic acid content, especially in diets based almost exclusively on it for a long period of time, is associated with elevated levels of plasma thiocyanate, various neurological syndromes, hypothyroidism and goitre(10,26,15,12).

Populations who regularly consume properly processed *cassava* roots however, are not exposed to high levels of cyanide (34,9). Home or industrial processing, particularly sun drying or fermentation, has been shown to almost completely eliminate its potential hydrocyanic acid content (36).

Other foods containing hydrocyanic acid

German workers who analysed the hydrocyanic acid content of grains and cereals, reported the presence of hydrocyanic acid in 19 out of 24 types of grain, and 28 out of 31 cereals. The content of hydrocyanic acid measured was between 0.1 and 45 micrograms per 100gram of dried mass (41).

Hydrocyanic acid levels of 12 leafy vegetables were measured by Nigerian researchers, who found that the values ranged from 4.32 – 23.8mg per 100g of dried mass (58).

Of 3 varieties of *Piper* species analysed, a cultivated variety of *Piper guineense* was highest in hydrocyanic acid and contained 85.8mg per 100g (59).

Prunus laurocerasus

The source of hydrocyanic acid for the various homoeopathic preparations currently available on the New Zealand market (manufactured by Weleda NZ Ltd), is apparently a ‘mother tincture’ (a hydroethanolic liquid extract) of leaves of the plant *Prunus laurocerasus* (Cherry laurel). This is a common European shrub, and although little information is available in the literature

regarding its medicinal uses, Cherry laurel is listed in the 1949 edition of the B.P.C. It is listed elsewhere as being of value in coughs, whooping cough, asthma, and in dyspepsia and indigestion (50). A recently published ethnopharmacobotanical survey reported use of the drupes of this plant as a hypotensive (56).

The B.P.C. monograph describes Cherry laurel as fresh leaves of *Prunus laurocerasus* collected as soon as they are fully grown. The leaves contain about 1.5% cyanogenic glycosides (48), mainly the glycoside prulaurasin (laurocerasin; a racemic mixture of prunasin and sambunigrin) which is decomposed by the enzyme prunase, with formation of glucose, hydrogen cyanide, and benzaldehyde.

Hydrocyanic acid content of Cherry Laurel leaves is reported as being in the region of 50-210mg/100gm, or 0.05 to 0.2% by the most recent source (6), although other authors report levels ranging from 0.1 to 5%, young leaves apparently yielding more than old (49, 50). A paper on the analysis of hydrocyanic acid levels in *Prunus laurocerasus* was located, but this is written in French and a copy of the full paper was unable to be obtained by the author in sufficient time before the deadline for completion of this report (52). Volatile oil, composed of benzaldehyde, benzyl alcohol, ursolic acid, and tannins, are also reported as being present in Cherry Laurel leaves (48).

Cherry laurel is used for the preparation of Cherry-laurel Water, which has been used as a flavouring agent and as a sedative in nausea and vomiting. Cherry-laurel Water was also formerly used, diluted 1 in 10, as an eye lotion. It was standardised to contain 0.1% of hydrocyanic acid, and the recommended dose was 2 to 8ml(51). The Swiss Pharmacopoeia once required this to be dispensed when Bitter Almond Water was prescribed.

The leaves are said to possess qualities similar to those of hydrocyanic acid, and the water distilled from them is used for the same purpose as that medicine.

No reports of adverse effects (or toxicity) attributable to ingestion of *Prunus laurocerasus* leaves, appear to have been published in the literature to date (1,48,49).

Related *Prunus* species

Weak spasmogenic as well as spasmolytic and calcium antagonist effects are produced by leaf extracts of the related *Prunus persica* (peach leaves) (53). The bark of *Prunus serotina* (Wild cherry), is widely regarded as having antitussive activity by western phytotherapists (55), although there appears to be little evidence of this. Good specimens of Wild Cherry bark are said to yield 0.05 to 0.16% of hydrocyanic acid (6, 51).

Hydrocyanic acid containing Preparations currently on the New Zealand

market:

As mentioned earlier, a wide range of plants including foodstuffs contain very small levels of hydrocyanic acid, but in most cases this compound is largely produced following metabolism of cyanogenic glycosides *in vivo*.

The author is not personally familiar with any phytomedicinal or dietary supplement preparation *containing defined quantities* of hydrocyanic acid available on the New Zealand market, and believes the only ones that are available to be homoeopathic in nature. The use of Bitter Almond Water and Cherry Laurel Water, once ingredients in pharmaceutical compounding, appears to have all but disappeared from modern Pharmacy practice.

Given that leaves of Cherry laurel are generally reported to contain an average of 0.1% of hydrocyanic acid (6,50), while the bark of Wild Cherry (*Prunus serotina*) is listed as containing 0.05 to 0.16% of hydrocyanic acid (6,51), the content of hydroethanolic tinctures or liquid extracts made from each of these two plants is probably similar in terms of hydrocyanic acid levels. Wild Cherry bark containing preparations are freely available 'over the counter' or through medical herbalists and naturopaths, and like Cherry Laurel leaves have a long history of safe use in humans.

The rationale behind a review of the classification status of Cherry Laurel-derived preparations, would appear to relate simply to the fact that a particular company has drawn attention to the hydrocyanic acid content of some of their preparations made from this plant. Presumably this is due to some kind of (perhaps historical) promotion of this compound itself as being somehow relevant to the alleged efficacy of the particular homoeopathic preparations manufactured from Cherry Laurel leaves.

My understanding is that the homoeopathic products listed as containing hydrocyanic acid, and available on the New Zealand market, are apparently based upon a 'mother tincture' which has the same content of hydrocyanic acid as that specified for Cherry Laurel Water in old editions of the B.P.C. (i.e. maximum 0.1% hydrocyanic acid). These products are apparently as follows:

Products for Internal consumption:

a) available OTC::

12% Aqua laurocerasus (made from fresh plant).

Aqua laurocerasus (Cherry Laurel Water), contains a maximum of 0.1% hydrocyanic acid, therefore a product containing 12% Cherry Laurel Water will contain no more than 0.012% hydrocyanic acid, which is equivalent to 0.12mg per 1ml (15 drop) dose. The pack sizes of this product are apparently usually 30ml, but sometimes 100ml. Total hydrocyanic acid content is therefore 3.6 to 12mg per pack.

b) available only through the Weleda pharmacy as requested by a doctor:

Fresh plant preparations with potencies ranging from 1x through to 6x (i.e., if made from a 'mother tincture' containing 0.1% hydrocyanic acid, these

preparations will contain no more than 0.01% hydrocyanic acid, which is equivalent to 0.1mg per 1ml (15 drop) dose. Total hydrocyanic acid content is therefore 3 to 10mg per 30ml or 100ml pack.

c) Products for parenteral (s.c.) administration (available through a doctors prescription):

Ampoules made from a Fresh plant (tincture?) 3x strength (i.e. if made from a 'mother tincture' containing 0.1% hydrocyanic acid, these preparations will contain no more than 0.0001% hydrocyanic acid, the actual mg content dependant upon the ampoule volume).

The Proposed Medsafe Classification of Hydrocyanic Acid

Prescription Only Medicine, with a Schedule exemption of 1 microgram per litre or per kilogram.

It is of interest that this exemption level is 1000 times less than that of the previous Medsafe classification of Hydrocyanic Acid, which was apparently as follows:

Previous Medsafe Classifications for Hydrocyanic acid

Restricted Medicine: Hydrocyanic acid, except in medicines containing less than 0.1% of Hydrocyanic Acid.

Pharmacy Only Medicine: Hydrocyanic acid, in medicines containing less than 0.1% Hydrocyanic acid.

Classifications of Hydrocyanic acid in other countries:

Germany – not classified.

Australia: Schedule 4 (POM); Hydrocyanic acid for therapeutic use.

Schedule exemption: 1 microgram per litre or per kilogram.

Proposals for reclassification as outlined in the Submission received from Weleda

The Submission for Reclassification of Hydrocyanic Acid received by Weleda New Zealand Ltd, maintains that the general application of a Prescription Only Medicine classification to product containing Hydrocyanic acid up to the schedule exemption level of 1 microgram per litre or per kilogram, is not substantiated by toxicity data (60). They propose that a lower classification be applied to product containing lower concentrations of Hydrocyanic acid, as follows:

Prescription Only Medicine: Hydrocyanic acid; for oral use in liquid or powder form in a pack containing more than 4 milligram; in solid dose form containing more than 4 milligram per dose.

Pharmacy Medicine: Hydrocyanic acid; for oral use in liquid or powder form in a pack containing 4 milligram or less; in solid dose form containing 4 milligram or less per dose.

The effect of this classification would be to make the 30ml pack sizes of the homoeopathic Cherry Laurel preparations containing hydrocyanic acid a Pharmacy Medicine, while those greater than 40ml, including the 100ml maximum pack size supplied by Weleda, would become a Prescription Only Medicine.

NB: The volume of Cherry-laurel Water (distilled from fresh Cherry-laurel leaves, and which contains 0.1% hydrocyanic acid, or 1000mg/litre) which would therefore be expected to have a fatal effect on a child, would be 5ml. This is within the adult dose range of 2 to 8ml for Cherry-laurel Water listed in earlier editions of Martindale (51), which would appear to indicate either a serious inconsistency in the presumed fatal dosage of hydrocyanic acid, and/or its content in this preparation, and/or that this preparation is highly poisonous. Given that it was listed in numerous earlier editions of Martindale without any strongly precautionary statement as to a poisonous nature, one can only wonder as to the source(s) of this inconsistency.

Conclusions

Possible toxicity of the various homoeopathic products currently available in New Zealand which have been made from a starting material of a 'mother tincture' of Cherry Laurel, standardised to contain no more than 0.1% hydrocyanic acid, would seem to be extremely unlikely. No case reports of toxicity attributable to ingestion of Cherry Laurel leaves appear to exist in the literature, and for hydrocyanic acid containing preparations derived from it alone, provided additional levels of this substance are not added after extraction from the plant, the chances of toxicity would seem remote. Such a situation is supported by a large body of evidence, as this report has briefly outlined, including the fact that these particular preparations have been diluted significantly following initial plant extraction, and have also been used clinically for many years without a single adverse effect being reported.

The abuse potential of these particular preparations would seem to be minimal, given what is known about the pharmacology of hydrocyanic acid and Cherry Laurel leaves.

Based upon the calculation earlier of a dose of 5mg of hydrocyanic acid perhaps being fatal to a 10kg child, and the documented fatal dose to adults being 50mg hydrocyanic acid, I consider that the proposal to reclassify this substance as Prescription Only and to a schedule exemption level of 1 microgram per litre or per kilogram, is excessively restrictive. To ingest a potentially fatal dose of a preparation of this strength, a total volume of 5,000 litres would need to be ingested.

As my report has shown however, there would appear to be a number of

inconsistencies which the M.C.C. should be aware of in terms of the current review of the classification status of hydrocyanic acid, namely:

- c) Inconsistencies in the alleged potential fatal dosage of hydrocyanic acid as documented in the reference texts, when one compares this to the stated therapeutic dose of Cherry Laurel Water BPC, containing a stipulated level of hydrocyanic acid.
- d) The fact that many other hydrocyanic acid-containing herbal or dietary supplement products apart from these homoeopathic ones are available on the Australasian market, and yet their content of hydrocyanic acid has not been specified or measured.
- c) The fact that the bioavailability of hydrocyanic acid as a metabolite formed in the body from precursor cyanogenic glycosidal compounds, is probably of more relevance from a safety and regulatory perspective, than actual levels of this substance itself in plant-based preparations.

Recommendations re suitable classification of hydrocyanic acid:

What I would propose based upon this information in its entirety, is:

General Sale Medicine: Hydrocyanic acid, in preparations for oral use in liquid or powder form in a pack containing no more than 1mg hydrocyanic acid.

Pharmacy Only Medicine: Hydrocyanic acid, except in preparations for oral use in liquid or powder form in a pack containing no more than 4mg hydrocyanic acid.

Prescription Medicine: Hydrocyanic acid, in preparations for oral use containing more than 4mg hydrocyanic acid, or preparations for parenteral use.

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