

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON CYANOGENIC GLYCOSIDES IN BITTER APRICOT KERNELS.

Background

1. Bitter apricot kernels have recently been marketed as a health food in the UK. They contain high levels of amygdalin, a cyanogenic glycoside. The Committee were asked to consider whether there were sufficient data to establish a maximum upper level for safe intake of cyanide or cyanogenic substances.
2. In the 1970s and 1980s, amygdalin (also known as laetrile or, though not a recognised vitamin, as vitamin B17) extracted from bitter apricot kernels was sold as a treatment for cancer. The treatment was never proven and was associated with significant toxicity. Sale of these extracts was restricted under the terms of "The Medicines (Cyanogenetic Substances) Order 1984".
3. The Medicines and Healthcare products Regulatory Agency (MHRA) has advised that the kernels would be considered foods regardless of the cyanide content, unless presented as medicines by claiming to treat, cure or prevent a medical condition.

Cyanogenic glycosides in foods

4. As well as bitter apricot kernels, low levels of cyanide are also present in almonds, sweet apricot kernels and in the stones of other fruits such as cherries and consequently cyanide is present in some foods¹. The maximum level of cyanide that can be present as a result of using such foods as flavourings is regulated under the terms of The Flavourings in Food Regulations 1992 (as amended). Otherwise the cyanide content of food is not specifically regulated except under the terms of the Food Safety Act 1990 which makes it an offence to sell or possess for sale food which is injurious to health.
5. Analytical data indicate that the bitter apricot kernels currently on sale have a mean cyanide (CN) content of 1450 mg/kg, approximately 0.5 mg CN/kernel. Data on the range of values for individual kernels are not available. The value of 1450 mg/kg is consistent with data from the literature² which reports cyanide contents of <0.05, 1-2 and >2000 mg/kg for low, medium and high amygdalin containing apricot kernels respectively.

6. A number of other cyanogenic glycosides are found in foods, including linamarin (cassava, lima beans), prunasin (ferns) and sambunigrin (elderberries)¹.

Reviews by other regulatory agencies

7. The database on cyanide toxicity is limited particularly with respect to chronic intake.

8. As a result of the occurrence of cyanide in food originating from flavouring substances, the Council of Europe³ reviewed cyanide toxicity and established a Tolerable Daily Intake (TDI). The TDI was based on data from a case-control study⁴ which considered the effects of chronic intake of inadequately processed cassava, thought to be linked to the neurological condition konzo. In this study konzo was associated with a cyanide intake of 0.19-0.37 mg/kg body weight (bw) per day. The Tylleskär *et al* (1992) study⁴ is considered in more detail in paragraph 19. An uncertainty factor of 10 was applied for inter-individual variation, resulting in a TDI of 20 µg/kg bw/day. An additional factor was not applied to extrapolate a lowest observed adverse effect level (LOAEL) to a no observed adverse effect level (NOAEL) since the condition was thought to be exacerbated by other dietary deficiencies such as of sulphate which would not be relevant to other populations. It was noted that the aetiology of konzo is not fully understood.

9. Safe intakes of cyanide from drinking water were considered by the World Health Organisation⁵. A TDI was established using data from a study in pigs fed 1.2 mg CN/kg bw/day for 6 months resulting in changes in behaviour and serum biochemistry⁶. This was used to establish a TDI of 12 µg/kg bw/day. An additional uncertainty factor was not applied to extrapolate from a LOAEL to a NOAEL since there were doubts about the biological significance of the observed changes.

10. In contrast, EFSA¹ concluded that there were insufficient chronic data to establish a TDI for cyanide but concluded that the current high level intake of 3-6 µg CN/kg bw/day from foods (notably certain types of marzipan) was not of concern.

Absorption and metabolism of cyanide.

11. Amygdalin (D-mandelonitrile-β-D-glucoside-6 -β-glucoside) (see fig 1, below) degrades to hydrogen cyanide, two molecules of glucose and benzaldehyde. Amygdalin hydrolysis is catalysed by the enzyme emulsin, a β-glucosidase also found in apricot kernels. Since β-glucosidase enzymes do not occur intracellularly in humans, swallowing of whole apricot kernels may not release much cyanide⁷, however, chewing or grinding increases toxicity by releasing emulsin from lysosomes. The enzymatic breakdown of amygdalin occurs most rapidly in alkaline conditions. The β-glucosidase may be deactivated in the acid environment of the stomach but can then be partially

reactivated in the alkaline environment of the gut⁸. Cyanogenic glycosides can also be hydrolysed by gut flora.

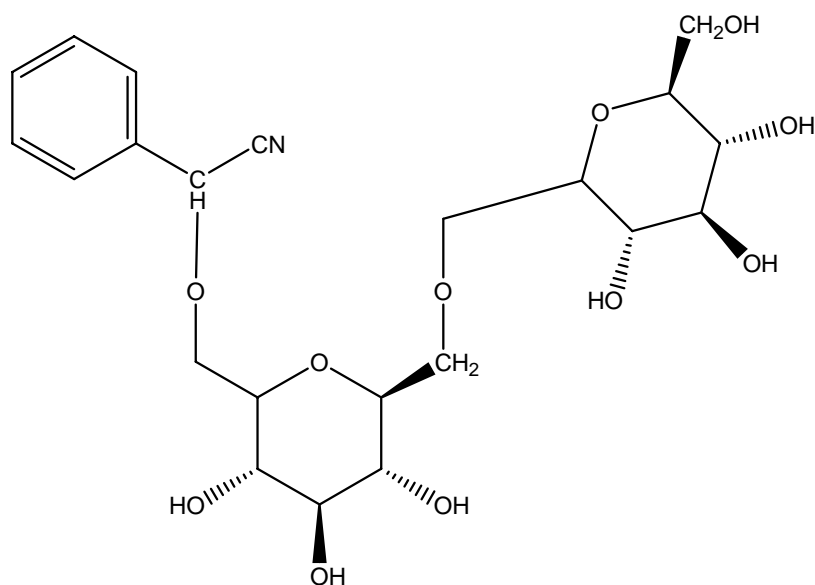


Fig 1. Structure of amygdalin.

12. After oral administration, hydrogen cyanide is readily absorbed and rapidly distributed within the body

Toxicity of cyanide and cyanogenic glycosides

Acute toxicity in humans

13. Cyanide has high acute toxicity with a very steep and absorption rate-dependent dose-response curve⁹. The lethal dose of cyanide in humans is in the range 0.5 to 3.5 mg/kg bw¹. Signs and symptoms of acute toxicity include headache, dizziness, mental confusion, stupor, cyanosis with twitching and convulsions, followed by terminal coma.

14. There are case reports of toxicity (including fatalities) resulting from the consumption of laetrile or amygdalin in a concentrated form, but also of toxicity resulting from the consumption of apricot kernels. Cyanide toxicity was also observed in an uncontrolled clinical trial of amygdalin¹⁰.

15. Suchard *et al* (1998)⁷ reported that a 41 year old female was found in a comatose and hypothermic state following the consumption of approximately 30 bitter apricot kernels. The patient responded to antidotal treatment and

subsequently recovered. The authors noted that 5 other cases of poisoning had been reported in the US from consumption of bitter apricot kernels for their amygdalin content. In an earlier case reported by Rubino and Davidoff (1979)¹¹, an adult female was hospitalised following the consumption of 20-40 kernels.

16. There are case reports of poisonings in children consuming kernels from wild apricots¹². The doses involved are unclear but the children were thought to have eaten more than 10 kernels. Similar cases have been reported in Gaza both from the wild apricot kernels and where the kernels were made into sweets without proper processing¹³.

17. In a case reported by Bromley *et al* (2005)¹⁴ an adult female presented at an emergency room feeling dizzy and unwell, having consumed 6 x 500 mg amygdalin tablets 30 minutes earlier. The toxicity was more significant than would be expected for the dose consumed. The authors concluded that the 3 g of vitamin C also consumed may have enhanced the toxicity of the amygdalin by promoting the release of cyanide from the molecule and decreasing stores of the amino acid cysteine which is involved in the detoxification of cyanide.

Chronic toxicity in humans

18. Several conditions have been observed in cassava eating populations which have been attributed to chronic cyanide intake. These include malnutrition, diabetes, congenital malformations, neurological disorders and myelopathy¹. Goitre is thought to have occurred where cyanogenic glycosides are present in the diet at levels greater than 10- 50 mg/kg food.

19. Konzo is a distinct form of tropical myelopathy characterised by abrupt onset of spastic paraparesis (slight paralysis of the lower limbs). Epidemics occur where processing times for cassava are reduced⁴. A number of epidemiology studies have considered konzo (see^{1,8}). In a konzo-affected population in former Zaire, the condition was associated with a cassava flour intake greater than 0.5 kg/day equivalent to an intake of 0.19 to 0.37 mg cyanide/kg bw/day⁴. Urinary thiocyanate levels (reflecting cyanide intake) were comparable in cases and controls but whole blood cyanide levels were elevated in 3/3 cases compared to 2/23 controls, suggesting that sustained high blood cyanide maintained by sulphur deficiency was associated with Konzo.

Cyanide toxicity in animals

20. Exposure to cyanide was reported to produce dose-related increasing ambivalence and slower response time to stimuli in pigs given oral doses of up to 1.2 mg/kg bw/day cyanide for 6 months⁶. Since behaviours demanding low energy were more affected it was suggested that an effect on glucose metabolism could be involved. There was a dose-dependent increase in fasting blood glucose which was evident after 12 weeks, and became statistically significant following 18 weeks of treatment. In the top dose group,

blood glucose was increased by up to 60%. Serum thyroxine and, notably, triiodothyronine were reduced at all doses, but markedly at the top dose only.

21. Rats were given drinking water containing up to 300 mg/L sodium cyanide for 13 weeks (NTP, 1993- discussed¹) (equivalent to approximately 12.5 mg/kg bw/day cyanide). No significant changes were apparent in haematology, clinical chemistry or urinary parameters. There were no treatment-related gross or histopathological changes in the rats. Slight changes were observed in the testes and spermatozoa of treated males. Comparable results were obtained from a 13 week study in mice. Testicular effects have also been observed in dogs fed a cassava or rice plus cyanide diet¹⁵. The data from these studies suggest that humans are more sensitive to cyanide toxicity since the lethal dose in humans is 0.5 –3.5 mg/kg bw.

22. There are no data available from chronic or reproductive toxicity studies.

Exposure assessment

23. The kernels currently available contain approximately 0.5 mg cyanide/kernel (information on variation between individual kernels is not available). Consumers are advised to eat 5 kernels in an hour, but no more than 10 in a day. This represents a cyanide intake of 2.5 mg in an hour, with a maximum of 5 mg in a day, equivalent to 42 µg/kg bw (1 hour) or 83 µg/kg bw/day. The latter figure is 4 and 8 fold higher than the TDIs set by the Council of Europe and WHO respectively.

24. Whilst the retailer of these kernels recommended that this intake should not be exceeded, other information is readily available from the internet which advises that those suffering from cancer should gradually increase their consumption to 5 kernels/hour, 6 to 10 times a day. This would represent a maximum intake of 15-25 mg cyanide/day (equivalent to 250-417 µg/kg bw).

Discussion and Conclusions

25. The database for the toxicity of cyanide and cyanogenic glycosides in humans is incomplete. The acute lethal dose for cyanide is in the range 0.5 to 3.5 mg/kg bw. Case reports suggest severe toxicity arising from the consumption of approximately 30 bitter apricot kernels in adults, fewer in children. The cyanide concentration of the kernels is known to be variable and is not included in published reports, making precise comparisons difficult.

26. There are also relatively few data on the effects of chronic cyanide intake in humans. Konzo is a neurological condition associated with cyanide intake from improperly processed cassava. These data were used by the Council of Europe to establish a TDI of 20 µg/kg bw/day for cyanide.

26. The available evidence on konzo indicates that there are many confounding factors, and whilst cyanide intake may contribute it is likely to be one of a number of possible causal factors specific to a high cassava diet.

27. There is no available evidence in adequately nourished humans to show that chronic intake of cyanogenic glycosides causes a cumulative hazard above that of repeated acute toxicity. However, data from animal studies suggest that adverse effects may result from chronic exposure to cyanides and cyanogenic glycosides. Data on biochemical and behavioural changes in pigs were used by the WHO to derive a TDI of 12 µg/kg bw/day, which is comparable to that established by the CoE.

28. Overall, the Committee concluded the limited chronic data available were not sufficient to propose a TDI.

29. The range for the acute lethal dose in humans is 0.5 to 3.5 mg/kg bw. A 100 fold uncertainty factor (10 to account for inter-individual variability and 10 to extrapolate from an effect level to a no effect level, taking into account the steep dose-response relationship) could be applied to the lowest lethal dose. This would indicate that a dose of 5 µg/kg bw would be unlikely to cause acute effects, ie. a nominal acute reference dose (ARfD). This is comparable to the TDIs of 12 and 20 µg/kg bw/day established by WHO and CoE respectively.

30. Taking the available evidence together, consumption of 1 kernel per day would result in a cyanide intake of 0.5-mg/day (equivalent to 8 µg/kg bw for a 60 kg adult) which is in the region of this nominal ARfD and the TDIs proposed by others and would be unlikely to be of concern. This level of intake represents a threshold above which, increasing intake becomes increasingly hazardous.

31. The consumption of 10 kernels/day recommended with the sampled product would represent an intake of 5 mgs cyanide (equivalent to 83.5 µg/kg bw). This is one sixth of the lowest lethal dose and would cause a consumer to exceed the TDIs set by CoE and WHO for cyanide by 4-8 times and the nominal ARfD established as above, by 8-16 times. Such intake would therefore be hazardous. In addition, readily available information recommends far higher intakes of the kernels, which could be severely toxic, or, lethal in some people. Given the background to the product, exceedance of the dose recommended on the packaging seems probable.

**COT Statement 2006/15
December 2006**

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