TOX/2006/13

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

CYANOGENIC GLYCOSIDES IN APRICOT KERNELS.

Introduction

1. Bitter apricot kernels have recently become available as a health food on the UK market. They contain high levels of amygdalin, a cyanogenic glycoside. The Committee are asked to consider whether there are sufficient data to establish a maximum upper level for acute and chronic intake of cyanide or cyanogenic substances.

Background

2. In the 1970s and 1980s, amygdalin (also known as vitamin B17 or laetrile) 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 such supplements was restricted under the terms of "The Medicines (Cyanogenetic Substances) Order 1984".

3. The Food Standards Agency (FSA) has become aware that bitter apricot kernels, although previously only available via the internet, are now available for sale on the UK market. The kernels come with advice regarding their consumption, pointing out the dangers of over-consumption and not endorsing the "alleged health benefits". However the FSA has concerns about their safety and on the effects of possible misuse.

4. The FSA has been advised by the Medicines and Healthcare products Regulatory Agency (MHRA) that the kernels (as opposed to extracts) would be considered foods regardless of the cyanide content unless they presented themselves as medicines by claiming to treat, cure or prevent a medical condition.

5. 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 are present in some other foods (see EFSA, 2004). The Flavourings in Food Regulations 1992 (as amended) set permitted proportions of cyanide arising from the use of flavouring substances. The standard permitted proportion for all types of food is 1 mg/kg with the following exceptions. Nougat, marzipan, nougat or marzipan substitutes or similar products may contain 50 mg/kg. Tinned stone fruits may contain 5 mg/kg. Alcoholic drinks may contain 1 mg/kg for each percentage of alcohol by volume therein.

6. Analytical data received from Buckinghamshire Trading Standards indicate that the bitter apricot kernels currently on sale have a cyanide content of 1450 mg/kg, approximately 0.5 mg/kernel. This is consistent with data from the literature (Holzbecher *et al.*, 1984) which reports cyanide contents of <50, 1000-2000 and >2000 mg/kg for low, medium and high amygdalin apricot kernels.

7. A number of other cyanogenic glycosides are present in foods include linamarin (cassava, lima beans), prunasin (ferns) and sambunigrin (elderberries) (EFSA, 2004).

Reviews by other regulatory agencies

8. As a result of its use in flavourings, cyanide toxicity has been assessed on a number of occasions, most recently by EFSA (2004) (see annex A). EFSA concluded that there were insufficient chronic data to establish a tolerable daily intake (TDI) for cyanide but that an intake of 3-6 μg/kg bw/day from foods (notably marzipan) was not of concern.

9. In contrast, a previous assessment by the Council of Europe (CoE, 2000) established a TDI from data on chronic intake of inadequately processed cassava. This was based on a study by Tylleskär *et al.* (see para 19 below) which linked konzo, a neurological condition, to a cyanide intake of 0.19-0.37 mg/kg bw/day. A 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 LOAEL to a 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 was not fully understood.

10. Cyanide in drinking water was reviewed by WHO (2003). A study in pigs given oral doses of cyanide ion for 6 months, in which changes in behaviour and serum biochemistry were observed at 1.2 mg/kg bw/day (see para 21), was used to establish a TDI of 12 μg/kg bw/day. An additional factor was not applied to extrapolate from a LOAEL to a NOAEL since there were doubts about the biological significance of the observed changes.

Absorption and metabolism of cyanide.

11. Amygdalin (D-mandelonitrile-β-D-glucoside-6-β-glucoside is a cyanogenic compound which breaks down to hydrogen cyanide, glucose and benzaldehyde. Amygdalin hydrolysis is catalysed by emulsin, a β-glucosidase also found in apricot kernels. Whilst swallowing whole apricot kernels may not release much cyanide (Suchard *et al.*, 1998), chewing or grinding increases toxicity by releasing the enzyme emulsin, from lysozymes, which catalyses amygdalin hydrolysis and thus increasing the amounts of cyanide released by the kernal. This occurs most rapidly in alkaline conditions.

Cyanogenic glycosides can also be hydrolysed by gastrointestinal flora (EFSA, 2004).

12. At the pH of the stomach, cyanide containing compounds predominantly break down to form hydrogen cyanide which can rapidly penetrate mucosal and cell membranes. At pH 7.4, only 1.6% of the hydrogen cyanide is dissociated allowing rapid diffusion though cell membranes.

Toxicity of cyanide and cyanogenic glycosides

13. The toxicity data are summarised in the EFSA opinion (see Annex A) and some of the key data are highlighted below.

Acute toxicity in humans

14. The lethal dose of cyanide in humans is thought to be in the range 0.5 to 3.5 mg/kg bw (quoted in EFSA, 2004). Acute signs include headache, dizziness, mental confusion, stupor, cyanosis with twitching and convulsions, followed by terminal coma (discussed EFSA, 2004).

15. There are case reports of toxicity resulting from the consumption of laetrile or amygdalin in a concentrated form, but also of toxicity resulting from the consumption of apricot kernels.

16. Suchard *et al.* (1998) reported that a 41 year old female was found in a comatose and hypothermic state following the consumption of approximately 30 apricot kernels (time period of consumption unclear). Five hours after consumption (and following some treatment), the patient's cyanide level in whole blood was 43.1 µM (normal 15.8 µM or less) and plasma thiocyanate 448 µM (normal 172-344 µM). The patient responded to antidotal treatment and was subsequently discharged. The authors noted that 5 other cases of poisoning have been reported in the US from consumption of apricot kernels (no more details available) for their amygdalin content.

17. There are case reports of poisonings in children from consumption of kernels from wild apricots (Sayre and Kaymakcalavu, 1964). 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 processing (Lasch and El Shawa, 1981)

Chronic toxicity

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 myelopathy (EFSA, 2004). 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 are thought to occur where processing times for cassava are reduced (Tylleskär *et al*., 1992). A population affected by annual outbreaks of konzo occurred was found to consume cassava soaked for one day and thus had higher exposure to dietary cyanide (mean urinary thiocyanate 757 μM) compared to an unaffected population (mean urinary thiocyanate 50 μM) where the cassava was soaked for three days before consumption.

20. Other studies on konzo are discussed in the EFSA review.

Cyanide toxicity in animals

21. Pigs were given oral doses of 1, 0.4, 0.7 or 1.2 mg/kg bw/day cyanide for 6 months (Jackson *et al.*, 1988). Exposure to cyanide was reported to produce dose-related increasing ambivalence and slower response time to stimuli. Since behaviours demanding low energy were thought to be more affected it was suggested that an effect on glucose metabolism could be involved. Fasting blood glucose was increased by 60%. Serum thyroxine and, notably, triiodothyronine were reduced at all doses, but this was statistically significant at the top dose only (decreases of 15 and 35% respectively) (details taken from CICAD 61, 2004. Original reference will be tabled at the meeting).

22. Rats were given drinking water containing up to 300 mg/L sodium cyanide for 13 weeks (NTP, 1993- discussed EFSA, 2004). The achieved dose was 23.6 and 23.5 mg/kg bw/day sodium cyanide in males and females respectively (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. A slight reduction was apparent in the cauda epididymal weights of the treated males and the number of sperm heads per testis was reduced in the top dose group. Comparable results were obtained from a 13 week study in mice. No fertility studies have been identified. Testicular effects have also been observed in dogs fed a cassava or rice + cyanide diet (Kamalu, 2993). 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 (see paragraph 14).

23. There are no data available from chronic toxicity studies.

Risk assessment

24. As noted above, the kernels contain approximately 0.5 mg cyanide/kernel. The packaging for the product sampled by Buckinghamshire Trading Standards states the following: “Eat no more than 5 kernels in a one hour period and in total, eat no more than 10 kernals in a 24 hour period”.

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 for a 60 kg adult. The latter figure is a 4- and 8- fold higher than the TDIs set by the Council of Europe and WHO respectively.

25. While this product sets recommendations as to the amount that should be consumed, other information is readily available from the internet which advises that those suffering from cancer should gradually increase their consumption to 5 kernels/hr 6 to 10 times a day. This would give a maximum intake of 15-25 mg cyanide/day (equivalent to 250-417 μg/kg bw in a 60 kg adult).

26. Advice is not provided by the company concerned on how the apricot kernels should be consumed. However, information readily obtained from the internet recommends that the kernels be ground and mixed with fruit juice to mask the bitter taste.

Questions for the Committee

27. The Committee are asked to comment on the information and to consider the following questions:

i. Would an intake of 5 mg cyanide/day would be of concern?

ii. Are the available data, from human or animal studies, adequate to establish an acute reference dose (per hour or per day) for cyanide? If so, what would the appropriate level be?

Secretariat
March 2006

REFERENCES

CoE (2000) Council of Europe Committee of Experts on Flavouring Substances 46th meeting-RD 4.13/1-46 data sheet on HCN.

EFSA (2004). Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on Hydrocyanic Acid in Flavourings and other Food Ingredients with Flavouring Properties. Question no EFSA-Q-2003-0145. EFSA Journal (2004) 105.

Holzbecher, M.D., Moss, M.A., Ellenberger, H.A. (1984). The Cyanide Content of Laetrile Preparations, Apricot, Peach and Apple seeds. Clinical Toxicology, 22, 341-347.

Jackson, L.C. Behavioural Effects of Chronic Sublethal Dietary Cyanide in an Animal Model: Implications for Humans Concuming Cassava (Mnihot esculenta). Human Biology 1988 Aug. 60 (4) 597-614.

CICAD (2004). Concise International Chemical Assessment Document (CICAD) 61, Hydrogen Cyanide and Cyanides: Human Health Aspects.

Kamalu, B.P. (1993). Pathological Changes in Growing Dogs Fed on a Balanced Cassava (*Manihot esculenta* Crantz) diet. British Journal of Nutrition, 69, 921-934.

The Medicines (Cyanogenetic Substances) Order 1984

Sayre, J.W., Kaymakcalavu, S. (1964) Hazards to Health. Cyanide Poisoning from Apricot Seeds among Children in Central Turkey. New England Journal of Medicine, 270, 1113- 1114.

Suchard , J.R., Wallace, K.L. Gerkin, R.D. (1989) Acute Cyanide Toxicity Caused by Apricot Kernel Ingestion. Annals of Emergency Medicine, 32:6, 742-744.

Tylleskär, T., Banea, M., Bikangi, N., Cooke, R.D., Poulter, N.H., Rosling, H. (1992). Cassava Cyanogens and Konzo, an Upper Motoneuron Disease Found in Africa. The Lancet, 339, 208-211.

WHO (2003). Cyanide in Drinking water. Background Document for development of WHO Guidelines for drinking water quality. WHO/SDE/WSH/03.04/05

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ANNEX A. EFSA OPINION ON HYDROCYANIC ACID IN FLAVOURINGS AND OTHER FOOD INGREDIENTS WITH FLAVOURING PROPERTIES.

For copyright reasons this document will not be included when this paper becomes publicly available. However the EFSA opinion can be found at the following web address:

http://www.efsa.eu.int/science/afc/afc_opinions/698/afc_opinion21_ej105_hydroacidinflav_en1.pdf