Food Standards Agency
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Buidheann Inbhe-Bìdhe

Anne Peat
Clerk to the Public Petitions Committee
TG.01
The Scottish Parliament
Edinburgh
EH99 1SP

Reference: FAS/0034

4 August 2011

Dear Anne

CONSIDERATION OF PETITION PE1376

I refer to Fergus Cochrane's letter to the Food Standards Agency in Scotland dated 25th March 2011 seeking a response to points raised during the discussion on the petition at the Committee's meeting held on 1 March (specifically, the points made by Nigel Don (cols 3481-2). To summarise:

Are there protective factors or inhibitors in foods such as fruit juice which naturally contain methanol that would not be present in foods sweetened with aspartame, so that methanol from the latter foods would be metabolised differently, resulting in adverse effects.

I am pleased to reply to your letter – as previously, our response covers the interests of the Agency as a whole.

Summary

1. Toxicity of methanol in humans is a result of the accumulation of the intermediate breakdown product formate/formic acid.

2. Studies in the literature suggest that the only relevant inhibitor of methanol metabolism that would be found in foods such as fruit juices, is ethanol. We agree that small amounts of ethanol are found in some food products, notably fruit juices. It is also possible that methanol released from bacterial breakdown of pectin in the human gut may be

6th Floor
St Magnus House
25 Guild Street
Aberdeen AB11 6NJ
T 01224 285102
F 01224 285106
Charles.Milne@foodstandards.gsi.gov.uk

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produced and absorbed more slowly than that released from rapid consumption of a beverage.

3. The levels of ethanol associated with the consumption of fruit juices are considerably less than the dose needed to block methanol metabolism experimentally or clinically. Therefore although methanol would be accompanied by ethanol in fruit juices it is highly unlikely that this would be sufficient to inhibit methanol metabolism.

4. Human volunteer studies show that exposure to methanol by inhalation at occupational levels result in an increase in blood methanol levels and increased urinary formate and methanol levels, but not increased blood formate. This demonstrates that formate is being produced from methanol and is being excreted but is not accumulating. Similar results occur in volunteer studies where high (larger than the ADI) doses of aspartame were given; this indicates that a single acute exposure to methanol arising from an aspartame-sweetened beverage would not be enough to result in an increased level of blood formate so that any difference in the pattern of absorption compared to methanol arising from fruit or fruit juice would not be relevant.

5. Taken together, this information suggests that even in the absence of ethanol, there is an amount of methanol that can be safely ingested and which is rapidly metabolised and cleared without formate accumulation in the blood without toxicity occurring.

Background

Methanol exposure

Exposure to methanol occurs as a result of amino acid metabolism within the body and from external sources such as food as well as occupational exposure[1,2]. Methanol in fruit and fruit juices is present as a result of the breakdown of pectin; in the human gut, further pectin is broken down by intestinal bacteria, producing additional methanol which is then absorbed by the body[2].

Methanol metabolism

In primates, methanol is sequentially oxidised to carbon dioxide[1,3] and then excreted as follows:

Methanol
↓
Formaldehyde via *alcohol dehydrogenase*

↓
Formate/formic acid via *formaldehyde dehydrogenase*

↓
Carbon dioxide via *10-formyl tetrahydrofolate synthetase*

Although the majority of methanol is metabolised as described above, a small proportion is also excreted unchanged in the urine and in the breath[1].

Methanol toxicity

Methanol toxicity occurs as a result of the accumulation of formic acid, an intermediate breakdown product. This compound specifically binds cytochrome oxidase, a cellular enzyme; inhibition of this enzyme results in a cascade of cellular damage, leading to overt adverse effects such as neurotoxicity[4].

Primates, including humans, are more sensitive to methanol than species such as rodents because they have lower levels of folate in the liver[5]. Folate is a co-factor which is required for the last step of methanol metabolism in which formic acid or formate is oxidised to carbon dioxide. Where humans are exposed to large doses of methanol, the capacity of the formate to carbon dioxide reaction is saturated and formate starts to accumulate in the blood and tissues, resulting in the characteristic neurological and visual toxicity associated with methanol. The minimum acute lethal dose of methanol for an adult is approximately 20 g, the minimum acute dose associated with toxicity to the eye is 8 g[1]. Modelling data suggest that a concentration of approximately 210 mg/kg bodyweight methanol is necessary to saturate the folate dependent part of the metabolic pathway[6]

Once methanol exposure has ceased, the formate is metabolised and cleared as above but some damage may have already occurred from the high blood formate levels. It is not possible to specify how long formate levels would need to be high to cause damage because it is the combination of concentration and time which is important.

Inhibitors of methanol metabolism: ethanol

It is well established that the first step of methanol metabolism can be blocked by ethanol as these compounds compete for the enzyme *alcohol dehydrogenase*, with ethanol being the preferred substrate. If the enzyme is saturated, ethanol is metabolised first and once the ethanol is metabolised, methanol metabolism would resume; meanwhile the slow excretion of unchanged methanol continues. This blocking effect of ethanol is used both experimentally to measure methanol production within the body and in the treatment of acute methanol poisoning[4].

The use of ethanol to treat methanol poisoning works because the block temporarily prevents the metabolism of methanol to formaldehyde; this results in methanol not being converted to formaldehyde and remaining in the blood. However, as noted earlier, a small proportion of blood methanol is excreted unchanged in urine and breath. Thus while high blood ethanol levels are maintained the blood levels of methanol gradually decrease to a level where, when ethanol is removed and methanol metabolism resumes, the amount of formate produced would not be sufficient to saturate the eventual formate to carbon dioxide reaction and dangerous levels are not formed. The recommended blood ethanol concentration for treatment of methanol poisoning is 1 g/L[4]. For a non-drinker the loading dose of ethanol to treat methanol poisoning is 600-700 mg/kg bodyweight (equivalent to 36-42 g in a 60 kg adult) with a maintenance dose of 66 mg/kg bodyweight per hour; chronic drinkers are treated with a higher maintenance dose[7].

The blocking effect of ethanol is also used experimentally, to allow the measurement of endogenous methanol production, for example, in one study volunteers were given two 75 g doses of a 40:60 % ethanol: water mix to block methanol metabolism for 5 ½ hours[3].

Other inhibitors of methanol metabolism

The enzymes mentioned above can be inhibited by a number of factors, both by specific chemicals and by negative feedback from reaction products. However, studies in the literature suggest that the only relevant inhibitor of methanol metabolism that would be found in foods such as fruit juices, is ethanol.

Methanol in foods

Methanol occurs naturally in fruit through the breakdown of pectin in the gut; this has been demonstrated in human volunteers, in which 1 kg apples was estimated to produce 500 mg methanol[2].

Aspartame releases 10% methanol by weight, therefore consumption of aspartame at the Acceptable Daily Intake – an estimate of the amount of an additive that can be routinely consumed every day over a lifetime with no appreciable health risk - (40 mg/kg body weight) would result in exposure to 40 x 60 = 2400 mg aspartame or 2400/10 = 240 mg methanol in a 60 kg adult or 40 x 20 =800 mg aspartame or 800/10 = 80 mg methanol in a 20 kg child. Alternatively consumption of a 500 ml bottle of cola sweetened with the maximum permitted level of aspartame (600 mg/L) would result in exposure to a maximum of 600mg x 0.5L = 300 mg aspartame or 300/10 = 30 mg methanol. To reach the ADI a 60 kg adult would have to consume 2400/600 = 4L cola and a 20 kg child 1.5L. This is equivalent to 8 or 3 x 500 ml bottles or, 12 or 4.5 x 330 ml cans in adults or children respectively.

Ethanol in foods

Ethanol is found in foods through the fermentation of naturally occurring sugars.

It has been reported that levels of ethanol in citrus products range from 90-900 mg/L with methanol levels of 10-80 mg/L being reported in the same samples[8].

Methanol and ethanol in foods

The United Kingdom Aspartame Awareness Campaign has argued that the methanol arising from aspartame behaves differently to the methanol that occurs in fruit or fruit juices because it is not accompanied by naturally occurring ethanol. We agree that aspartame sweetened soft drinks such as cola would not contain ethanol but do not consider this to be relevant since the quantities of ethanol needed to block methanol metabolism are significantly greater than those occurring naturally. For example to achieve a 5 ½ hour block in endogenous methanol metabolism to allow it to be measured[2], a dose of 2 x 75 g of a 40:60% ethanol: water mix was used (equivalent to a spirit such as vodka); the ethanol content is estimated to be 0.4 x 150 = 60g. To ingest this amount of ethanol from fruit juice, an individual would have to consume 67 Litres (60/0.9= 67) of fruit juice containing the maximum reported level of 900 ppm (0.9 g/L) ethanol.

It has further been suggested that the methanol released from the breakdown of pectin in the human gut is not absorbed or is absorbed more slowly. However, increased concentrations of methanol have been detected in the breath (and by inference blood) following consumption of pectin or fruit[9]. Whilst pectin breakdown could result in slower production and therefore absorption of methanol, than would be the case following consumption of, for example, a diet drink, the absence of any indication of formate accumulation (see below) demonstrates this is not relevant. In both instance the amounts of methanol are small and comparable with the levels produced within the body from normal amino acid metabolism.

Volunteer studies of methanol or aspartame exposure

Where methanol is inhaled occupationally at the generally accepted maximum exposure level of 8 hours at 200 ppm an amount equivalent to approximately 1.9 g methanol is absorbed[10], this is not accompanied by ethanol but blood formate levels do not increase[11,12, 13, 14,15]. Similarly, human volunteers given large doses of aspartame (up to 5 times the ADI)[16, 17, 18,19] have not shown any evidence of increased blood formate, although blood methanol and urinary formate and methanol do increase, showing that some methanol has been produced and metabolised, but without the formate persisting in the blood. It should be noted that methanol was below the limit of detection in the blood of volunteers given aspartame at approximately the level of the ADI.

References

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In March 2011 the Committee on Toxicity (COT) issued a statement on the effects of chronic dietary exposure to methanol. This concluded that, although uncertainties remain because there have been few studies of long-term repeated exposure to methanol, either in animals or in humans, from the evidence available amounts of methanol consumed through food, including from aspartame, would not result in build up of formate and so are unlikely to cause harmful health effects. The statement is available from the following link:

http://cot.food.gov.uk/pdfs/cotstatementmethanol201102lay.pdf

Mr McDonald refers to this statement in his exchange of letters with the COT published on your website.

In May 2011, the European Food Safety Authority (EFSA) was asked by the Commission to bring forward the full re-evaluation of the safety of aspartame to be delivered in 2012. Previously planned for completion in 2020, the review of this individual sweetener is part of the systematic re-evaluation of all

authorised food additives in the European Union. This is also alluded to in the exchange between Mr McDonald and the COT.

There is no evidence of health concerns with the currently permitted levels of aspartame. There is an ongoing need to review any new relevant properly accredited scientific information as it becomes available.

I hope the above has addressed the issues raised and should you require any clarification or any further information, please do not hesitate to contact me.

Yours sincerely

PROFESSOR CHARLES MILNE
Director, Scotland