



Maisons-Alfort, 9 November 2006

OPINION**of the French Food Safety Agency on the assessment
of risk from consumption of an
“energy” drink containing substances other than technological
additives: taurine, D-glucuronolactone, inositol, vitamins B₂, B₃, B₅, B₆
and B₁₂.**

LA DIRECTRICE GENERALE

The French Food Safety Agency (Afssa) was asked by the Directorate General for Consumer Protection on 10 August 2006 to assess the risks from consumption of an “energy” drink containing substances other than technological additives: taurine, D-glucuronolactone, inositol, and vitamins B₂, B₃, B₅, B₆ and B₁₂.

After consulting the “Human Nutrition” expert committee which met on 28 September 2006, Afssa expresses the following opinion:

The product:

The application concerns an “energy” drink containing in particular caffeine (80 mg/250 mL), taurine (1000 mg/250 mL), D-glucuronolactone (600 mg/250 mL), inositol (50 mg/250mL) and five vitamins : B₂ (1,5 mg/250 mL), B₃ (20,5 mg/250 mL), B₅ (5 mg/250 mL), B₆ (5 mg/250 mL) and B₁₂. (5 µg/250 mL). The drink is described as “intended particularly to support intense activity and to enliven body and mind”.

The intake recommended by the company is two small cans per day, i.e. a maximum daily intake of 160 mg of caffeine, 2 g of taurine, 1.2 g of D-glucuronolactone, 3 mg of vitamin B₂, 41 mg of vitamin B₃, 10 mg of vitamin B₅, 10 mg of vitamin B₆ and 10 µg vitamin B₁₂. It should be stressed that consumption of two small cans provides doses of taurine and D-glucuronolactone that are approximately 10 times (2000 mg) and one thousand times (1200 mg) higher than the daily doses provided in diet respectively (which rarely exceed 180 mg per day for taurine (Laidlaw *and al.*, 1990) and 1 to 2 mg per day for D-glucuronolactone).

The product targets individuals with “intense activity”. This wording is ambiguous: the product labelling in other European Community countries claim effects on performance in the majority of cases and effects on recovery and concentration abilities in some cases: this leads the reader to believe that the wording refers to “physical activity”: the wording “enlivens the body and mind” and “energy drink” in the French labelling also suggests that people with intense physical activity and/or intense mental activity could represent a potential target for the product.

Evaluation history of the dossier

The product is not authorised for marketing in France following a rejection by the French Public Hygiene Council (CSHPF) on 10 September 1996. In parallel, at a Community level the evaluation conducted by the Scientific Committee on Food (SCF) (SCF, 1999) concluded in 1999 but it was impossible to ensure with certainty that the taurine and D-glucuronolactone content in the product did not carry any health risk: it therefore recommended that more detailed studies be conducted.

Supplementary toxicological data (administration of the drink to mice) evaluated on 27 March 2001 by Afssa (Afssa, 2001) and on 5 March 2003 by the SCF (SCF, 2003), were hindered by study methodology which made the effects difficult to interpret.

Experimental toxicological data in rats (toxicokinetics and subacute toxicity of taurine and D-glucuronolactone) evaluated on 5 March 2003 by SCF (SCF, 2003) and on 5 May 2003 by Afssa (Afssa, 2003) do not establish the safety of taurine and D-glucuronolactone at the recommended doses: in contrast they provide information which raises a suspicion that D-glucuronolactone may

exhibit renal toxicity and that taurine may cause adverse neurobehavioural effects. The Afssa opinion also stated that the effect of taurine on the thyroid gland should be studied in greater depth: the Afssa opinion of 5th March 2003 (SCF, 2003) also observed that the consumer surveys presented show that large amounts of this type of drink may be consumed and pointed out that the nutritional benefit of the drink had not been demonstrated in the target populations. The Danish and Norwegian food safety expert bodies reached similar conclusions.

A new analysis submitted by the company which mentions methodological bias in the toxicological studies it had produced previously resulted in an Afssa opinion of 30 January 2006 (Afssa, 2006) which stated that:

“As a further review of the dossier casts doubt on the toxicological studies submitted previously because of methodological bias not described until now, doubt exists as to the methodological choices made and on the overall scientific process.

Afssa therefore considers that :

- In nutritional terms, the product formulation does not meet the needs of people undertaking intense activity.
- The wording on the labelling not to exceed two cans per day does not prevent the safety limits being exceeded for vitamins B3 and B6.
- The comments in the dossier do not answer the questions raised about the safety of the product at the recommended concentrations.

As a result Afssa considers that none of the information provided leads it to change the conclusions of its previous opinions.

The working group of the Additives Panel of the European Food Safety Authority (AESA) also pointed out on 17 February 2005 (AESA, 2005) that the bias described by the claimant was insufficient in itself to clear the questions raised by the hyperactivity, neuromotor and renal effects seen.

The new Afssa mandate

In keeping with the principle of free trade of products legally manufactured and/or marketed in other member states, marketing of these products can not be impeded unless there is an established risk to health. Afssa was asked again to examine, the following questions in particular:

- What are the dangers that a consumer faces when absorbing the substances in question?
- Is it possible to describe these dangers particularly from examining information obtained from relevant dose-response models?
- Where applicable, in view of the recommendations for use proposed by the company and of the consumer studies conducted in other states, what is the likelihood of the adverse effects identified occurring if the drink is consumed?

Experimental toxicological assessments :

In the absence of any further scientific information provided by the company it is not possible to further characterise the potential dangers described in the previous opinions referred to above. The choice of doses used in the toxicological studies which is not justified by the company does not allow the determination of a no observed adverse effect level and upper safe levels for intake of taurine and D-glucuronolactone. It is therefore impossible based on the available information to establish a dose effect relationship which could characterise the risk to human beings under the recommended consumption conditions nor establish any likelihood of adverse effects occurring.

D-Glucuronolactone

The histological renal changes observed in the 1980 study in the rat were reported in the previous Afssa opinions.

Whilst this effect does not confirm a clear nephrotoxic effect, the information produced does not unequivocally exclude this possibility. The initial hypothesis advanced by the company of a local irritant effect due to calculi or mineral deposits secondary to an increase in the urinary

concentration of D-glucuronolactone and/or its metabolites is not clearly established from the evidence provided. The possibility of infection was not investigated in the study. The company's argument that the strain of rat was inappropriate for the study does not remove the question raised by the experimental findings, without additional investigation.

Taurine

The behavioural abnormalities observed, hyperactivity and the locomotor effect described in the previous opinions are warning signals for neurotoxicity which should be considered were these to occur. The study methodological bias described by the applicant does not allow to discount the effects which were observed (particularly self-mutilation).

Adverse effects found in human beings

It should be noted that the drink combines several agents liable to cause neuropsychological problems : caffeine, taurine (which has been linked to psychotic crisis by Fekkes *et al.* (1994)), and inositol (Atack, 1996).

Despite its marketing being prohibited in France, information has been recorded by the French anti poisons and toxicovigilance centres (CAPTV) on documented notifications which show a link with consuming the drink in 9 people. The subjects' symptoms were agitation, tachycardia and gastro-intestinal disorders. These findings should be considered in light of the experimental data reported above. These reports only provide information about the acute effects of the product as any long term risks can be only be assessed from experimental data.

One case report concerned mania being induced after consuming the drink (Machado-Vieira *et al.*, 2001).

Nutritional intake :

✓ *Vitamins B₂, B₃, B₅, B₆ and B₁₂*

There is no nutritional benefit in proposing high doses of these vitamins to people undergoing intense physical or mental activity (ANC 2001).

✓ *Caffeine intake*

The adverse effects of high caffeine intake were described in the previous opinions, in particular the publication of Ogawa and Ueki (2003) which showed worsening of seasonal manic depressive syndromes following high caffeine consumption.

The CSAH recommendation of 21 January 1999 together with recent analysis (Bech *et al.*, 2005 ; Cnattingius *et al.*, 2000; Matijasevich *et al.*, 2006; Sata *et al.*, 2005) leading to a recommendation that pregnant women should reduce their caffeine consumption to less than 300 mg per day, emphasises the need to take account of the large inter-individual variability in caffeine metabolism (Grosso et Bracken, 2005 ; Sata *et al.*, 2005). In addition, this high caffeine drink may be consumed in conjunction with usual dietary caffeine consumption, which is estimated to be in the region of 200 mg per day in the United States and in the European Community (Frary *et al.*, 2005).

Cardiovascular effects:

On exercise, an increase in systolic ejection volume (SEV) was seen after consuming the product during the post-exercise recovery period (Baum et Weiss, 2001).

This increase in cardiac output is due to an increase in SEV simply by stimulation and is independent of the training-induced adaptive response. This is worrying in the exercise situation. In the absence of further information this effect could amplify the well described situation in some people in whom caffeine ingestion can lead to excessive arterial blood pressure at peak exercise (Sung *et al.*, 1990).

Interaction of the product with alcohol:

Combination of the caffeine-aurine D-glucuronolactone mixture with alcohol is considered by CSAH in its 2003² evaluation. Concomitant alcohol consumption is common in countries in which the product is already marketed (Ferreira *et al.*, 2004a).

Potentiating effects on the excitatory actions of alcohol and inhibition of its depressive actions has been described (Ferreira *et al.*, 2004a). By potentiating the excitatory effects of alcohol and reducing its depressive effects the product reduces perception but not the reality of alcohol intoxication: reduced perception of alcohol intoxication may encourage both further alcohol consumption and inappropriate risk-taking. Some national authorities (Canada, Ireland and Sweden) have distributed a population warning, recommending that the product should not be consumed in association with alcohol and/or recommending that a warning be placed on the product stating that it must not be consumed in association with alcohol.

Conclusion of the committee

As a result the committee considers that there is no information provided which leads it to change the conclusions of the previous opinions.

Based on available data and the experimental studies performed it is not possible to characterise the risk from this product and particularly from the high doses of taurine and D-glucuronolactone compared to dietary intake.

In addition, as for any product the company must ensure its product is safe for the consumer. There is no question however that the data produced and evaluated by the committee do not provide a guarantee of safety under the recommended conditions of use. Further studies are required:

- To exclude or confirm the suspicions of nephrotoxic and neurotoxic risks.
- To answer the scientific uncertainties about the safety of use of the product in order to ensure the drink is safe for the consumer.

Afssa conclusion:

In view of this information Afssa:

1. **Considers that whilst the studies submitted by the company do not themselves provide an irrefutable demonstration of an established risk due to consumption of this drink, the assessment of these studies does not allow the product to be recommended for consumption.**
2. **Therefore supports the analysis of the committee that further studies need to be conducted, based on a reliable methodology and designed to exclude or confirm the suspected side effects due to high doses of taurine and D-glucuronolactone.**
3. **Also stresses that some actual situations of use of the drink (sport, concomitant consumption of alcohol) are, according to published data, associated with increased cardiovascular risk from exercise and with the risk of reduced perception of the effects of alcohol, which are nevertheless preserved.**

Key words : caffeine, amino acid, “energy drink“, behaviour, cardiovascular.

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