Opinion of the Scientific Committee on Food

on

Additional information on “energy” drinks

(expressed on 5 March 2003)
Opinion on Additional information on “energy” drinks

Terms of reference

The Committee is asked to review additional information submitted on energy drinks and indicate if the conclusions in its opinion of 21 January 1999 need to be modified.

Background

The SCF opinion of 1999

The Committee adopted an opinion on so-called “energy” drinks in 1999, which evaluated the safety of caffeine, taurine and D-glucurono-γ-lactone as constituents of “energy” drinks (SCF, 1999).

For caffeine, it was concluded that the contribution of “energy” drinks to overall caffeine intake was not a matter of concern for non-pregnant adults. For children who do not normally consume much tea or coffee, and who might substitute “energy” drinks for cola or other soft drinks, consumption of “energy” drinks might represent an increase in daily caffeine exposure compared with their previous intake. The Committee considered that this could result in transient behavioural changes, such as increased arousal, irritability, nervousness or anxiety. For pregnant adults, the Committee concluded that while intakes of caffeine up to 300mg/day appeared to be safe, the question of possible effects on pregnancy and the offspring at regular intakes above 300mg/day remained open. This suggested that moderation of caffeine intake, from whatever source, was advisable during pregnancy.

For taurine and glucuronolactone, the Committee was unable to conclude that the safety-in-use of these constituents in the concentration ranges reported for "energy" drinks had been adequately established. Further studies would be required to establish upper safe levels for daily intake of taurine and glucuronolactone.

The Committee noted that possible interactions of constituents of "energy" drinks have not been well studied and considered that possible interactions between caffeine, taurine and alcohol may warrant investigation in humans, particularly under conditions of exercise and consequent dehydration through sweating.

Submission of further data

Since the publication of its 1999 opinion, four further submissions of data have been received from one manufacturer of “energy” drinks (Red Bull GmbH, 2000, 2001, 2002a,b). These comprised:

- a 13-week oral toxicity study in the mouse on Red Bull® given in the drinking water
- a 13-week oral gavage study in rats on taurine;
- a 13-week oral gavage study in rats on glucuronolactone;
- a review of other toxicology studies on taurine and glucuronolactone;
- information on the use of taurine in human medicine;
- an evaluation of the possibility of interactions between taurine, caffeine and glucuronolactone;
- an evaluation of the possibility of interactions between taurine and alcohol and caffeine and alcohol;
- results from a survey of the consumption of “energy” drinks in Austria and derived new exposure estimates;
- remarks on the SCF opinion of 1999.

The Committee was also asked by the petitioner to take into account published reports and statements from the Australian New Zealand Food Authority (ANZFA, 2000) and the UK Food Standards Agency (FSA, 2001a).

Other relevant developments in the EU

The Committee also noted other developments in the EU since its last opinion in 1999:

- The Agence Française de Sécurité Sanitaire des Aliments, reviewed the 13-week mouse oral toxicity study on Red Bull®, concluding that authorisation of the use of various substances in “energy” drinks was not acceptable since harmlessness at the concentrations recommended by the petitioner had not been demonstrated (AFSSA, 2001).
- The UK Committee on Toxicity published a statement on the reproductive effects of caffeine in the context of intakes from all food sources, including “energy” drinks (COT, 2001). It drew similar conclusions to those in the 1999 SCF opinion, commenting that caffeine intakes above 300 mg/day show a plausible association with low birth weight and spontaneous abortion. Based on this, the UK Food Standards Agency issued advice for pregnant women that they should limit their intake of caffeine to less than the equivalent of four average cups of coffee a day; the estimated “energy” drink equivalent to this was 4 cans a day (FSA, 2001b).
- A review of the health effects of “energy” drinks (stimulant drinks), commissioned by the Minister of State at the Department of Health and Children in the Republic of Ireland, has been published (Stimulant Drinks Committee, 2002). It made a number of recommendations covering labelling, concerns about marketing and promotion, further research needs, and advice to pregnant women, and cautioning against both consumption by children under 16 years of age and consumption in association with sport or exercise.
- A number of EU Member States have raised concerns about “energy” drinks in response to anecdotal cases of acute symptoms requiring medical attention in young people consuming “energy” drinks, in most cases in conjunction with alcohol and/or drugs used socially.
- A meeting of EU Member States in February 2002 to discuss perceived safety issues around “energy” drinks, concluded that the Commission should not take any action, but noted that new data had been submitted to the SCF and the position should be reconsidered once a new SCF opinion became available (FSA,
An amendment to the EC labelling directive (EC, 2000) was agreed, to come into effect by July 2004, requiring that beverages, other than those based on coffee or tea, containing more than 150 mg caffeine/l should be labelled “high caffeine content” and the exact amount present indicated on the label (EC, 2002).

**Intake data**

The Committee noted that in its earlier opinion it used a figure of 500 ml of “energy” drink as the “likely consumption on any one day by regular consumers” (SCF, 1999). Two new surveys of intake of “energy” drinks have become available, one from Austria (Red Bull GmbH, 2001) and one from Ireland (Stimulant Drinks Committee, 2002). Details of these surveys are given in Annex 1. For this evaluation, the Committee has chosen from the new data mean chronic, high chronic and acute consumption estimates for regular consumers, as shown in Table 1. The estimate for acute consumption of 750 ml/day would give intakes of 240 mg caffeine/day, 3000 mg taurine/day and 1800 mg/day glucuronolactone, assuming the “energy” drinks contained maximum levels of 320, 4000 and 2400 mg/l of caffeine, taurine and glucuronolactone respectively.

**Table 1: Intake estimates used by the Committee**

<table>
<thead>
<tr>
<th>Consumption</th>
<th>No. of 250ml cans/day</th>
<th>ml/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean chronic</td>
<td>0.5</td>
<td>125</td>
</tr>
<tr>
<td>High chronic</td>
<td>1.4</td>
<td>350</td>
</tr>
<tr>
<td>Acute</td>
<td>3.0</td>
<td>750</td>
</tr>
</tbody>
</table>

Note that for acute consumption the Committee used 3 cans/day as a reasonable high consumption, this amount being higher than the 90th percentile recorded in the Austrian survey (2.6 cans/day) and being the average reported in the Irish survey for the most number of cans consumed in a single session. The Committee was aware that amounts up to 8-12 cans/day were reported by a few extreme consumers in both surveys.

**Toxicological studies**

A 13-week mouse oral toxicity study on Red Bull® (RCC, 2000) and 13-week rat oral toxicity and toxicokinetic studies on taurine (WIL, 2001a) and on glucuronolactone (WIL, 2001b) have been submitted. The key findings in these new studies are summarised and discussed below, in the context of data reviewed previously by the Committee (SCF, 1999). Details of the studies are given in Annex 2.

**13-week mouse oral toxicity study on Red Bull®**

Mice were given Red Bull® (RB) either undiluted or as a mixture with tap water at concentrations of 0, 33, 50 or 100% in the drinking water *ad libitum* for 13 weeks from 6 weeks of age (RCC, 2000). There were significant reductions in body weight in all treated groups, most likely attributable to observed reductions in food intake. Considerable dose-related increases in water/fluid intake, ranging from 27% to 115% compared with controls, were seen in all treated groups. These were not unexpected,
given the proportions of tap water replaced by RB, a fluid of much higher osmolarity. Many of the statistically significant findings in haematology, clinical chemistry and urinalysis, which were seen mainly in the 100% RB groups, are almost certainly attributable to the increased fluid intakes and glucose loading from the sucrose in RB. Disturbances in fluid balance would not be expected to occur in humans consuming “energy” drinks as part of their normal diet. Due to the effects on body weight, an overall no-observed-adverse-effect level (NOAEL) cannot be determined from this study. Neither does this study provide any useful data for the safety assessment of the individual constituents, caffeine, taurine or glucuronolactone, since the mode of administration did not allow very high amounts of the individual constituents to be consumed by the mice (see Annex 2).

Studies on taurine

The new toxicokinetic data on taurine in rats (WIL, 2001a), showing ready bioavailability and peak plasma levels one hour after oral administration, are in accordance with findings from the limited published data on humans. Human studies showed significant increases in plasma taurine 90 minutes after consumption of a taurine-rich meal with levels declining to background within 180-270 minutes (Trautwein and Hayes, 1995). These results also corroborate those from an unpublished human study by Taisho Pharmaceuticals, using radiolabelled taurine, which showed peak serum levels at 1-2 hours after oral administration, declining by 7 hours (Watanabe, cited in Red Bull GmbH, 2001). Other human data suggest that taurine is absorbed orally via an active transport mechanism in the gut wall (Ahlman et al., 1993, 1995a,b).

The possible accumulation of taurine has also been investigated. The new rat toxicokinetic study only sampled on study days 0 and 90 but the results did not indicate any accumulation (WIL, 2001a). On the other hand, Trautwein and Hayes (1995) concluded, from a study in which 400 mg taurine was given daily for 7 days to humans, that there was accumulation of taurine in the plasma and a slight increase in whole blood taurine levels.

In the new 13-week oral toxicity study, rats were given taurine at doses of 0, 300, 600 and 1000 mg/kg bw/day, dissolved in deionised water, orally by gavage once daily for 13 weeks from 6 weeks of age (WIL, 2001a). There were no persistent effects on body weight or food consumption and no histopathological changes in organs or tissues in any dose group. However, there were dose-related behavioural changes in both sexes of all three dosed groups. These were persistent increased activity most noticeable 1 hour after dosing, occasional chewing of limbs, and a possible decrement in motor performance on a rotarod. These findings, together with the toxicokinetic data, showing peak plasma levels at 1 hour, and the lack of increased locomotor activity when measured some hours after dosing, suggest that taurine may have exhibited an acute, central pharmacological effect in this study. Taurine is known to be present at high concentrations in the brain where it acts as a neuromodulator (see later). Previous sub-chronic studies on rats, reviewed earlier by the Committee (SCF, 1999), mostly involving administration of taurine in the drinking water or by intraperitoneal injection have, if anything, reported unchanged or reduced activity, though one study did report enhanced exploratory activity. The results of the new sub-chronic study show that 1000 mg/kg bw/day is a clear
effect level for behavioural changes while the lower doses of 300 and 600 mg/kg bw/day are marginal effect levels in males but clear effect levels in females. Thus, a NOAEL for behavioural effects in rats has not been established.

Of the other studies on taurine mentioned by the petitioner (Red Bull® GmbH, 2001), all have been reviewed previously by the Committee (SCF, 1999), with the exception of a developmental toxicity study by Yamada et al. (1981), which showed no adverse effects, either prenatally or postnatally, from gavage administration of taurine at 300, 1000 or 3000 mg/kg bw/day to rats on days 7-17 of gestation.

The submission (Red Bull GmbH, 2001) also included an extensive review of the clinical use of taurine in humans in conditions including diabetes, epilepsy, congestive heart failure, hypertension, liver disease and cystic fibrosis, concluding that “No adverse health effects attributable to taurine have been reported in more than 30 clinical investigations reported over a period of 30 years. In many cases taurine has proved medically beneficial.” The Committee was aware of these studies at the time of its earlier opinion (SCF, 1999).

Studies on glucuronolactone

The new toxicokinetic data on glucuronolactone in rats, showing bioavailability and lack of accumulation, with peak plasma levels 1-2 hours after oral administration (WIL, 2001b), are in accordance with findings from the limited published data on humans.

In the new 13-week toxicity study, rats were given glucuronolactone at doses of 0, 300, 600 and 1000 mg/kg bw/day, dissolved in deionised water, orally by gavage once daily for 13 weeks from 6 weeks of age (WIL, 2001b). There were no significant, treatment-related effects, apart from vacuolation and inflammatory changes localised to the papilla of the kidney in females at 600 and 1000 mg/kg/day, with a NOAEL of 300 mg/kg bw/day. The petitioner has commented that the occurrence of the lesions only in females may be related to the higher acidity and osmolality of urine in the female rat and went on to comment that the osmolality of human urine is considerably less than that of the Sprague-Dawley rat. However, in the Committee’s view, the mechanistic cause of the kidney lesions remains unclear.

The submission (Red Bull GmbH, 2001) reviewed some additional studies on glucuronolactone, including a study on growing hamsters (Di Filippo and Blumenthal, 1972) that had not previously been seen by the Committee. The previous SCF opinion specifically commented that there were no studies in mammalian species that included administration of high doses of glucuronolactone to growing animals, and that knowledge of the influence, if any, of high doses of glucuronolactone on blood glucose homeostasis and metabolic pathways involving glucose would be relevant for risk assessment in relation to children and diabetics (SCF, 1999). The purpose of the 28-day hamster study was to investigate whether glucuronolactone could prevent experimental cholelithiasis when given in the drinking water at doses up to 5.25%, equivalent to an intake of approximately 500 mg/kg bw/day. There were no clinical signs of toxicity and body weights in treated groups were comparable to controls.
Potential for interactions between constituents of “energy” drinks

The petitioner submitted an evaluation by an outside expert, based on the existing literature, which discussed the possibility of interactions between caffeine, taurine and glucuronolactone (Red Bull GmbH, 2002a). The evaluation considered the fate of the compounds in the body (toxicokinetics) and their known effects (toxicodynamics).

There are extensive data on the toxicokinetics of caffeine and taurine but less information on glucuronolactone. Consideration of the chemical nature of the three parent compounds and their metabolites, and the fact that differing processes are involved in their absorption, distribution, metabolism and excretion did not, in the expert’s view, raise any a priori reasons to expect any toxicokinetic interactions, even at high intakes of any one constituent. This was supported by known physiology and citation of existing studies.

The physiological handling and lack of toxicological effects of glucuronolactone (other than on the female rat kidney - see above) did not, in the expert’s view, raise any a priori reasons to expect toxicodynamic interactions from this constituent. Caffeine and taurine, on the other hand, each affect the functioning of the central nervous system, kidneys and heart, thus there is a need to consider the potential for toxicodynamic interactions between these two constituents. Data relevant to these possible interactions are discussed below.

Some of the data on caffeine derives from in vitro studies using high concentrations that would not be achieved in vivo following ingestion. For example, caffeine mobilises calcium, decreasing intracellular calcium concentrations (Otun et al., 1991), but only at in vitro concentrations that are around 200-fold higher than the plasma/tissue concentrations that would be achieved after consuming 160 mg of caffeine as a single dose, say, from 0.5 l of “energy” drink (Red Bull GmbH, 2002a). Nevertheless it should be noted that calcium disturbances (reduced blood levels) were seen in the mouse study on Red Bull®.

Central nervous system

Caffeine is a central nervous system stimulant whereas taurine generally act as an inhibitory neuromodulator. Caffeine exerts stimulatory effects by blocking the inhibitory action of adenosine at its binding sites, with subsequent increases in the levels in some brain regions of several neurotransmitters, including adrenaline, noradrenaline, tryptophan and dopamine (Schlosberg, 1984; Hadfield and Milio, 1989; Kirch et al., 1990; Hughes 1996; Dager et al., 1999; Schuckit, 2000). It also modulates the effects of GABA and serotonin (Kaplan et al., 1992; Nehlig, 1999). Taurine, on the other hand, depresses the activity of excitable membranes in the brain (Iida and Hikichi, 1976; Huxtable, 1992). Centrally, taurine acts as an agonist of the more sedating glycine receptors and inhibits the more excitatory actions of NMDA receptors and glycine neurotransmitter function (De Saint et al., 2001; Font et al., 2001). It therefore could modulate the excitatory actions of some other amino acids (Saransaari and Oja, 1999, 2000).
While these data may appear to indicate that if there were any interaction, taurine might reduce caffeine-mediated excitation, the Committee noted that caffeine and taurine act on different receptors and moreover, in the rat study on taurine (see earlier), there was a stimulatory action on locomotor activity 1 hour after administration in all treated groups.

Kidney

Both caffeine and taurine can have short-term diuretic actions, causing loss of body water and sodium. Taurine acts via inhibition of central release of the anti-diuretic hormone, vasopressin (Hussy, 2001). Caffeine does not inhibit vasopressin release but has a direct action on kidney tubule functions, such as ionic reabsorption and renal perfusion, probably via adenosine receptor blockade (Daly, 1993). A high dose of taurine in the drinking water, equivalent to about 1500 mg/kg bw, was required to elicit diuresis and natriuresis in rats (Mozaffari and Schaffer, 2001), whereas 1g or more intravenously over 15 minutes (about 15 mg/kg bw) was sufficient in sensitive humans with liver cirrhosis and ascites (Gentile et al., 1994).

Bearing in mind that taurine is rapidly absorbed across the gut via an active transport mechanism, the diuretic effects in normal subjects with an acute consumption of 750 ml of “energy” drink containing 3g of taurine are difficult to predict. The Committee noted that since caffeine and taurine act via different mechanisms, any diuretic effects could be additive.

Cardiovascular system

Caffeine can increase heart rate, force of contraction of heart muscle and blood pressure. Taurine, on the other hand, depresses the activity of excitable membranes in the heart (Huxtable, 1992). Caffeine enhances catecholamine synthesis and release from adrenal cells in vitro, probably related to its effects on intracellular calcium (Matsumura et al., 2000; McKenzie and Marley, 2002). Numerous in vivo studies have shown oral caffeine at doses of 6 mg/kg bw or more increases plasma catecholamine concentrations, especially adrenaline, in a dose-related manner during exercise (Bangsbo et al., 1992; Van Soeren et al., 1993; Anderson and Hickey, 1994; Graham and Spriet, 1995; Jackman et al., 1996; Kamimori et al., 2000), though one study giving 8.8 mg/kg in an “energy” drink found no increase (Wemple et al., 1997). The acute consumption estimate for “energy” drinks of 750 ml is equivalent to a caffeine intake of 4 mg/kg bw for a 60 kg adult. There is no evidence that taurine increases catecholamine release; if anything it has an inhibitory effect on excessive sympathetic activity in rat models of hypertension, with reduction of plasma catecholamines (Yamamoto et al., 1985; Sato et al., 1987; Trachtman et al., 1989). Neither does taurine given alone have any effect on heart rate or blood pressure in rats or humans (Mozaffari and Schaffer, 2001; Gentile et al., 1994).

Both taurine and caffeine influence the activity of angiotensin II, an endogenously formed substance that raises arterial blood pressure and reduces the excretion of sodium and water by the kidney, but their action on angiotensin II is in opposite directions. In vivo caffeine augments the action of angiotensin II on the kidney and may raise plasma renin levels (Ohnishi et al., 1987; Holycross and Jackson, 1992; Brown et al., 1993;
Tseng et al., 1993), whereas taurine attenuates the effects of circulating angiotensin II (Schaffer et al., 2000).

In view of the above data, the Committee considered that if there are any cardiovascular interactions between caffeine and taurine, taurine might reduce the cardiovascular effects of caffeine.

**Potential for interactions between constituents of “energy” drinks and alcohol**

In its earlier opinion (SCF, 1999), the Committee commented on the lack of research on the effects of “energy” drinks in combination with alcohol and/or fluid loss during exercise. The petitioner commented that there would be serious ethical problems in conducting research to study directly the combined effects of high blood alcohol concentrations with exercise, dehydration and consumption of “energy” drinks in humans. The petitioner therefore submitted an evaluation by an outside expert (Red Bull GmbH, 2002b), based on the existing literature, which discussed the possibility of interactions between alcohol and taurine or caffeine, including consideration of whether sweating and dehydration might predispose to additional effects.

The expert (Red Bull GmbH, 2002b) considered the acknowledged health risks in situations of fluid and electrolyte loss through excessive sweating, pointing out that when more than 7% of body water is lost or hyponatraemia (blood sodium below 135 mEq/l) occurs, symptoms such as lung congestion, confusion, disorientation, muscle weakness, loss of coordination, headache, nausea and vomiting can occur, and that in extreme situations these can progress to cardio-respiratory arrest and death.

**Taurine and alcohol**

Studies on the effect of co-administration of alcohol and taurine on behaviour have used different routes of administration of alcohol, varying doses, and differ in the order in which taurine and alcohol were administered (Ferko, 1987). The results were inconsistent and showed little or no clinical interaction (Aragon et al., 1992; Boggan et al., 1978; Ferko and Boyock, 1987). Taurine has antagonistic activity to alcohol in several situations, including ethanol-induced sleep time (McBroom et al., 1986; Ferko, 1987), effects of acute ethanol on memory (Vohra and Hui, 2000), and alcohol-induced liver and gastric mucosal damage (Timbrell et al., 1995; Xieyonglixiao et al., 1998). These effects are possibly mediated through taurine’s facilitation of the activity of the liver enzyme, aldehyde dehydrogenase, which metabolises alcohol, thereby reducing blood levels of alcohol (Messiha, 1979; Theofanopoulos et al., 1998a,b). In contrast, intraventricular co-administration of alcohol and taurine may increase the sedating effects of alcohol in mice and rats (Ferko, 1987; Mattucci-Schiavone and Ferko, 1985; Yarbrough et al., 1981), a situation in which taurine’s influence on aldehyde dehydrogenase in the liver would not be evident. Alcohol intoxication or hypo-osmotic stress cause release of endogenous taurine in several areas of the brain (Lallemand et al., 1998,200: Quertemont et al., 2000; Ward et al., 2000; Guizouarn et al., 2000), but the significance, if any, of this observation for exogenous taurine is unclear. These co-administration studies indicate that some alcohol-taurine interactions are possible, including protective ones, but the effects are neither marked nor consistent.
Both taurine (Gentile et al., 1994) and alcohol centrally inhibit the release of the antiuretic hormone, vasopressin, and the Committee considered that they could act additively to increase water and sodium loss from the body in the short-term.

Caffeine and alcohol

The widely held belief that caffeine can antagonise the depressant effects of alcohol and drugs is generally supported by the extensive literature on this subject. Both animal and human studies indicate a modest, antagonistic effect of caffeine on the effects of alcohol, but the effects are usually only seen with simpler tasks and at lower blood alcohol concentrations (Moskowitz and Burns, 1971; Osborne and Rogers, 1983; Kerr et al., 1991; Liguori et al., 1997; Kerr and Hindmarch, 1998; Liguori and Robinson, 2001; Warburton et al., 2001). In humans, for example, the antagonistic activity of caffeine has been shown in driving-related tasks of tracking, divided attention and some aspects of reaction time after 2-5 standard alcoholic drinks. Most of the studies show the effects of caffeine are dose-dependent and that caffeine does not affect blood alcohol concentrations. Other studies have shown little if any ability of caffeine to antagonise the psychomotor effects of alcohol (Newman and Newman, 1956; Forney and Hughes, 1965; Mushill, 1979; Nuotto et al., 1982) and some have even raised the possibility that caffeine might enhance the effects of alcohol, especially during the early phase of drinking where some stimulatory properties of alcohol predominate (Hughes and Forney, 1961; Lowe, 1981; Osborne and Rogers, 1983; Dews, 1984). The majority of studies suggest that caffeine would not exacerbate the adverse effects of alcohol and at lower blood alcohol levels caffeine may improve performance.

Human case reports

The Committee was aware of a number of anecdotal reports of acute, adverse effects in young persons consuming “energy” drinks, usually together with alcohol and/or drugs used socially, such as ecstasy and amphetamines. The effects mentioned included, tremors, seizures, drowsiness, muscle weakness, dizziness, nervousness, tachycardia, palpitations, nausea, vomiting, headache, bronchospasm and hyperventilation. One case of myocardial infarction in a 23-year-old playing football (Rallis, 2001) and one case of sudden unexplained adult death syndrome, possibly resulting from cardiac dysrhythmia, in an 18-year old playing basketball (Stimulant Drinks Committee, 2002) have also been reported. The Committee had very little information about any of these cases and was not aware that any had been written up in the medical literature. The co-consumption of alcohol and/or drugs noted in most of these cases makes interpretation particularly difficult. Thus, there is no confirmation of any causal relationship between the reported effects and the consumption of “energy” drinks. Under these circumstances, the reports can only be noted.
Conclusions

Taurine

In its previous opinion on “energy” drinks, the SCF commented as follows on taurine (SCF, 1999):

“Toxicological studies did not reveal any indication for a genotoxic, carcinogenic or teratogenic potential of taurine. However, there is no adequate study on chronic toxicity/carcinogenicity. Investigation of subacute/subchronic toxicity has also been fragmentary. Overall, the available data are insufficient to establish an upper safe level for daily intake of taurine.”

The new 13-week study in rats provided further useful information in that it showed no significant changes in pathological measures, but it did show the occurrence of significant behavioural effects (increased activity and self-chewing), and possibly impaired motor performance, which could be mediated via a pharmacological action on the central nervous system. In view of this the Committee is of the opinion that focused neurological studies are now needed.

The Committee concluded that these effects should be taken into account in human risk assessment, noting that behavioural effects were observed at the lowest dose tested of 300 mg/kg bw/day. This effect level is 36-fold above the estimated human intake of taurine (8.3 mg/kg bw for a 60 kg adult) at the mean chronic daily intake for “energy” drinks, and 6-fold above the more relevant estimate for acute intake (50 mg/kg bw for a 60 kg adult). The absence of a NOAEL for these effects precludes the setting of an upper safe level for daily intake of taurine. The Committee’s reservations are expressed in the context of an estimated acute intake of taurine of up to 3000 mg/day from consumption of “energy” drinks, compared with the highest estimated intake of taurine from naturally occurring sources in the diet of 400 mg/day.

Glucuronolactone

In its previous opinion on “energy” drinks, the SCF commented as follows on glucuronolactone (SCF, 1999):

“Human metabolic considerations indicate the body is likely to handle small quantities of glucuronolactone without any problems. However, the intake of glucuronolactone from consumption of some "energy" drinks is possibly as much as two orders of magnitude greater than that from the rest of the diet. There is very little information available for risk assessment of glucuronolactone at such intakes. While there is no indication from the available data that there is any risk to health from consumption of high amounts of glucuronolactone, there is a lack of scientific evidence to support the safety of glucuronolactone present in beverages at concentrations that may result in intakes as much as two orders of magnitude greater than that obtained from the rest of the diet. As was the case with taurine, there is insufficient information on which to set an upper safe level for daily intake of glucuronolactone.”
The new 13-week study provided useful information indicating that in rats, there were no adverse effects except on the kidney. The NOAEL for these effects was 300 mg/kg bw, which is around 20-fold above the estimate of high chronic intake of glucuronolactone of 14 mg/kg bw/day for a 60 kg adult. The hamster study and the new 13-week rat study both provided information showing no effects on body weight gain in growing animals. However, the 1999 opinion also pointed out that rodents may not be an appropriate model for man since they can metabolise exogenous glucuronolactone to vitamin C whereas primates, including man, do not possess this metabolic pathway.

The Committee therefore reiterates its earlier conclusion (SCF, 1999) that there is a lack of scientific evidence to support the safety of glucuronolactone present in beverages at concentrations that may result in intakes several-fold higher than that usually obtained from the rest of the diet. Due to the lack of relevant data it is not possible to set an upper safe level for daily intake of glucuronolactone. The Committee’s reservations are expressed in the context of an estimated high chronic intake of glucuronolactone of 840 mg/day and an acute intake of up to 1800 mg/day from consumption of “energy” drinks, compared with the estimated intake of glucuronolactone from naturally occurring sources in the diet of 1-2 mg/day.

Caffeine

The Committee’s earlier opinion on caffeine (SCF, 1999) remains unchanged (see “Background”).

Interactions between constituents of energy drinks, alcohol and exercise

The Committee considers it unlikely that glucuronolactone would have any interaction with caffeine, taurine, alcohol or the effects of exercise.

The Committee concluded that consideration of the potential for interactions between caffeine and taurine has not ruled out the possibility of stimulatory effects from both substances at the level of the central nervous system. At the cardiovascular level, if there are any interactions between caffeine and taurine, taurine might reduce the cardiovascular effects of caffeine. The main area for likely additive interactions is in the diuretic actions of caffeine and taurine, which could be further enhanced by ingestion of alcohol. This, coupled with loss of body fluids via sweating on exercise, could, theoretically, result in short-term dehydration. While the Committee notes that some of the anecdotally reported symptoms in humans are compatible with loss of body water and sodium, it is also apparent that they may equally well be related to the intake of high amounts of alcohol and/or drugs reported in many of these cases. It is therefore not possible to draw definitive conclusions about effects in humans.
References


A new intake survey has been conducted in Austria (Red Bull GmbH, 2001), the EU country with the highest per capita “energy” drink consumption. Consumption has not significantly changed in recent years, indicating, according to the petitioner, that Austria can be regarded as a saturated market. The aim of the survey was to record chronic and acute consumption patterns among ‘regular users’ of “energy” drinks. ‘Regular users’ were defined as those who consumed at least one “energy” drink per week.

The survey was conducted in 2001 on 8500 Austrians aged 15 years and over. Forty-two percent of the sample consumed “energy” drinks at least occasionally and 12% were regular users. The 1007 regular users were further questioned in detail about their consumption habits. “Energy” drink consumers were more often male (55% of consumers, 59% of regular users) than female and were also largely in the age range 15-30 years (46% of consumers, 61% of regular users).

**Chronic consumption**

Regular users were asked to recall the number of cans of “energy” drink they had consumed the previous week (7 day recall - 7DR), the number of cans they usually drank in one week (food frequency questionnaire - FFQ), and the number of cans they had consumed in the previous 24 hours (24-hour recall - 24HR). From these, estimates of both mean and high consumption may be made. The statistical distribution of intake was very skewed with a large number of “small” consumers and a few “extreme” consumers. There was good consistency between the estimates obtained using the three different indicators (7DR, FFQ and 24HR) for the mean daily quantities consumed by regular users, as shown in Table 1.

**Table 1: Mean daily chronic consumption of “energy” drink by regular users**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>No. of 250 ml cans/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>7DR</td>
<td>0.45</td>
</tr>
<tr>
<td>FFQ</td>
<td>0.47</td>
</tr>
<tr>
<td>24HR</td>
<td>0.52*</td>
</tr>
</tbody>
</table>

* Including consumers and non-consumers on that day
Intakes by high consumers are shown in Table 2. Again there was good agreement between the two indicators. Note that the 24HR data cannot be used for this estimate.

**Table 2: High chronic consumption of “energy” drink by regular users***

<table>
<thead>
<tr>
<th>Indicator</th>
<th>No. of 250 ml cans 90th percentile</th>
<th>No. of 250 ml cans 95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>7DR</td>
<td>7/week = 1/day</td>
<td>10/week = 1.4/day</td>
</tr>
<tr>
<td>FFQ</td>
<td>6/week = 0.9/day</td>
<td>10/week = 1.4/day</td>
</tr>
</tbody>
</table>

* N = 1007 regular users

**Acute consumption**

Acute intakes are shown in Table 3. Regular users were asked both about the maximum amount of “energy” drinks they had ever consumed at one time and for their 24HR. The first question could lead to biased answers and so the 24HR figures are shown below as these are considered more likely to be accurate.

**Table 3: Acute consumption of “energy” drink by regular users**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>No. of 250 ml cans/day Mean</th>
<th>No. of 250 ml cans/day 90th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>24HR</td>
<td>1.7</td>
<td>2.6</td>
</tr>
</tbody>
</table>

**Irish survey**

The review commissioned in Ireland (Stimulant Drinks Committee, 2002) included information on consumption of “energy” drinks, as part of a market research survey conducted during July 2001, using face-to-face interviews with 625 people in the Republic of Ireland and 635 people in Northern Ireland, aged 11-35 years. In Northern Ireland and Republic of Ireland respectively, 51% and 37% of participants reported ‘ever’ consuming “energy” drinks and 10% and 11% reported consuming “energy” drinks frequently. Among ‘ever’ consumers, average consumption was 3 (250 ml) cans/week and for the 95th percentile consumers it was 8 cans/week. The most number of cans consumed in a single session among ‘ever’ consumers averaged approximately 3 cans, rising to 8 cans among the highest consumers; the comparable figure for 11-14 year-olds was approximately 2 cans. These results are similar to those obtained in the Austrian survey.
ANNEX 2

Details of toxicological studies submitted on Red Bull®, taurine and glucuronolactone

13-week mouse oral toxicity study on Red Bull®

Groups of 20 mice/sex/dose were given Red Bull® either undiluted or as a mixture with tap water at concentrations of 0, 33, 50 or 100% in the drinking water ad libitum for 13 weeks from 6 weeks of age. The study (RCC, 2000) was conducted in compliance with Good Laboratory Practice (GLP) regulations and conforming to 1981 OECD Guidelines (OECD, 1981).

Mean intakes of Red Bull® (RB) during the study period were equivalent to 89, 145 and 427 g/kg bw/day and 126, 188 and 520 g/kg bw/day in 33, 50 and 100% RB male and female groups respectively. Intakes of the individual constituents of interest were as shown in Table 5:

Table 1: Intakes of caffeine, taurine and glucuronolactone

<table>
<thead>
<tr>
<th>Percentage RB in drinking water</th>
<th>Caffeine mg/kg bw/day</th>
<th>Taurine mg/kg bw/day</th>
<th>Glucuronolactone mg/kg bw/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>33</td>
<td>27</td>
<td>39</td>
<td>342</td>
</tr>
<tr>
<td>50</td>
<td>44</td>
<td>58</td>
<td>554</td>
</tr>
<tr>
<td>100</td>
<td>131</td>
<td>159</td>
<td>1625</td>
</tr>
</tbody>
</table>

The significant findings were a reduction in mean body weight in all groups receiving RB compared with controls. Terminal body weights were significantly reduced by 11%, 12% and 15% in males and 8%, 6% and 12% in females in 33, 50 and 100% RB groups respectively. Food intake was transiently reduced at the start of the study in the 33 and 50% RB groups and during most of the study, by around 9%, in both sexes given 100% RB. Water/fluid consumption was significantly higher in all treated groups compared with controls throughout the study. Average differences from controls were +40%, +48% and +115% in males and +27%, +27% and +67% in females, in 33, 50 and 100% RB groups respectively.

There were statistically significant increases in blood glucose in females given 33 or 50 % RB and in both sexes at 100% RB. Other significant findings were decreases in mean corpuscular haemoglobin concentration, platelet count and reticulocyte count in males receiving 100% RB. Creatinine was reduced in 100% RB females. Alkaline phosphatase levels were raised in 100% RB males. Calcium was reduced in 50% RB males and 100% RB males and females. Sodium was reduced in 100% RB males and chloride increased in 100% RB females. Total protein and absolute albumin concentrations were reduced in...
100% RB males and females. The urine of 100% RB males had increased specific gravity and osmolality.

Both absolute and relative weights of the inguinal fat pad were reduced in all treated male groups, suggesting the reductions in body weight may have been attributable to a reduced proportion of body fat. There were no treatment-related macroscopical or microscopical findings, apart from a reduction in liver centrilobular fat vacuolation in 100% RB males.

13-week rat oral toxicity study on taurine

Groups of 20 rats/sex/dose were given taurine at doses of 0, 300, 600 and 1000 mg/kg bw/day, dissolved in deionised water, orally by gavage once daily for 13 weeks from 6 weeks of age (WIL, 2001a). The study was conducted in compliance with GLP regulations and to a protocol in accordance with US Food and Drug Administration Redbook II Guidelines (FDA, 1993).

In a concurrent toxicokinetic study on separate animals, 12 animals/sex/dose were given the same dosages as in the main toxicology study and blood samples taken from 3 animals/sex/dose, at time 0 (immediately prior to dosing), 1, 2, 4, 8 and 24 hours following dosing on days 0 and 90 of the study, for estimation of plasma taurine levels. Blood samples were collected from concurrent controls (6 animals/sex) on the same days at 0, 2 and 8 hours following dosing with vehicle.

There were no treatment-related deaths and only transient higher body weight gains in some treated groups. Food consumption was unaffected by treatment. There were some statistically significant differences in haematological and clinical chemistry parameters measured at 4, 8 and 13 weeks between treated and control groups, but the differences were small and none were seemingly treatment-related. There was a dose-related reduction in urinary pH in both sexes, which was probably attributable to the presence of acidic taurine in the urine.

Small but significant reductions in absolute and relative thyroid/parathyroid gland weights in males at 1000 mg/kg and in females at 300, 600 and 1000 mg/kg were attributable to control values that were relatively high compared with laboratory historical controls and concurrent controls in the glucuronolactone study (see later). Because of the differences in thyroid weights at necropsy, serum TSH and T₄ were measured. The only finding was a significant reduction in TSH levels in 600 mg/kg males at 4 weeks. There were no treatment-related gross or microscopic findings in any organs or tissues, including the thyroid.

Clinical observations were performed on all animals at the time of dosing and about 1 hour after dosing. Significant behavioural changes were observed 1 hour after dosing. Table 6 shows the results of the 1-hour observations over the 13 weeks of the study.
Table 2: Clinical observations (Total occurrences/No. of animals) 1 hour after dosing with taurine

<table>
<thead>
<tr>
<th>Dose (mg/kg bw/day)</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>300</td>
<td>600</td>
<td>1000</td>
<td>0</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>Number of animals</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Observations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased activity</td>
<td>1/1</td>
<td>5/4</td>
<td>4/4</td>
<td>11/8</td>
<td>3/2</td>
<td>36/10</td>
<td>29/10</td>
</tr>
<tr>
<td>Chewing of forelimb(s)</td>
<td>0/0</td>
<td>0/0</td>
<td>2/2</td>
<td>3/3</td>
<td>0/0</td>
<td>3/2</td>
<td>3/3</td>
</tr>
<tr>
<td>Chewing of hindlimb(s)</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1/1</td>
<td>0/0</td>
<td>1/1</td>
<td>2/2</td>
</tr>
<tr>
<td>Chewing of cage</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1/1</td>
<td>0/0</td>
<td>0/0</td>
<td>1/1</td>
</tr>
<tr>
<td>Hyper-reactive to touch</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1/1</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

Increased activity was recorded in all treated groups compared with controls, particularly in females. The increase in frequency and number of animals exhibiting this behaviour was similar in 300 and 600 mg/kg males and females and greatest in the 1000 mg/kg groups. The frequency was similar in the first and last months of the study showing that tolerance did not develop over time. Chewing on forelimbs and hindlimbs was also seen in a few animals among 600 and 1000 mg/kg males and in all groups of treated females. The frequency was highest among 1000 mg/kg females.

These findings were followed up in a functional observation battery conducted at 6 and 12 weeks on control and 1000 mg/kg groups. There were occasional observations in the treated group, mostly in females, of greater alertness in the home cage, cage biting, higher arousal in the open field, more energetic reactions to approach, touch and startle response stimuli and jumping, biting or attacking in response to tail pinch. However, all but one of these behaviours was seen in only single animals and none of the differences were statistically significant. Impaired performance on the rotarod was seen in both sexes of the 1000 mg/kg group; the mean length of time they remained on the rotarod compared with controls was reduced by 49% and 52% in males and females respectively at 6 weeks and by 24% and 18% in males and females respectively at 12 weeks. Due to high variability within groups, none of these reductions were statistically significant. In a 60 minute test for locomotor activity run on individual animals at 6 and 12 weeks, a significant reduction in mean ambulatory activity and a non-significant reduction in mean total activity were seen in 1000 mg/kg males at 6 weeks. There were no effects in males at 12 weeks or in females at 6 or 12 weeks.

In the toxicokinetic study, plasma taurine levels increased in a dose-related manner, reaching peak $C_{\text{max}}$ values at around 1 hour after dosing and generally returning to baseline values by 24 hours. Plasma taurine levels 2 hours after dosing were 21-51% of the values measured at one hour. Initial half-life was less than 1 hour and terminal half-life ranged from 8.7 to 40 hours. Plasma concentrations 24 hours after dosing were comparable with control values both on study day 0 and on day 90. Area under the plasma-time concentration curve (AUC) values were similar on study days 0 and 90. Both $C_{\text{max}}$ and AUC were proportional to dose. This study showed that taurine is readily bioavailable following oral administration and that it does not accumulate.
13-week rat oral toxicity study on glucuronolactone

Groups of 20 rats/sex/dose were given D-glucuronolactone at doses were 0, 300, 600 and 1000 mg/kg bw/day, dissolved in deionised water, orally by gavage once daily for 13 weeks from 6 weeks of age (WIL, 2001b). The study was conducted in an almost identical manner to the study on taurine described above, in compliance with GLP regulations and to a protocol in accordance with FDA Redbook II Guidelines (FDA, 1993). In this study no functional observation battery was performed. A concurrent toxicokinetic study on separate animals was conducted to the same protocol as described earlier for the taurine study.

There were no deaths and only transiently higher body weight gains in some treated groups. There were no significant effects on food consumption, apart from higher food consumption in 300, 600 and 1000 mg/kg females in week 10-11.

There were some statistically significant differences in haematological and clinical chemistry parameters measured at 4, 8 and 13 weeks between treated and control groups, but the differences were small and none were seemingly treatment-related. In urinalysis, the only significant differences were in males: an increase in total volume at 600 mg/kg, a lower specific gravity at 600 and 1000 mg/kg and a lower pH at 1000 mg/kg at 13 weeks.

There were no significant effects on organ weights, but histopathological changes were found in the kidneys of females in the 600 and 1000 mg/kg groups. These changes included cytoplasmic vacuolation, and inflammatory changes. Cytoplasmic vacuolation was present in 50% of all groups including controls but the incidence of mild as opposed to minimal change was dose-related (1/20, 1/20, 5/20, 8/20 in control, 300, 600 and 1000 mg/kg groups). No inflammatory changes were seen in the controls or 300 mg/kg group, but they were seen in 2/20 females in the 600 mg/kg group and in 3/20 females in the 1000 mg/kg group. Although inflammatory changes are typically seen in the presence of mineralisation, calculi or crystaluria, none of these types of change were observed, neither was there any evidence of urinary bladder irritation. No treatment related effects were seen in the kidneys of males.

In the toxicokinetic study, plasma glucuronolactone levels increased in a dose-related manner, reaching peak C\textsubscript{max} values at around 1-4 hours on study day 0 and at 1 hour on study day 90. The half-life ranged from 0.89 to 3.9 hours. AUC values were similar on study days 0 and 90. Both C\textsubscript{max} and AUC were proportional to dose. These results show that glucuronolactone is bioavailable following oral administration and that it does not accumulate.