European Food Safety Authority

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SCIENTIFIC OPINION

The use of taurine and D-glucurono-γ-lactone as constituents of the so-called "energy" drinks [1]

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food

(Question No EFSA-Q-2007-113)

Adopted on 15 January 2009

PANEL MEMBERS

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SUMMARY

Following a request from the Commission, the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) has been asked to evaluate the safety-in-use of taurine and D-glucurono-γ-lactone as constituents of the so-called "energy" drinks.

In the present opinion the Panel evaluates the safety of taurine and D-glucurono-γ-lactone as individual ingredients of so-called "energy" drinks based on the new studies provided by the petitioner.

The Panel does not evaluate the safety of "energy" drinks as such.

Taurine and D-glucurono-γ-lactone are constituents of the so-called "energy" drinks, but they also occur at much lower levels as natural ingredients in food, and they are also normal human metabolites. Previous Scientific Committee on Food (SCF) Opinions have summarized safety studies of taurine and D-glucurono-γ-lactone, but the safety-in-use of these

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two ingredients at the levels of exposure expected from their use in "energy" drinks could not be established at that time.

In the absence of new chronic and acute exposure data, the exposures used in this opinion are based on the data reported by the SCF in 2003, i.e. a daily mean chronic consumption of 0.5 cans per person and a high chronic exposure at the 95th percentile of 1.4 cans per regular consumer. The Panel notes that actual exposure data on "energy" drink consumption, especially for adolescents and young adults, may need to be collected. Based on the assumption that a can contains 250 mL and 4000 mg/L taurine and 2400 mg/L D-glucurono-γ-lactone, the SCF calculated that these values result in a mean daily exposure to 500 mg taurine (8.3 mg taurine/kg bw/day for a 60 kg person) and 300 mg D-glucurono-γ-lactone (5.0 mg D-glucurono-γ-lactone/kg bw/day for a 60 kg person). The 95th percentile exposure of regular users would amount to 1400 mg taurine/day (23.3 mg/kg bw/day for a 60 kg person) and 840 mg D-glucurono-γ-lactone /day (14 mg/kg bw/day for a 60 kg person).

If it is assumed that this amount of chronic consumption is relevant to occasional exposure of children of 25 kg body weight, then their exposure (on a body weight basis) would be about 2.5 times higher than that for adults (60-65 kg body weight). It must be emphasized that these estimates relate to chronic exposures by average and high consuming adults, and would not reflect the occasional and sporadic exposure that might occur in children. If the frequency of exposure for children would be 2.5 times lower than for adults, then the average chronic exposure for children, on a body weight basis, would be the same as for adults. If children were to consume the adult intake of 0.5 and 1.4 cans per person only once per week, then the average chronic exposure to "energy" drinks and their constituents for children, on a body weight basis, would be one third of that for adults.

These estimates for the daily exposure to taurine and D-glucurono-γ-lactone from "energy" drinks are higher than the estimated mean daily exposure to taurine from omnivore diets which was estimated to be at most 400 mg/day, and that of D-glucurono-γ-lactone from naturally occurring sources in the diet estimated to amount to 1-2 mg/day.

The SCF Opinion of 2003 used 3 cans/day as a reasonable high (acute) 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 highest number of cans consumed in a single session. The SCF also indicated that it was aware that amounts of up to 8-12 cans/day were reported by a few extreme consumers in both surveys, which would result in an intake of 4800-7200 mg D-glucurono-γ-lactone and 8000-12000 mg taurine per day, equivalent to 80-120 mg D-glucurono-γ-lactone/kg bw/day and 133-200 mg taurine/kg bw/day for a 60 kg person.

The SCF Opinion of 2003 and the recent BfR Opinion mention a number of anecdotal and case reports of acute, adverse effects, including fatalities, in individuals consuming "energy" drinks, containing caffeine, taurine and D-glucurono-γ-lactone. In these cases "energy" drinks had either been consumed in very high amounts (1420 mL), in combination with physical exercise, or more frequently together with alcohol. The Panel considers that it is possible that the effects reported in recent publications by Iyadurai and Chung, Nagajothi *et al.* and Terlizzi *et al.* could be due to the well known side effects of high caffeine intake, while the assumption of a causal relationship with taurine intake is lacking scientific evidence.

Taurine

Upon oral exposure taurine is readily bioavailable in the systemic circulation. The Panel concludes that new ADME data support the contention that oral exposure to taurine was not

increasing taurine levels in the brain, because in rat studies, brain taurine levels did not increase after dosage.

The SCF already concluded in 1999 that toxicological studies did not reveal any indication for a genotoxic, teratogenic or carcinogenic potential of taurine.

It can be concluded that the NOAEL derived from a new 13-week oral neurotoxicity study in male and female rats including functional observational battery and locomotor activity tests, confirmed the NOAEL established in the prior 13-week study, described already by the SCF in 2003, of 1000 mg taurine/kg bw/day, and provided evidence for a NOAEL of 1500 mg taurine/kg bw/day for behavioural effects. The results of this study were sufficient to address the concerns raised previously, notably the observation of increased activity and possible decrements in motor skills on the rotarod.

The NOAEL of at least 1000 mg/kg bw/day for pathological changes is respectively 120-fold higher than the estimated mean and 43-fold higher than the estimated 95th percentile exposure to taurine from "energy" drinks only, when calculated for a 60 kg person. Given that taurine is a natural body constituent, the Panel concludes that these margins of safety are sufficiently large to conclude that exposure to taurine at the levels mentioned above is not of safety concern.

D-glucurono-γ-lactone

The SCF already concluded that the available data indicate that D-glucurono-γ-lactone administered orally to humans is rapidly absorbed, metabolised and excreted as glucaric acid, xylitol and L-xylulose. Animals, such as rodents, which can synthesise vitamin C endogenously do so from glucuronic acid and such animals can also convert exogenously administered D-glucurono-γ-lactone into vitamin C. However, primates, including man, and guinea pigs do not possess this metabolic pathway. The SCF concluded that for this reason, the rodent may be an inappropriate model for man in the study of the effects of D-glucurono-γ-lactone. The Panel concludes that data in the literature indicate that synthesis of vitamin C is only a minor pathway of D-glucurono-γ-lactone metabolism in the rat and of limited relevance to the safety assessment of exogenous D-glucurono-γ-lactone.

In 2003 the SCF evaluated a 13-week oral toxicity rat study with D-glucurono-γ-lactone and concluded that the cause of the kidney lesions remained unclear.

The petitioner has now provided data from a new 13-week oral (gavage versus drinking water) toxicity study of D-glucurono-γ-lactone in rats, with specific focus on the kidneys. This study used the same rat strain as the previous study reported in the SCF Opinion of 2003. Extensive urinalysis and histopathological examinations demonstrated no treatment-related effects. Based on the results of this study, the NOAEL for daily oral administration of D-glucurono-γ-lactone in rats was 1000 mg/kg bw/day, the highest dose tested.

Toxicological studies on the genotoxic, teratogenic or carcinogenic potential of D-glucurono-γ-lactone were not available. However, D-glucurono-γ-lactone is a normal human metabolite formed from glucose and there are no structural alerts for mutagenicity or carcinogenicity. At physiological pH it is in equilibrium with glucoronic acid, its immediate precursor. D-glucurono-γ-lactone and its hydrolysis product glucuronic acid are endogenous metabolites in humans and other mammals, they occur naturally in several dietary sources and are readily metabolized to innocuous products and excreted. Furthermore, in the high dose 13-week rat studies there was no evidence of any effect on the gonads which might indicate the need for reproductive toxicity studies.

The NOAEL for D-glucurono-γ-lactone of 1000 mg/kg bw/day is 200-fold higher than the estimated mean and 71-fold higher than the estimated 95th percentile exposure to D-glucurono-γ-lactone from "energy" drinks only, when calculated for a 60 kg person.

Given the fact that D-glucurono-γ-lactone is a natural body constituent the Panel concludes that these margins of safety are sufficiently large to conclude that exposure to D-glucurono-γ-lactone at the levels mentioned above is not of safety concern.

Overall, the Panel concludes that the exposure to taurine and D-glucurono-γ-lactone at the levels currently used in "energy" drinks and mentioned in the present opinion is not of safety concern.

The ANS Panel agrees with the considerations of the SCF Opinion from 2003 on the fact that it is unlikely that D-glucurono-γ-lactone would have any interaction with caffeine, taurine, alcohol or the effects of exercise. The Panel also concludes, based on the new data available, that additive interactions between taurine and caffeine on diuretic effects are unlikely. Other interactions between taurine and caffeine were not investigated.

Key words:

Taurine, CAS No. 107-35-7, D-glucurono-γ-lactone, CAS No. 32449-92-6, "energy" drinks.

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BACKGROUND AS PROVIDED BY THE COMMISSION

On 21 January 1999 the Scientific Committee on Food (SCF) expressed an opinion on caffeine, taurine and D-glucurono-γ-lactone as constituents of the so-called "energy" drinks. For taurine and D-glucurono-γ-lactone, the SCF was unable to conclude that the safety-in-use of taurine and D-glucurono-γ-lactone in the concentration ranges reported for these constituents in "energy" drinks had been adequately established. It indicated that further studies would be required to establish upper safe levels for daily intake of taurine and D-glucurono-γ-lactone.

In 2002, following the submission of new information by a manufacturer of "energy" drinks and the publication of reports and statements on the issue by the Australian New Zealand Food Safety Authority and the UK Food Standard Agency, the SCF was asked by the Commission to indicate if the conclusions of its opinion of 1999 needed to be revised. On 5 March 2003, the SCF expressed an opinion on additional information on "energy" drinks.

Concerning taurine, the SCF indicated that the new 13-week study in rats provided further useful information and 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 SCF was of the opinion that focused neurological studies were needed. The SCF 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/day 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/day 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 SCF's reservations were expressed in the context of an estimated acute intake of taurine 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.

Concerning D-glucurono-γ-lactone, 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/day, which is around 20-fold above the estimate of high chronic intake of D-glucurono-γ-lactone 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 SCF therefore reiterated its earlier conclusion (SCF, 1999) that there is lack of evidence to support the safety of D-glucurono-γ-lactone 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 was not possible to set an upper safe level for daily intake of D-glucurono-γ-lactone. The SCF's reservations were expressed in the context of an estimated high chronic intake of D-glucurono-γ-lactone 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 D-glucurono-γ-lactone from naturally occurring sources in the diet of 1-2 mg/day.

Following these opinions, and taking into account the remarks made by the SCF, a manufacturer of "energy" drinks has submitted new data on the safety-in-use of taurine and D-glucorono-γ-lactone as constituents of the so-called "energy" drinks.

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to:

- review the data submitted on the safety-in-use of taurine and D-glucurono-γ-lactone as constituents of the so-called "energy" drinks
- consider, if appropriate, to provide a scientific opinion on the safety-in-use of taurine and D-glucurono-γ-lactone as constituents of the so-called "energy" drinks.

ACKNOWLEDGEMENTS

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ASSESSMENT

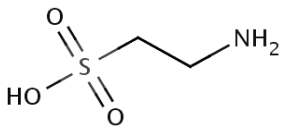
In the present opinion the Panel evaluates the safety of taurine and D-glucurono-γ-lactone as individual ingredients of the so-called "energy" drinks based on the new toxicological studies provided by the petitioner. The Panel does not evaluate the safety of "energy" drinks as such.

1. Technical data

1.1. Chemistry

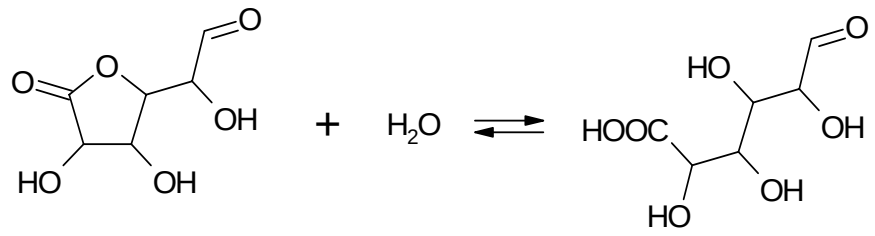
Taurine

Taurine (CAS No. 107-35-7) occurs naturally in food, especially in seafood and meat, and it is a normal metabolite in humans. It is a metabolic product of sulphur-containing amino acids, and it is mainly biosynthesised from cysteine in the liver (SCF, 1999). Its molecular weight is 125.15 g/mol, the molecular formula is $C_2H_7NO_3S$ and the structural formula is as shown:



D-glucurono-γ-lactone

D-glucurono-γ-lactone (CAS No. 32449-92-6) is a normal human metabolite formed from glucose. At physiological pH it is in equilibrium with glucuronic acid, its immediate precursor (see figure below). Glucuronic acid occurs in plants, mainly in gums, but as it is in polymeric combination with other carbohydrates it is not readily available. Glucuronic acid is also an important constituent of fibrous and connective tissues in all animals (SCF, 1999). The molecular weight of D-glucurono-γ-lactone is 176.12 g/mol, the molecular formula is $C_6H_8O_6$ and the structural formula is as shown:



D-glucurono-γ-lactone D-glucuronic acid

1.2. Manufacturing Process

The petitioner provided adequate information on the production process of taurine, retrieved from supplier information describing the general principle of the process. Taurine can be made from monoethanolamine and sulphuric acid as the starting materials or from ethylene oxide and sodium hydrogen sulphate as the starting materials. The crude production is followed by purification steps.

The petitioner provided adequate information on the production process of D-glucurono-γ-lactone, retrieved from supplier information describing the general principle of the process. D-glucurono-γ-lactone is made from nitric acid and starch as the starting materials. The crude production is followed by purification steps.

1.3. Specifications

The petitioner indicated that taurine used in "energy" drinks complies with US pharmacopoeia specifications (US Pharmacopeia, 2005). Purity is not less than 98.5 %.

The petitioner provided the following specifications for D-glucurono-γ-lactone and indicated that the methods for determining these specifications meet the requirements of several pharmacopoeias or regulations describing testing methods. D-glucurono-γ-lactone is a white crystalline powder and its purity is not less than 98.5 %. Impurities identified by HPLC include glucuronic acid <0.19%, other identified constituents each at <0.05 % and in total <0.15% and unknown constituents each at <0.05 % in total <0.15 %. Melting range is 170-176 ^{o}C, its appearance in solution is clear and colourless, the acidity of a 10% solution in water is 3.7-4.1, the loss on drying is <0.2%, heavy metals are present at <0.001% (10 mg/kg), arsenic at <2 mg/kg, iron at < 2 mg/kg, copper at < 2 mg/kg, chloride at <100 mg/kg, ammonia at < 200 mg/kg and sulphate at < 100 mg/kg. Specifications for microbial purity were also provided by the petitioner.

1.4. Methods of analysis in foods

The petitioner indicated that taurine can be determined in "energy" drinks after derivatization with dabsylchloride by HLPC with UV detection, and that D-glucurono-γ-lactone can be quantified in "energy" drinks by HPLC without derivatization.

1.5. Reaction and fate in foods, stability

The petitioner indicates that samples of "energy" drinks were stored at 20 ^{0}C for 24 months and tested at defined time-points for the levels of taurine and D-glucurono-γ-lactone. Based on the results obtained it could be concluded that taurine and D-glucurono-γ-lactone in the "energy" drink were stable during these 24 months of storage at 20 ^{0}C.

1.6. Case of need and use levels

According to the petitioner taurine and D-glucurono-γ-lactone are to be used as constituents of so-called "energy" drinks together with caffeine.

A submission from the Austrian National Food Authority (1996) included a list of the content of 32 "energy" drinks taken from a published review of drinks on the Austrian market. Some "energy" drinks did not contain taurine. In those drinks in which taurine was present and its concentration declared, one contained 300 mg/L, one 2000 mg/L and 11 contained 4000 mg/L. For the exposure estimates done in 2003 the SCF assumed that the "energy" drinks contained maximum levels of 4000 mg/L taurine and 2400 mg/L of D-glucurono-γ-lactone (SCF, 2003).

1.7. Exposure

No new data on exposure were available to the Panel.

In 2003 the SCF established a mean chronic consumption of 0.5 cans per person per day (250 mL per can) (SCF, 2003). High chronic exposure was estimated by the SCF to be 1.4 cans per person per day. This figure was based on the 95th percentile exposure of regular users, a group which represents 12% of the total population.

Based on the assumption that a can contains 250 mL and 4000 mg/L taurine and 2400 mg/L D-glucurono-γ-lactone the SCF calculated that these values result in a mean daily exposure to 500 mg taurine (8.3 mg taurine/kg bw/day for a 60 kg person) and 300 mg D-glucurono-γ-lactone (5.0 mg D-glucurono-γ-lactone /kg bw/day for a 60 kg person). The 95th percentile exposure to regular users would amount to 1400 mg taurine/day (23.3 mg/kg bw/day for a 60 kg person) and 840 mg D-glucurono-γ-lactone /day (14 mg/kg bw/day for a 60 kg person).

The mean daily exposure to taurine from omnivore diets was determined to be around 58 mg (range from 9 to 372 mg) and to be low or negligible from a strict vegetarian diet (Rana and Sanders, 1986). In another study, taurine exposure was estimated to be generally less than 200 mg/day, even in individuals eating a high meat diet (Laidlaw *et al.,* 1990). And in another study, taurine consumption was estimated to vary between 40 and 400 mg/day (Hayes and Trautwein, 1994).

The SCF Opinion mentioned an estimated exposure to D-glucurono-γ-lactone from naturally occurring sources in the diet of 1-2 mg/day (SCF, 2003). The SCF also concluded that "Human metabolic considerations indicate the body is likely to handle small quantities of glucuronolactone without any problems. However, the exposure to glucuronolactone resulting from consumption of "energy" drinks is possibly as much as two orders of magnitude greater than that from the rest of the diet." The mean exposure to D-glucurono-γ-lactone would be 300 mg/day, and at the 95th percentile exposure would be 840 mg/day.

The chronic exposures by average and high adult consumers have been estimated by the SCF (2003) to be 0.5 and 1.4 cans per person per day. The petitioner indicates that if it was assumed that this level of chronic consumption is relevant to occasional exposure of children of 25 kg body weight (about 6 to 7 years of age), then their exposure (on a body weight basis) would be about 2.5 times higher than that of adults (60-65 kg body weight). The petitioner emphasizes that these estimates relate to chronic exposures by average and high consuming adults, and would not reflect the occasional and sporadic exposure that might occur in children. If the frequency of exposure of children would be 2.5 times lower than in adults, then the average chronic exposure of children, on a body weight basis, would be the same as for adults. If children were to consume the adult intake of 0.5 and 1.4 cans per person only once per week, then the average chronic exposure of children, on a body weight basis, would be one third of that in adults.

The SCF Opinion (2003) used 3 cans/day as a reasonable high (acute) 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 SCF also indicated that it was aware that amounts up to 8-12 cans/day, were reported by a few extreme consumers in both surveys, which would result in an intake of 4800-7200 mg D-glucurono-γ-lactone and 8000-12000 mg of taurine per day, equivalent to 80 - 120 mg D-glucurono-γ-lactone/kg bw/day and 133-200 mg taurine/kg bw/day.

1.8. Existing authorisations and evaluations

In 1999, the SCF adopted an opinion on so-called "energy" drinks, which evaluated the safety of caffeine, taurine and D-glucurono-γ-lactone as constituents of "energy" drinks (SCF, 1999). The SCF (1999) concluded that toxicological studies did not reveal any indication for a genotoxic, teratogenic or carcinogenic potential of taurine.

At that time, the SCF was unable to conclude that the safety-in-use of taurine and glucuronolactone in the concentration ranges reported for "energy" drinks had been adequately established. The SCF commented that "there is insufficient information on which to set an upper safe level for daily intake of these constituents."

In 2001, the Agence Française de Sécurité Sanitaire des Aliments (AFSSA), reviewed a 13-week mouse oral toxicity study on "energy" drinks, 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 AFSSA reiterated the same conclusions in three subsequent opinions (AFSSA, 2003, 2006a, 2006b).

In 2003 the SCF was asked to review additional information submitted on "energy" drinks and indicate if the conclusions in its opinion of 21 January 1999 needed to be modified. The SCF 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, 2001; 2002).

The SCF (2003) concluded the following on 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 and that the effects reported in a 13-week study 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/d 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/d 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."

The SCF (2003) concluded the following on glucurono-γ-lactone:

> "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/d, which is around 20-fold above the estimate of high chronic intake of glucuronolactone of 14 mg/kg bw/d 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."

In 2005, a statement was expressed by the EFSA Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on studies designed to investigate the safety-in-use of taurine and D-glucurono-γ-lactone in "energy" drinks (EFSA, 2005).

2. Biological and toxicological data

Previous SCF Opinions have summarized safety studies of taurine and D-glucurono-γ -lactone (SCF, 1999; SCF, 2003) and a previous EFSA Statement from the AFC Panel commented on studies designed to further investigate the safety-in-use of taurine and D-glucurono-γ-lactone in "energy" drinks (EFSA, 2005).

The present opinion only describes in detail those studies that were submitted after the publication of the SCF Opinion in 2003 and the EFSA Statement in 2005.

2.1. Absorption, distribution, metabolism and excretion

Taurine

The SCF Opinion already concluded that new toxicokinetic data submitted at that time on taurine in rats showing ready bioavailability and peak plasma levels one hour after oral administration are in accordance with findings from the limited published data for humans (SCF, 2003). 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). The SCF indicates that these results also corroborate those from an unpublished human study using radiolabelled taurine, which showed peak serum levels at 1-2 hours after oral administration, declining by 7 hours (SCF, 2003). Other

human data suggest that taurine is absorbed orally via an active transport mechanism in the gut wall (Ahlman *et al.,* 1993; 1995a, b).

Results from a new study on absorption, tissue distribution, metabolism and elimination of taurine given orally to rats were provided by the petitioner. In this study (Sved *et al.,* 2007) three biodisposition studies with taurine were performed in male and female adult rats at dosages of 30 and 300 mg/kg bw. A single dose of ^{14}C taurine was rapidly absorbed, distributed to tissues and excreted unchanged in the urine. Elimination of radioactivity from intracellular pools was slow. Pre-treatment of animals for 14 days with unlabelled taurine did not significantly affect the fate of ^{14}C taurine. Daily administration of unlabelled taurine for 14 days did not result in an increase in total taurine in the brain. It was concluded that the data indicated that exogenous taurine rapidly equilibrates with endogenous body pools and that any excess is rapidly eliminated by the kidneys.

Based on these data which revealed that brain taurine levels did not increase after dosing, the petitioner concluded that the possibility that taurine may exhibit acute, central pharmacological effects mediated by an action on the central nervous system was scientifically improbable.

D-glucurono-γ-lactone

The SCF (1999) already concluded that the available data indicate that when D-glucurono-γ-lactone is administered orally to humans it is rapidly absorbed, metabolised and excreted as glucaric acid, xylitol and L-xylulose.

The SCF Opinion of 2003 stated that the toxicokinetic data on D-glucurono-γ-lactone in rats, showing bioavailability and lack of accumulation, with peak plasma levels 1-2 hours after oral administration, were in accordance with findings from the limited published data on humans (SCF, 2003).

Animals, such as rodents, which can synthesise vitamin C endogenously do so from glucuronic acid and such animals can also convert exogenously administered D-glucurono-γ-lactone into vitamin C (SCF, 1999). However, primates, including man, and guinea pigs do not possess this metabolic pathway. The SCF concluded that for this reason, the rodent may be an inappropriate model for man in the study of the effects of D-glucurono-γ-lactone.

In 2003, the SCF reiterated the 1999 Opinion that rodents may not be an appropriate model for humans since they can metabolise exogenous D-glucurono-γ-lactone to vitamin C whereas guinea pigs and primates, including humans, do not possess this metabolic pathway. However, the petitioner indicates that synthesis of vitamin C is only a minor pathway of D-glucurono-γ-lactone metabolism in the rat and argues that, although of nutritional importance, it is of limited relevance to the safety assessment of exogenous D-glucurono-γ-lactone. This is supported by more recent literature data demonstrating that D-glucurono-γ-lactone is predominantly metabolised in rats via the pentose pathway and that the flux through the pathway that results in synthesis of ascorbic acid from D-glucurono-γ-lactone is relatively small (Kondo *et al.,* 2006; Linster and Van Schaftingen, 2007).

2.2. Toxicological data

2.2.1. Acute oral toxicity

In an acute toxicity study of taurine in Wistar rats, a 50% taurine suspension in 1.0% carboxymethylcellulose (CMC) solution was administered in a volume of 10 mL/kg bw. No dead animals were observed during the observation period of 14 days, and the authors indicate that this suggests that the LD_{50} value of taurine is higher than 7000 mg/kg bw upon oral administration (Kihara *et al.,* 1991).

2.2.2. Short-term and sub-chronic toxicity

Taurine

In 2003 the SCF evaluated a newly submitted 13-week rat study with taurine at dose levels of 0, 300, 600 and 1000 mg/kg bw/day which showed no significant changes in pathological measures, but did show the occurrence of significant behavioural effects (increased activity and self-injury such as self-chewing), and possibly impaired motor performance, which could have been mediated via a pharmacological action on the central nervous system. In view of this, the SCF was of the opinion that focused neurological studies were needed. The absence of a NOAEL for these effects precluded the setting of an upper safe level for daily exposure to taurine.

The petitioner argued that there had been bias in the original study observations and the EFSA Working Group (EFSA, 2005) agreed that the observations reported in this study on certain behavioural patterns of the animals had not been well described in the original submission and could be discounted since there was no evidence of self-injury. However, the EFSA Working Group also concluded that, even combined with the expert analyses provided, this information was insufficient in itself to address all the concerns raised previously, notably the observation on increased activity and possible decrements in motor skills on the rotarod.

Therefore, the petitioner has now provided data from a specifically-designed, new 13-week oral (gavage and drinking water) neurotoxicity study of taurine in male and female rats which was performed according to FDA and OECD principles of Good Laboratory Practice. The objective of this study was to evaluate any potential neurotoxic effects of taurine when administered to rats for 13 weeks either by gavage or by way of drinking water, and to address the reliability of observations noted in the previous 13-week taurine toxicity study. Beginning in the second week of the acclimatization period, all animals (180 males and 180 females) were tested twice in the functional observational battery (FOB) and locomotor activity paradigms. After initial evaluations, outliers in locomotor activity were eliminated from the study. The remaining animals were randomized based on their performance on the rotarod test. Finally, the mean and standard deviation of the locomotor activity results were analyzed to ensure that group means and variances were approximately equal before initiation of dosing, thereby minimizing subsequent skewing of these data. Potential functional deficits were assessed using a FOB and a measure of spontaneous locomotor activity. This study was conducted in a "blinded" manner, in which the actual dose level for each group (gavage and drinking water) were unknown to the personnel conducting the study, in order to remove human bias from all aspects of the study.

Taurine in the vehicle, deionized water, was administered orally by gavage once daily for 13 weeks to 2 groups of 20 male and 20 female Cr1:CD(SD) rats at dose levels of 600 and 1000 mg/kg bw/day. In addition taurine was administered *ad libitum* in drinking water for 13 weeks to 2 groups of 20 male and 20 female Cr1:CD(SD) rats at target dose levels of 1000 and 1500 mg/kg bw/day (actual mean taurine intake levels obtained with drinking water were 1095 and 1117 mg/kg bw/day for the males and females respectively in the low dose group and 1647 and 1656 mg/kg bw/day for the males and females respectively in the high dose group). Concurrent control groups received the vehicle by gavage and drinking water respectively, on comparable regimes. Clinical examinations were performed daily and detailed physical examinations were performed weekly. These examinations were conducted "blinded" with respect to treatment. Individual body weights and water consumption were recorded twice weekly and food consumption was recorded weekly. Functional observational battery and locomotor activity data were recorded for all animals prior to the initiation of dose administration and during study weeks 0, 6 and 12. Complete necropsies were conducted on all animals, and selected tissues and organs were collected at the scheduled necropsy.

The results indicated that there were no test-article-related deaths, clinical findings or macroscopic findings. No test-article-related effects were observed on body weights or food consumption. Some differences were observed in water consumption when rats were supplied taurine *ad libitum* in the drinking water. Increases in water consumption in the 1000 and 1500 mg/kg bw/day group males were noted only for study days 0 to 3 and/or 3 to 7 (both in g/animal/day and g/kg bw/day). The petitioner indicates that these differences were considered test-article-related, but not considered adverse effects and that they occurred temporarily and were considered to reflect adaptation to the osmotic property of the test article.

There were no test-article-related effects on FOB parameters (home cage, handling, open field, sensory, neuromuscular and physiological observations). Locomotor activity counts (total and ambulatory) and patterns were unaffected by test article administration.

Based on these results the petitioner concluded that the oral administration of taurine at dose levels of 600 and 1000 mg/kg bw/day was well tolerated by male and female rats and did not result in any behavioural changes. The Panel concluded that this study confirmed the NOAEL derived from the earlier study which included histopathology (1000 mg/kg bw/day – the highest dose tested). In addition, it provided evidence of a NOAEL of 1500 mg/kg bw/day (actual level approximately 1650 mg/kg bw/day) for behavioural effects.

D-glucurono-γ-lactone

For D-glucurono-γ-lactone the SCF concluded that the 13-week study in Crl:CD(SD) rats showed that there were no significant, treatment-related effects, "apart from vacuolisation and inflammatory changes localised to the papilla of the kidney in females at 600 and 1000 mg/kg bw/day, with a NOAEL of 300 mg/kg bw/day" (SCF, 2003).

The study reported cytoplasmic vacuolation in 6/20 and 4/20 males in the control and 1000 mg/kg bw/day groups respectively and in 11/20, 9/20, 11/20 and 11/20 females in the control, 300, 600 and 1000 mg/kg bw/day groups respectively. The incidence was not increased by treatment. The lesions were described as mild (grade 2) rather than minimal (grade 1) in 1/20 and 0/20 males in the control and 1000 mg/kg bw/day groups and in 1/20, 1/20, 5/20 and 8/20 females in the control, 300, 600 and 1000 mg/kg bw/day groups respectively. Therefore the data indicated that there was a slight dose-related increase in severity in the treated females in comparison to the treated males. However the petitioner noted that for all rats used in the

study, a range of other effects in the kidneys were reported, such as inflammatory changes, nephropathy, pyelitis, indicative of renal problems.

The petitioner argued that the occurrence of the renal observations were incidental, related to background lesions usually occurring in this rat strain. The SCF concluded that the cause of the kidney lesions remained unclear. The petitioner also indicated 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 considered less than of the Sprague-Dawley rat. However, the SCF stated that in their view the mechanistic cause of the kidney lesions remains unclear (SCF, 2003).

In a statement (EFSA, 2005) the Working Group on Additives of the AFC Panel noted that the guinea pig might be a better model for human, in terms of its metabolism of D-glucurono-γ-lactone. But they expressed considerable reservations about a study on D-glucurono-γ-lactone in guinea pigs as proposed by the petitioner. The Working Group particularly noted that the proposed study in guinea pigs with D-glucurono-γ-lactone in drinking water could be difficult to perform (e.g. mortality) and interpret (e.g. lack of extensive background data on this species), and that in view of these potential difficulties, consideration should be given to whether this study could be justified on animal welfare grounds.

The Working Group suggested that a more productive strategy might be to undertake mechanistic studies to support the hypothesis put forward by the petitioner that the rat kidney effects were not relevant for human risk assessment.

The petitioner has now provided data from a new 13-week oral (gavage versus drinking water) toxicity study of D-glucurono-γ-lactone in the Crl:CD(SD) rat strain, with specific focus on the kidneys. This study used the same rat strain as the previous study reported in the SCF Opinion of 2003 and was performed according to FDA and OECD principles of Good Laboratory Practice. In this new study, D-glucurono-γ-lactone was administered orally by gavage once daily for 13 consecutive weeks to 4 groups of Cr1:CD(SD) rats at dose levels of 0, 300, 600 and 1000 mg/kg bw/day. In addition D-glucurono-γ-lactone was administered *ad libitum* in drinking water for 13 weeks to another 4 groups of Cr1:CD(SD) rats at target dose levels of 0, 300, 600 and 1000 mg/kg bw/day. Each group consisted of 20 males and 20 females. Actual mean D-glucurono-γ-lactone intake levels obtained in the drinking water groups were 311 and 322 mg/kg bw/day for the males and females respectively in the low dose group, 598 and 635 mg/kg bw/day for the males and females respectively in the mid dose group and 980 and 1066 mg/kg bw/day for the males and females respectively in the high dose group. Concurrent control groups of 20 males and 20 females received the vehicle by gavage and drinking water respectively on comparable regimens.

Clinical examinations were performed daily, and detailed physical examinations were performed weekly. Individual body weights and water consumption were recorded twice weekly. Serum chemistry evaluations were performed on all animals prior to the initiation of dose administration (study week 2), during study weeks 4 and 8, and at the scheduled necropsy (study week 13) and at time-points during 0 to 6 hours and 6 to 24 hours after dose administration from the gavage groups during study weeks 4, 8 and 13. Urine samples were collected from the drinking water groups on the same schedule (same time of day). Complete necropsies were conducted on all animals, and selected organs were weighed at the scheduled necropsy. Selected tissues were examined microscopically from all animals. Results revealed no test article-related deaths. There were no effects on clinical observations, food or water consumption, body weights, clinical pathology parameters, organ weights or clinical chemistry parameters representing renal function. Extensive urinalysis demonstrated no

treatment related effects, and no differences between gavage and drinking water groups. There were no test article-related macroscopic or microscopic findings.

Histopathological examinations revealed focal inflammation in the kidneys in a few male and female animals, scattered among the groups, including controls. The petitioner indicates that inflammation was observed in only a small number of animals at each dose level, that it was unilateral and not treatment-related and that these background lesions are typical for this strain of rats.

There were no compound-related observations of vacuolization of the cells lining the collecting tubules. The petitioner also indicated that a greater number of rats in this new study had healthy kidneys in comparison to the first study. There were no differences between the gavage and drinking water groups. There was no significant incidence of cytoplasmic vacuolization in any groups. The petitioner also indicated that in light of the difference between the two studies the slides have been carefully reassessed, and that cytoplasmic vacuolization has been confirmed not to be present. The petitioner also stated that the pathologist who undertook the histopathological examination has indicated that the effect in the previous study was most likely a preparation artifact which was exacerbated by the generally poor health status of the kidneys in the rats at that time. Vacuolisation of renal collecting tubules may arise as an artifact using normal fixation techniques.

The petitioner concluded that based on the results of this and the previous study, the NOAEL for daily oral administration of D-glucurono-γ-lactone to rats was 1000 mg/kg bw/day, the highest dose tested in both studies. The Panel agrees with this NOAEL derived from the recent 13-week rat study which was performed under GLP.

2.2.3. Reproductive and developmental toxicity

The SCF already concluded in 1999 that toxicological studies did not reveal any indication for a teratogenic potential of taurine (SCF, 1999).

Studies on reproductive and developmental toxicity for D-glucurono-γ-lactone were not available. However the petitioner indicates that this substance and its hydrolysis product glucuronic acid are endogenous metabolites in humans and other mammals, that they occur naturally in several dietary sources and are readily metabolized to innocuous products and excreted. Furthermore there were no effects on the gonads in the 13-week rat studies. Therefore the Panel concluded that there was no need for reproductive toxicity studies.

There are no new studies available.

2.2.4. Mutagenicity

The SCF already concluded that toxicological studies did not reveal any indication for a genotoxic potential of taurine (SCF, 1999).

In a study on the antimutagenic activity of lactones in *Escherichia coli*, D-glucurono-γ-lactone was reported to be not mutagenic to *E. coli* strains WP2 and WPs (Kuroda *et al.*, 1986).

There are no new studies available.

2.2.5. Carcinogenicity and long-term studies

The SCF already concluded that toxicological studies did not reveal any indication for a carcinogenic potential of taurine (SCF, 1999). But the SCF also indicated that there is no adequate chronic toxicity/carcinogenicity study for taurine.

Long term studies on D-glucurono-γ-lactone were not available. However this substance and its hydrolysis product glucuronic acid are endogenous metabolites in humans and other mammals, they occur naturally in several dietary sources and are readily metabolized to innocuous products and excreted. Furthermore, there was no evidence of any putative preneoplastic or hyperplastic lesions in the 13-week rat studies, which might indicate the need for a long term carcinogenicity study.

2.2.6. Human data

Available human data from the use of taurine in human medicine do not give any indication of safety concerns (Franconi *et al.,* 1995; Takahashi and Nakane, 1978; Fukuyama and Ochiai, 1982; Airaksinen *et al.*, 1980; Mantovani and DeVibo, 1979; Marchesi *et al.,* 1975; Mutani *et al.,* 1975; Azuma *et al.,* 1983a; 1983b; 1985; 1992; 1994; Fujita *et al.,* 1987; Yamori *et al.,* 1996; Krøll and Lund, 1966; Yamamoto *et al.,* 1994; Gentile *et al.,* 1994; Matsuyama *et al.,* 1983; Podda *et al.,* 1990; Kimura *et al.,* 1992; Obinata *et al.,* 1996; Durelli *et al.,* 1982; 1983; Nyland *et al.,* 1989; Kopple *et al.,* 1990; Thompson 1988; Darling *et al.,* 1985; Carrasco *et al.,* 1990; Belli *et al.,* 1987; Colombo *et al.,* 1988; Smith *et al.,* 1991; De Curtis *et al.,* 1992; Skopnik *et al.,* 1991; Colombo *et al.,* 1990).

In these separate studies taurine has been administered, mostly by oral ingestion on a daily basis for periods up to one year, and with daily doses generally in the 3-6 g range, to a large number of patients (adults, children and even infants) suffering from a wide variety of serious diseases. Taurine has also been administered parenterally at a daily dose of 0.64 g for 20 months or by intravenous administration at daily doses of 12 g for 15 days and 18 g for 60 days. Although the principal aim of these clinical studies was not to evaluate potential adverse effects of chronic administration of taurine it is apparent that these doses produced no adverse health effects. Such information has revealed that oral daily ingestion of taurine doses in the 3-6 g range for periods up to one year, did not produce adverse health effects.

The SCF Opinion of 2003 refers to a number of anecdotal reports of acute, adverse effects in young persons consuming "energy" drinks, containing caffeine, taurine and D-glucurono-γ-lactone, usually together with alcohol and/or 'social drugs', such as ecstasy and amphetamines. The adverse effects reported included tremors, seizures, drowsiness, muscle weakness, dizziness, nervousness, tachycardia, palpitations, nausea, vomiting, headache, bronchospasm, hyperventilation and also myocardial infarction and sudden unexplained death possibly resulting from cardiac dysrhythmia (SCF, 2003). The SCF already concluded the following: "The co-consumption of alcohol and/or drugs noted in most of these cases makes interpretation of effects due to the "energy" drinks 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".

New human data on the assessment of "energy" drinks have been compiled in a recent BfR Opinion (BfR, 2008) reporting recent Swedish and American studies (Lehtihet *et al.*, 2006; Wiklund *et al.*, 2004; Steinke *et al.*, 2007; American Heart Association; 2007; Iyadurai and Chung; 2007). In a Swedish publication possible adverse reactions of "energy" drinks

including three cases of death are discussed, focussing on a potential contributing role of taurine associated with its known effects e.g. in osmoregulation and on the cardiovascular system. The three fatalities occurred after "energy" drinks had been consumed in combination with alcohol, whereby the forensic examinations including autopsy yielded negative results concerning medicaments and drugs, values between 0.59 and 0.87 parts per thousand of ethanol in blood samples, but no clear causes of death. In a further case, severe adverse effects arose after consumption of an "energy" drink in combination with physical efforts: A 31-year-old regularly trained man consumed 750 mL of an "energy" drink while taking part in a 3,000 m competition. He developed a poor general condition with a rhabdomyolysis and acute kidney failure with tubular necrosis diagnosed one week after the competition (Lehtihet *et al.*, 2006).

Two new cases of "energy" drink-related tachycardias, in one individual associated with orthostatic intolerance, were reported by other authors (Nagajothi *et al*., 2008; Terlizzi *et al.*, 2008). In the Terlizzi study, consumption was reported to amount to 4 to 5 cans of "energy drinks" a day.

In addition, cases of four patients who suffered generalised cerebral seizures after consuming a high dose of "energy" drinks, without there being any reports of parallel alcohol consumption were reported (Iyadurai and Chung, 2007).

Overall, the results also raised the issue of combination effects and possible interactions between, amongst others, taurine and alcohol, between taurine and caffeine and between taurine and D-glucurono-γ-lactone.

The SCF Opinion already evaluated the possibility of interactions between taurine, caffeine and D-glucurono-γ-lactone and considered it unlikely that D-glucurono-γ-lactone would have any interaction with caffeine and taurine. The SCF concluded (2003) "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 levels of the central nervous system".

The SCF also noted that "since caffeine and taurine act via different mechanisms, any diuretic effects could be additive" and that "Both taurine (Gentile *et al.,* 1994) and alcohol centrally inhibit the release of the antidiuretic hormone, vasopressin and the Committee considered that they could act additively to increase water and sodium loss from the body in the short-term".

New data have recently been published (Riesenhuber *et al.,* 2006) describing results from a study investigating the possible additive diuretic effects of caffeine and taurine in a cross-over design in which 12 healthy male volunteers each received four different test drinks (750 mL of "energy" drink containing 240 mg caffeine and 3 g taurine, the three other test drinks that lacked caffeine, taurine or both). Effects on urinary output, urinary osmolarity and natriuresis were compared by mixed model analyses. Urinary output and natriuresis increased significantly with caffeine alone and in the caffeine-taurine group. This study demonstrated that the diuretic potential and natriuretic effects of the tested "energy" drinks were largely mediated by caffeine and that there were no additive interactions between taurine and caffeine. The petitioner concluded that this study does not support the possibility of interactions between taurine and caffeine.

To investigate possible cardiovascular effects of the combined exposure to caffeine and taurine with "energy" drinks an orientational study was conducted in healthy volunteers with low blood pressure (8 women, 7 men, average age of 26 years) in a state of physical rest (Steinke *et al.*, 2007; American Heart Association, 2007). The test persons had abstained from caffeine for 48 h before the start of the study and throughout the study period. After an initial examination during which blood pressure and heart rate were measured and an ECG was

carried out, each participant consumed 500 mL of "energy" drink containing a total of 80 mg caffeine and 1000 mg taurine. The examinations were repeated at intervals of up to 4 hours. On each of the following five days the participants again drank 500 mL and on the seventh day the procedure of the first day was repeated. Four hours after consumption of the beverage, systolic blood pressure had increased by 7.9 % (day one) or 9.6 % (day seven) and heart rate had been raised by 7.8 % (day one) or 11 % (day seven). Over the duration of the study this means an increase of blood pressure by 10 mm Hg and of heart rates of 5 to 7 beats per minute. No habituation could be determined following several days exposure since the effects were slightly enhanced on the seventh day. Until the submission of further findings the researchers recommended that patients with high blood pressure or cardiac diseases and corresponding medication should refrain from consuming "energy" drinks because of a possible health risk.

3. Discussion

In the absence of new chronic and acute exposure data, the exposure assessment is based on the data reported by SCF (2003), i.e. a daily mean chronic consumption of 0.5 cans per person and a high chronic exposure at the 95th percentile of 1.4 cans per regular consumer. The Panel notes that actual exposure data on "energy" drink consumption, especially for adolescents and young adults, may need to be collected.

These estimates for the daily exposure to taurine (mean 500 mg/day; 95th percentile 1400 mg/day) or D-glucurono-γ-lactone (mean 300 mg/day; 95th percentile 840 mg/day) from "energy" drinks are higher than the estimated mean daily exposure to taurine from omnivore diets which was estimated to be at most 400 mg/day and that of D-glucurono-γ-lactone from naturally occurring sources in the diet estimated to amount to 1-2 mg/day (SCF, 2003).

The Panel concludes that assuming that children were to consume within the adult intake range of 0.5 and 1.4 cans per person only once per week, then the average chronic exposure of children to "energy" drinks and their constituents, on a body weight basis, would be one third of that in adults.

The SCF Opinion (2003) used 3 cans/day as a reasonable high (acute) 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 SCF also indicated that it was aware that amounts of up to 8-12 cans/day were reported by a few extreme consumers in both surveys.

Taurine

Results from a new study on absorption, tissue distribution, metabolism and elimination of taurine given orally to rats were provided by the petitioner (Sved *et al.,* 2007). The Panel concludes that these new ADME data support the contention that oral exposure to taurine was not increasing taurine levels in the brain.

In 2003 the SCF evaluated a 13-week rat oral toxicity study of taurine and concluded that focused neurological studies were needed and that the absence of a NOAEL for these effects precluded the setting of an upper safe level for daily exposure to taurine.

The Panel evaluated a new 13-week oral rat toxicity and neurotoxicity study in male and female rats which included FOB and locomotor activity tests. The new study confirmed the NOAEL of 1000 mg/kg bw/day for pathological changes established in the earlier 13-week study described already by the SCF in 2003 and provided evidence for a NOAEL of 1500 mg/kg bw/day for behavioural effects. The results of this study were sufficient to address the concerns raised previously, notably the observation of increased activity and possible decrements in motor skills on the rotarod.

The NOAEL of at least 1000 mg/kg bw/day for pathological changes is 120-fold higher than the estimated mean and 43-fold higher than the estimated 95th percentile exposure to taurine from "energy" drinks only, when calculated for a 60 kg person.

Given that taurine is a natural body constituent, the Panel concludes that these margins of safety are sufficiently large to conclude that exposure to taurine at the levels mentioned above is not of safety concern.

D-glucurono-γ-lactone

In 2003 the SCF evaluated a 13-week rat oral toxicity study with D-glucurono-γ-lactone and concluded that the cause of the kidney lesions remained unclear.

The petitioner has now provided data from a new 13-week oral (gavage versus drinking water) toxicity study of D-glucurono-γ-lactone in rats, with specific focus on the kidneys. This study used the same rat strain as the previous study reported in the SCF Opinion of 2003. Extensive urinalysis and histopathological examinations demonstrated no treatment-related effects. Based on the results of this study, the NOAEL for daily oral administration of D-glucurono-γ-lactone was 1000 mg/kg bw/day, the highest dose tested.

Toxicological studies on genotoxic, teratogenic or carcinogenic potential of D-glucurono-γ-lactone were not available. However, D-glucurono-γ-lactone is a normal human metabolite formed from glucose and there are no structural alerts for mutagenicity or carcinogenicity. At physiological pH it is in equilibrium with glucuronic acid, its immediate precursor. D-glucurono-γ-lactone and its hydrolysis product glucuronic acid are endogenous metabolites in humans and other mammals, they occur naturally in several dietary sources and are readily metabolized to innocuous products and excreted. Furthermore there was no evidence of any effect on the gonads in the high dose 13-week studies which might indicate the need for reproductive toxicity studies.

The NOAEL for D-glucurono-γ-lactone of 1000 mg/kg bw/day is 200-fold higher than the estimated mean and 71-fold higher than the estimated 95th percentile exposure to D-glucurono-γ-lactone from "energy" drinks only, when calculated for a 60 kg person.

Given the fact that D-glucurono-γ-lactone is a natural body constituent the Panel concludes that these margins of safety are sufficiently large to conclude that exposure to D-glucurono-γ-lactone at the levels mentioned above is not of safety concern.

Combined exposure

The SCF Opinion of 2003 and the recent BfR Opinion (BfR, 2008) mention a number of anecdotal and case reports of acute, adverse effects, including fatalities, in individuals consuming "energy" drinks, containing caffeine, taurine and D-glucurono-γ-lactone. In these cases, "energy" drinks had either been consumed in very high amounts (1420 mL), in combination with physical exercise or more frequently together with alcohol. The SCF

Opinion of 2003 also takes into account that drugs, such as ecstasy and amphetamines may have been involved. The effects mentioned included tremors, seizures, drowsiness, muscle weakness, dizziness, nervousness, tachycardia, palpitations, nausea, vomiting, headache, bronchospasm, hyperventilation and also myocardial infarction and sudden unexplained death possibly resulting from cardiac dysrhythmia (SCF, 2003; BfR, 2008; Lehtihet *et al.,* 2006; Iyadurai and Chung; 2007, Nagajothi *et al*., 2008; Terlizzi *et al.*, 2008). The SCF concluded the following: "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". With regard to some actual reports (e.g. Iyadurai and Chung; 2007, Nagajothi *et al*., 2008; Terlizzi *et al.*, 2008) the Panel considers that it is possible that the effects could be due to the well known side effects of high caffeine intake, while the assumption of a causal relationship with taurine intake is lacking scientific evidence.

These results also raised the issue of combination effects and possible interactions between, amongst others, taurine and alcohol, between taurine and caffeine and between taurine and D-glucurono-γ-lactone.

The SCF Opinion (SCF, 2003) already evaluated the possibility of interactions between taurine, caffeine and D-glucurono-γ-lactone and considered it unlikely that D-glucurono-γ-lactone would have any interaction with caffeine and taurine. The SCF 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".

Results from a new study provided by the petitioner (Sved *et al.,* 2007) revealed that brain taurine levels did not increase after dosing. The Panel concludes that these new ADME data support the contention that oral exposure to taurine was not increasing taurine levels in the brain and that this largely rules out the possibility of stimulatory effects from taurine at the level of the central nervous system.

The SCF (2003) also noted that "since caffeine and taurine act via different mechanisms, any diuretic effects could be additive" and that "Both taurine (Gentile *et al.,* 1994) and alcohol centrally inhibit the release of the antidiuretic hormone, vasopressin and the Committee considered that they could act additively to increase water and sodium loss from the body in the short-term".

New data have recently been published (Riesenhuber *et al.,* 2006) describing results demonstrating that the diuretic potential and natriuretic effects of the tested "energy" drinks were largely mediated by caffeine and that there were no additive interactions between taurine and caffeine. The Panel concludes that the diuretic potential and natriuretic effects of "energy" drinks may be largely mediated by caffeine and not by taurine.

In a recent study, possible cardiovascular effects of the combined exposure to caffeine and taurine with "energy" drinks were investigated (Steinke *et al.*, 2007; American Heart Association, 2007). Four hours after consumption of 500 mL of "energy" drink containing a total of 80 mg caffeine and 1000 mg taurine, systolic blood pressure had increased by 7.9 % (day one) or 9.6 % (day seven) and heart rate had been raised by 7.8 % (day one) or 11 % (day seven). Over the duration of the study this means an increase of blood pressure by 10 mm Hg and of heart rates of 5 to 7 beats per minute. Until the submission of further findings the researchers recommended that patients with high blood pressure or cardiac diseases and corresponding medication should refrain from consuming "energy" drinks because of a

possible health risk. The Panel notes that the studies were not designed to show whether the effects were due to caffeine or taurine.

Overall, the ANS Panel concludes that the diuretic potential and natriuretic effects of the tested "energy" drinks are largely mediated by caffeine. Other interactions between taurine and caffeine were not investigated.

CONCLUSIONS AND RECOMMENDATIONS

In the present opinion the Panel evaluates the safety of taurine and D-glucurono-γ-lactone as individual ingredients of the so-called "energy" drinks based on the new studies provided by the petitioner. The Panel does not evaluate the safety of "energy" drinks as such.

In the absence of new chronic and acute exposure data, the exposure is based on the data reported by the SCF in 2003. The Panel concluded that actual exposure data on "energy" drink consumption, especially for adolescents and young adults, may need to be collected.

The Panel concludes that the exposure to taurine and D-glucurono-γ-lactone at the levels presently used in "energy" drinks and mentioned above is not of safety concern.

The ANS Panel agrees with the considerations of the SCF Opinion from 2003 that it is unlikely that glucurono-γ-lactone would have any interaction with caffeine, taurine, alcohol or the effects of exercise. The Panel also concludes, based on the new data available, that additive interactions between taurine and caffeine on diuretic effects are unlikely. Other interactions between taurine and caffeine were not investigated.

DOCUMENTATION PROVIDED TO EFSA

1. Kroes R. and Renwick, A.G. Summary report regarding the safety in Use of Taurine and D-glucuronolactone as constituents of "energy" drinks.
2. Final report. A 13-week oral (gavage and drinking water) neurotoxicity study of taurine in male and female rats (WIL-42306). Submitted by Red Bull GmbH.
3. Final report. A 13-week oral (gavage versus drinking water) toxicity study of D-glucuronolactone in rats (WIL-423012). Submitted by Red Bull GmbH.
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GLOSSARY / ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism, Excretion
AFSSA	Agence Française de Sécurité Sanitaire des Aliments
ANZFA	Australia New Zealand Food Authority
BfR	Federal Institute for Risk Assessment
CMC	Carboxymethylcellulose
EFSA	European Food Safety Authority
FSA	Food Standards Agency
HPLC	High performance liquid chromatography
NOAEL	No Observable Adverse Effect Level
SCF	Scientific Committee on Food