

New Human Data on the Assessment of Energy Drinks

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Energy drinks are beverages which contain caffeine mostly together with the substances taurine, inositol and glucuronolactone, frequently in high concentrations. In the past there have been cases of fatalities with a possible link to the consumption of energy drinks in conjunction with alcohol intake or intensive physical activity without, however, a causal relationship being proved. Scientists take into consideration the fact that the typical energy drink ingredients mutually potentiate their toxicological effects and could, therefore, lead to health-relevant impairments of body functions.

In Europe there are different provisions concerning the sale of energy drinks. In Germany, for instance, distribution is only possible under specific conditions; in France there are more extensive limitations on ingredients. The Federal Institute for Risk Assessment (BfR) has repeatedly advocated clear indications on the labels of energy drinks. They should recommend that certain groups of consumers like children, pregnant women, lactating women and individuals who are sensitive to caffeine should refrain from consuming energy drinks. Moreover, reference should be made to possible adverse effects in conjunction with intensive physical activity or the consumption of alcoholic beverages.

Based on new research the Federal Institute for Risk Assessment (BfR) provides information on more recent human data on the possible health risks posed by the consumption of energy drinks. It draws attention to reports that cardiac dysrhythmia, seizures, kidney failure and fatalities occurred after consuming energy drinks. The question about the causal relationship is still open.

Attention should also be drawn to findings which indicate that test persons no longer realistically assess their dwindling responsiveness caused by alcohol consumption under the influence of energy drinks. The objective measurements of their psychomotor abilities revealed that energy drinks did not compensate for specific motor and visual impairments caused by alcohol. The parallel consumption of alcohol and energy drinks can, therefore, lead to an individual misjudging his ability to perform.

BfR reiterates its earlier recommendation of providing detailed information on the product labels. Furthermore, BfR advises consumers with high blood pressure and heart disease to show restraint when consuming energy drinks until robust studies are available. BfR recommends uniform European provisions on the placing on the market of energy drinks.

1 Subject matter of the assessment

Up to now, the production and placing on the market of caffeine-containing lemonades with more than 250 mg caffeine per litre to which taurine, inositol and glucuronolactone have been added (energy drinks), has been approved in Germany pursuant to the general decrees in accordance with § 54 Food and Feed Code (LFGB) and exemptions pursuant to § 68 paras 1 and 2 No. 1 LFGB respectively.

Based on the existing exemptions, consideration was given to allowing the use of

- caffeine up to max. 320 mg/l,
- taurine up to max. 4000 mg/l,
- inositol up to max. 200 mg/l and

- glucuronolactone up to max. 2400 mg/l

in the production of caffeine-containing lemonades through a legal ordinance. Against this backdrop the Federal Institute for Risk Assessment (BfR) conducted a literature search on possible health risks linked to the consumption of these beverages and updated its earlier assessment.

2 Results

The suspicion expressed in the BfR expert opinion of 18 March 2002 [1] that the safety of energy drinks is to be questioned in the circumstances in which they are possibly drunk by some consumers, is substantiated by more recent human data. Against this backdrop BfR upholds the existing recommendation concerning the provision of comprehensive information on product labels, "In addition to the currently prescribed labelling on a high caffeine content (Directive 2002/67/EC), it is recommended – on the grounds of preventive health protection – that information should be provided on the packaging of energy drinks that

- adverse effects cannot be ruled out when larger amounts of these beverages are consumed in conjunction with intensive physical activity or with intake of alcoholic beverages;
- beverages of this kind, particularly when consumed in larger amounts, are not recommended for children, pregnant women, lactating women or individuals who are sensitive to caffeine."

In this context, BfR draws attention to the fact that in other European and non-European countries corresponding information (e.g. Finland, Canada), limitations on ingredients (e.g. France) or bans (e.g. Denmark, Norway) are already in place or are recommended for energy drinks [2, 3].

BfR points to the need for clarification whether certain risk groups, for instance because of existing health disorders, have a heightened sensitivity to possible adverse effects after consuming energy drinks.

Until the submission of corresponding robust studies, on the grounds of preventive health protection BfR advises patients with high blood pressure or heart disease to exercise moderation when consuming energy drinks.

With reference to the current reassessment of energy drinks by the European Food Safety Authority (EFSA) [3], BfR recommends an EU-wide uniform approach for the placing on the market of energy drinks.

3 Reasons

3.1 Prior assessments of energy drinks, also when mixed with alcoholic beverages

BfR and its predecessor Institute have already adopted a critical position on several occasions about the health assessment of energy drinks, also when combined with ethanol. Amongst other things, they recommended information in this respect on the label [e.g. 4, 1]. In each case they based their comments on the current opinions of the Scientific Committee on Food (SCF) from 1999 [5] and 2003 [6]. In this context reference is made to the fundamental opinions of 26 April 2000 [7], 18 March 2002 [1] and 19 August 2003 [4] expressed by BfR and its predecessor institute. In the expert report of 18 March 2002 [1] attention also focused on the reports from Sweden, Ireland and Greece about adverse cardiac and central nervous effects and two fatalities where a possible association was seen between the consumption of energy drinks and alcohol intake or intensive physical activity without a causal relationship being proved. Furthermore, the results of a survey amongst German poison information and treatment centres on the health impairments caused by energy drinks from September 2002 should be mentioned. It is difficult to interpret these findings which include seizures, tachycardia (increased heart rate), cardiac dysrhythmia, rhabdomyolysis (decline of skeletal muscle cells), agitation, hypertonia (high blood pressure), respiratory disorders and psychotic conditions because partly alcohol, medicine and drugs, were also taken in addition to the consumption of energy drinks.

As far as the combined intake of energy drinks and ethanol is concerned, in the above-mentioned expert opinions the possibility of various interactions from the parallel consumption of ethanol, caffeine, taurine and glucuronolactone was considered. Given the influence of the individual components on the same organ system (e.g. central nervous system, cardiovascular system for ethanol, caffeine and taurine) or the similarity of toxicological effects (e.g. diuretic effect of ethanol, caffeine and taurine, reprotoxic and addictive effects of ethanol and caffeine), there could be a synergistic effect of possible toxicological relevance compared to the use of the isolated substances.

Regarding the data on the toxicological assessment of caffeine, reference is made to the expert opinions of 18 March 2002 and 19 August 2003 [1, 4] (cf. also 3.2.5).

The following excerpt from an expert opinion of 24 June 2004 presents the previous level of knowledge on the assessment of energy drinks combined with the intake of ethanol:

"...Regarding the joint intake of caffeine and ethanol and the possibility of resulting relevant synergistic effects concerning diuresis, addiction potential, genotoxicity and carcinogenicity, no experimental or clinical data are known. Only incomplete information, as stated also elsewhere, is available on central nervous interactions [8, 9, 10]. For instance robust studies on the psychomotor and mental parameters which are of decisive importance for safety on the roads and at the workplace are not available. The available contradictory results [11-18] were in some cases the consequence of time differences in administration [9]. It is also assumed that ethanol and caffeine show complex dose-dependent interactions and that for the same test parameter, depending on the dose, they can manifest both potentiating and antagonistic effects [10]. Reliable findings could only, therefore, be obtained if combinations of several doses of both agents were tested in broad dose ranges. These requirements are not met by the studies in which ethanol and caffeine by means of synergistic effects, e.g. increased the reaction time (doses: 150 mg caffeine/person, 2.2 ml ethanol/kg body weight) (80) and reduced the ability of men to concentrate (dose: 300 mg caffeine-sodium benzoate, 30 ml 70%

ethanol) [12]. The last-mentioned study also elucidates how gender-specific the effects and interactions are since the individual substances increased the ability of women to concentrate (whereas they reduced this ability in man) and when administered jointly they had an antagonistic effect in women. In the literature it is pointed out that the dependence of the results not only on gender but also on age, physical and mental state and on the influence of possible withdrawal symptoms after abstinence had not been taken sufficiently into account. For that reason definitive statements on interactions between caffeine and ethanol were premature [10].

It should be noted that from behavioural tests in animals a synergistic effect of the combined administration of ethyl alcohol and caffeine is also known [19, 20]. The cited authors repeatedly warned about a possibly fatal misjudgement by consumers in particular in terms of road and workplace safety that caffeine could reverse or alleviate the relevant effects of alcohol.

Data are available from animal experiments which point to an amplification of embryotoxic ethanol effects through caffeine [21-23]. However, caffeine doses were selected here which are above the level of human exposure. No reliable epidemiological human studies are available. From epidemiological studies BfR does not have any indications that caffeine, when consumed with ethyl alcohol, has a coteratogenic effect. However, this question was not sufficiently examined [24].

Finally, elevated caffeine concentrations were measured in the plasma and serum in various human studies in conjunction with the combined administration of ethyl alcohol and caffeine [16, 25]. This could be the consequence of the reduced metabolism of caffeine caused by ethyl alcohol [25], which is also suspected on the basis of studies in mice [26].

Also the available animal experiments, in which the effects of the joint administration of taurine and ethanol were examined, showed partially agonistic and partially antagonistic impact of taurine on the alcohol-related effects with variations in dose, administration route and regimen [27, 28-37].

For instance, significant interactions were observed in one behavioural test in mice given at the same time ethanol (0, 1.0, 1.5, 2.0 and 2.5 g/kg body weight, applied as a 20%(v/v) solution in distilled water) and taurine (0, 30, 45 and 60 mg/kg body weight) i.p.. Whereas the administration of taurine (30 or 45 mg/kg body weight) led to a reduction in movement activity in the animals given 1.0 g ethanol/kg body weight, the taurine intake (all doses) in animals treated with 2.0 g ethanol/kg body weight led to an increase in movement activity compared to the animals who were given a sodium chloride solution in addition to ethanol [28].

In several animal experiments it was also shown that, depending on the test model, taurine can shorten or prolong the ethanol-induced sleep time [31-37].

There is a suspicion that antagonistic taurine effects are linked to the stimulating effect of taurine on the aldehyde dehydrogenase activities involved in ethanol metabolism [38, 39].

SCF also sees a possible interaction between taurine and ethanol [6]. It points out more particularly that both taurine [40] and ethanol centrally inhibit the release of the antidiuretic hormone (vasopressin). Hence, they could have an additive effect which could lead in the short-term to increased water and sodium loss from the body.

BfR is not aware of any interactions between glucuronolactone and ethanol. Nor does it believe they are likely [6] ..."

By way of summary it can be noted that, as in the previous expert opinions of 18 March 2002 [1] and 19 August 2003 [4], the health assessment of the normal consumption of energy drinks (without added alcohol) already involves several fundamental uncertainties. For instance, the inadequate level of knowledge does not permit at the present time the definition of an upper level for taurine or glucuronolactone up to which daily intake can be considered safe [6]. Furthermore, interactions between caffeine and taurine have not been sufficiently examined [6]. Aside from these uncertainties, in the case of the combined consumption of energy drinks and ethanol, possible additional risks resulting from the insufficiently examined interactions described above between the ingredients of energy drinks and ethanol have to be taken into account. The Scientific Committee on Food (SCF) of the European Commission deems the additive interactions of caffeine and taurine concerning the diuretic effect to be probable. They could be further enhanced by ethanol and could theoretically lead, in conjunction with fluid loss through sweating, to short-term dehydration [6].

Against this back BfR has formulated fundamental concerns about the combined consumption of energy drinks and alcoholic beverages:

- There is a considerable need for research and clarification (e.g. elaboration of action profiles for the individual substances considering high intake levels, studies on the possible interactions between the ingredients with and without the additional effects of alcohol and/or physical activity).
- In addition to the currently prescribed labelling on high caffeine content (Directive 2002/67/EC), information on the packaging of energy drinks about the problems linked to mixing alcohol with energy drink ingredients is recommended.

3.2 New data on the assessment of energy drinks, also when mixed with alcoholic beverages

A literature search was carried out and information was sought from the Swedish sister authority of BfR, the National Food Administration (Statenslivsmedelsverk, Uppsala), about the outcome of planned human studies on the health effects of the consumption of energy drinks. The results of the Swedish studies [41,42], as well as other relevant findings, are presented below.

3.2.1 Swedish study – Cases with severe symptoms possibly linked to energy drinks

In one hospital with a catchment area of approximately 500,000 people, cases of disease and fatalities were observed in which energy drinks consumption is possibly involved [41]. In each of the following four cases the individuals had consumed alcohol and energy drinks:

Case 1: A 19-year-old woman had consumed, one evening in 2000, around six drinks made from Red Bull and vodka with her friends. Around 7 pm she had a meal. According to her friends she did not take any further food or beverages after midnight and was not particularly drunk when she separated from her friends at 3 am. The next morning she was found dead in her bed. She had not left behind a farewell letter or any signs that could be linked to her death.

The forensic examination yielded the picture of a haemorrhagic pulmonary oedema. The forensic analysis was negative concerning medicines, drugs and toxins. In one blood sample

from her thigh 0.87 parts per thousand of ethanol were detected. Aside from these forensic findings no clear cause of death could be established [41].

Case 2: A 31-year-old woman, who had gone dancing with friends one evening in 2001 drank Red Bull and vodka in the course of the evening. Whilst dancing the woman was suddenly no longer responsive and collapsed. Immediate attempts were made to resuscitate here. When the emergency doctor arrived, the patient had a weak pulse in the carotid artery and needed artificial respiration. During transport to hospital her pulse fell out which is why extended heart-lung reanimation was initiated. On arrival at the hospital ventricular fibrillation occurred. 15-fold defibrillation within 20 minutes was not successful.

The forensic examination merely revealed slight connective tissue deposition in the cardiac musculature and a slight fatty liver. 0.63 parts per thousand of ethanol were found in a blood sample from her thigh. Screening for medicaments and drugs proved negative. Aside from the forensic study results, no clear cause of death could be established.

Interpretation: see Case 3.

Case 3: An 18-year-old man had spent a week preparing intensively in summer 2005 for his theoretical driving test. The case history revealed that he had consumed at least a few cans of Red Bull every day "in order to maintain his level of concentration". Together with his friends he was watching television when he suddenly collapsed. Attempts were made by a neighbour, a trained fireman, to resuscitate him. The forensic examination revealed an extensive cerebral oedema, a comprehensive pulmonary oedema and light to moderate connective tissue deposits in the cardiac musculature.

The ensuing examination identified 0.59 parts per thousand of ethanol in the blood from his thigh and 0.80 parts per thousand of ethanol in urine but no signs of drugs or anabolic steroids. The forensic examination could not establish any clear cause of death.

Interpretation of cases 2 and 3:

The forensic examinations identified moderate isolated connective tissue deposits in the cardiac muscles of the deceased patients (cases 2 and 3). It was not possible to determine their genesis but according to the hospital pathologist they were a frequent clinical finding in post-mortem examinations. It was known that connective tissue deposits in the heart are arrhythmogenic [43]. Whether the moderate deposits, which were observed in the described cases, could pose a higher risk of cardiac dysrhythmia, was a question that still had to be answered [41].

Case 4: A 20-year-old man had suffered from epilepsy as a child around the age of 8 but had been free of attacks and had not undergone any treatment since then. He had been admitted to hospital one morning suffering from acute seizures. The case history revealed that the previous evening he had drunk Red Bull and vodka (approximately 35 cl vodka). The ensuing CT examination with a contrast agent and the EEG did not provide any clear explanation.

Interpretation: The authors point out that taurine can lead to hypoglycaemia (very low blood sugar). Seizures were a relatively frequent phenomenon in emergency hospitalisation. In the majority of cases the ensuing examination did not identify any cause. The patient had suffered from an earlier epilepsy in childhood and had consumed alcohol the previous evening. He probably also had a disrupted sleep cycle and perhaps secondary hypoglycaemia with reduced glycogenolysis in the liver. A causal (primary) relationship between taurine and the seizures could, therefore, be deemed to be very unlikely. Theoretically, taurine could lead to

hypoglycaemia *in vivo* with a reduction in the seizure threshold. *In vitro* it could be observed that taurine can bind to the insulin receptors or directly stimulate insulin release in the beta cells [41, 44].

Energy drink consumption not combined with alcohol:

Case 5: A 31-year-old, active football referee who trained regularly went to an outpatient's clinic showing signs of loss of appetite and a poor general condition one week after taking part in a 3,000 m competition. The examination revealed rhabdomyolysis and acute kidney failure with tubular necrosis. The maximum S-creatinine value was 835 $\mu\text{mol/l}$.

At the follow-up examination the patient's health was completely restored and there was no reduction in kidney function. Auto-antibodies and the conventional examination results were normal. The case history revealed that the patient had drunk three cans of Red Bull before the competition.

Interpretation: The authors believe it is conceivable that taurine caused the rhabdomyolysis. The patient had been comprehensively examined without finding an explanation for the rhabdomyolysis. The distance covered by the patient was short compared with his physical capacity. One possible explanation model was that he was relatively dehydrated and had sought to remedy this by consuming 750 ml energy drink. The following could have been considered the possible genesis for the rhabdomyolysis: hyperosmolarity could have contributed, through intracellular accumulation of the taurine without sodium exchange, to major swelling and necrosis (death) of the myocytes (muscle cells) [41].

In the Swedish publication the following study findings were presented within the framework of the discussions:

An open, non-randomised study for 10 patients with chronic haemodialysis ("blood washing"), in which 100 mg taurine/kg body weight/day were administered, had to be abandoned prior to expiry of the 10 weeks before all the patients had been integrated. The reason given was that the patients suffered, amongst other things, from severe dizziness. On average the plasma level of taurine increased by ~ 3,600%. The intramuscular taurine content increased by approximately 295% [45].

Interpretation [41]: Patients with chronic renal insufficiency have low taurine levels both in plasma and intramuscularly [45] which could possibly be of relevance for the muscle weakness, cardiac insufficiency and neurological symptoms which frequently incurred in this group of patients. The accumulation of taurine in patients with chronic renal insufficiency was relevant; haemodialysis would not suffice to regulate the taurine level. The symptoms had receded once taurine intake had been halted. However, renewed administration of half the dose (50 mg taurine/kg/day) led to their reappearance. The authors, therefore, concluded that this group of patients should avoid taurine-containing energy drinks [45].

Lehtihet *et al.* [41] furthermore pointed out that according to information from the National Poisons Information Centre in Ireland (NPIC) 17 cases had been reported between 1999 and 2005 involving two fatalities in conjunction with the consumption of energy drinks. In these cases the symptoms confusion, tachycardia and seizures had been observed. BfR contacted the Irish Centre and asked for information.

Furthermore, the authors discussed [41], with reference to conditions in Japan, a speculative theory about possible associations between sudden unexplained fatalities and a stressful

working life ("Karoshi" in Japanese), moderate alcohol consumption and major taurine intakes. This intake had been established in Japan from the intake of food and folk medicines.

Lehtihet *et al.* [41] discussed the findings in conjunction with the results explained in Chapter 3.2.2 and mainly focused on the amino acid taurine. It is regarded as a conditionally semi-essential amino acid which is involved in various key physiological processes, e.g. as a neuromodulator and transmitter substance in the central nervous system. Its main task is osmoregulation in interaction with sodium, for instance in the myocardium (cardiac muscle), the skeletal musculature and the kidneys. Given that with energy drinks far more taurine is ingested (250 ml dose contains maximum 1000 mg taurine) than with a normal diet (maximum natural intake is estimated to be 400 mg/day [6]), they point to the inadequate level of knowledge about the maximum acceptable daily intake of taurine, its interactions with caffeine and ethanol in conjunction with physical effort or dehydration and about the general safety of energy drinks.

3.2.2 Swedish study on the cardiac impact of energy drinks

10 test persons aged between 19 and 30 were given a) no beverage, b) 750 ml energy drink, c) 750 ml energy drink with 70-110 ml vodka 30 minutes prior to physical activity. In contrast to a) the heart rate variability (HRV) fell with b) and fell even further with c) after consuming the beverage within 30 minutes of commencing physical activity. A lower HRV is seen as an indication of a reduced balance in the heart's nervous system. This correlates with an elevated risk of arrhythmias, which in turn is seen as an elevated risk for sudden cardiac death. The available study could not, however, identify any elevated incidence of arrhythmias. According to the authors the results indicate that, under the above-mentioned exposure conditions, there are elevated risks particularly for individuals with congenital arrhythmias [41, 42].

3.2.3 American study on the cardiac impact of energy drinks

At the "American Heart Association's Scientific Sessions 2007" J.K. Kalus reported on an orientational study concerning the cardiovascular effects of energy drinks which was conducted in healthy test persons (8 women, 7 men) with low blood pressure and an average age of 26 in a state of physical rest [47, 48, 49, 50]. 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 an energy drink (2 cans) containing a total of 80 mg caffeine and 1000 mg taurine. The examinations were repeated half an hour later and after 1, 2, 3 and 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. The researchers noted an increase in systolic blood pressure of 10 mm Hg and an increase in heart rate of 5 to 7 beats per minute in the four hours after consumption of the beverage. No habituation could be determined following several days intake since the effects were slightly enhanced on the seventh day. The ECG revealed a minor prolongation in the QTc time which was not, however, significant. 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 researchers pointed to uncertainties concerning the importance of these findings for the intake of energy drinks in combination with alcoholic beverages or physical activity. In the case of the latter blood pressure and pulse were higher and people with unknown heart problems could be affected [47, 48, 49, 50].

3.2.4 Case reports on the occurrence of central nervous disorders with a possible link to the consumption of energy drinks

Iyadurai and Chung [51]) reported on four patients who suffered generalised cerebral seizures after consuming a high but not after consuming a low dose of energy drinks without there being any reports of parallel alcohol consumption. For instance a healthy 25-year-old man developed generalised cerebral seizures on two occasions with a four-month gap after consuming energy drinks each time on an empty stomach. Prior to this he had never had symptoms of this kind nor did they occur after six months' abstinence from energy drinks. In the case of the last exposure he had consumed 1420 ml (2 x 24 ounces) of an energy drink 30 to 60 minutes prior to the seizure. Two other patients suffering from migraine manifested seizures after energy drink consumption whereby in one case the energy drink was taken on a empty stomach, in the second case in conjunction with the use of caffeine tablets. A fourth patient, who suffered from a seizure for the fourth time, was quoted as saying that he only had seizures when he consumed more than 1420 ml of an energy drink.

The authors reported that none of the patients suffered renewed seizures following abstinence and that the prior seizures had only occurred after consumption of high amounts of an energy drink. Neurological examinations did not reveal any signs of a different cause.

The authors pointed out that taurine shows both anti-convulsive and epileptogenic properties in animal experiments. It is known that caffeine can trigger seizures at high doses and that in epilepsy patients the threshold for the onset of seizures may be lower.

Information was posted on the Internet about the onset of a seizure in a 14-year-old diabetic girl having drunk one can of an energy drink [52].

Attention is drawn to the triggering of a manic episode in a manic-depressive patient after he had consumed three cans of Red Bull on two days with a three-day interval [53].

3.2.5 Prospective cohort study on maternal caffeine consumption

Weng *et al.* [54] recorded in a perspective cohort study involving 1,063 women published in 2008 the course of pregnancy up to the 20th week of pregnancy. They observed that compared to pregnant women with no caffeine intake, the women who were exposed daily to 200 mg caffeine were at increased risk of miscarriage (15% versus 12%) and that the corresponding risk for pregnant women with caffeine intakes of more than 200 mg was considerably higher (25% versus 12%). This result was independent of the type of caffeine-containing preparation.

3.2.6 Current inquiries by BfR to the German Poison Information and Treatment Centres (GIZ) and BVL on notifications of health impairments following the consumption of energy drinks

In January and February 2008 BfR contacted BVL (Federal Office of Consumer Protection and Food Safety) and the German Poison Information and Treatment Centres about reports of health impairments following the consumption of energy drinks. BVL was not aware of any reports of this kind since 2005. Information is currently available from six of the nine GIZ in the Federal Republic of Germany which indicates that a total of 91 reports (double reporting possible) about adverse effects following the consumption of energy drinks between 2001 and 2007 (in some cases shorter reporting periods for individual GIZ) were known. The health impairments were observed in part after consumption of very high levels of energy

drinks and/or combined intake with alcoholic beverages, medicines or drugs. It is not possible to evaluate the findings with a view to identifying causal relations because the summary depiction does not give access to the main details. This also applies to a fatality involving a young adult who died before the emergency doctor arrived. He had consumed unknown amounts of an energy drink and vodka at a party. The spectrum of symptoms described which included stomach pain, high blood pressure, tachycardia (increased heart rate), ventricular fibrillation, visual disorders, seizures and myoclonia (muscular twitching) largely corresponded to what is already known from the available reports.

This situation reveals the need for targeted studies to record the exact circumstances under which energy drinks may possibly lead to adverse effects and also to clarify possible causal relationships.

3.2.7 Interaction between the individual ingredients of energy drinks, and with ethanol: New findings

3.2.7.1 Combination of caffeine and taurine

In a double-blind study 8 female and 6 male students aged between 18 and 23 were either given the placebo or 100 mg caffeine and 1000 mg taurine in tablet form. This was deemed to be a similar intake to a can of Red Bull (80 mg caffeine and 1000 mg taurine). The active substance combination had no effect on short-term memory. It did, however, cause a significant reduction in heart rate (with unchanged blood pressure) 45 minutes after consumption. 70 minutes after consumption the heart rate returned to normal and a significant increase in blood pressure was observed. The authors suspect that the reduction in pulse resulted from blood pressure-induced bradycardia (lowering of the heart rate) caused by caffeine and that this effect was possibly potentiated by taurine [55].

Riesenhuber *et al.* [56] investigated a possible diuretic effect of caffeine in combination with taurine in a blind crossover trial involving twelve male test persons aged between 18 and 28. After a 12-hour liquid fast, they were given 750 ml of one of four energy drink preparations which contained 240 mg caffeine and 3 g taurine or only one or neither of the two components. Urine volume, urinosmolarity and sodium excretion in urine were measured whereby the first two parameters were significantly increased by caffeine and the caffeine-taurine mixture but not by taurine. Overall, it was shown that under the test conditions fluid and sodium excretion was mainly influenced by caffeine in the moderately dehydrated test persons and that there were no related synergistic effects of caffeine and taurine [56].

3.2.7.2 Combination of taurine and ethanol

From experimental studies it is known that taurine and ethanol interact in the central nervous system (CNS) [57]. Both taurine and ethanol have positive allosteric, modulator effects on neuronal ligand-mediated Cl⁻ channels (e.g. GABA_A (gamma-amino butyric acid_A) and glycine receptors) and inhibitory effects on other ligand and tension-mediated cation channels (e.g. NDMA (N-methyl-D-aspartate) and Ca²⁺ channels). Microdialysis studies showed that ethanol increases the extra-cellular taurine concentrations in numerous brain regions whereby the functional consequences are still not clear. It is assumed that the endogenous taurine system is an important modulator of ethanol effects on the CNS [57]. New findings in rats indicate that taurine is an endogenous ligand of the glycine receptors in the nucleus accumbens and that taurine, similar to ethanol, leads to an increase in the dopamine concentration in this region [58]. Given these findings and the fact that the mesolimbic dopamine system is involved in reward-driven behaviour and the onset of dependency, this raises the

question whether the taurine-mediated activation of the mesolimbic, dopaminergic neurons could be linked to the subjective effects of the energy drinks. Given the current unsatisfactory level of knowledge, it is not possible to answer this question. The authors, however, believe it is questionable whether – given the greater difficulties for taurine to cross the blood-brain barrier, sufficient taurine concentrations could be reached in the brain after energy drink consumption in order to activate the dopaminergic neurons. It is uncertain whether the administration of taurine can influence mesolimbic dopamine function, which is altered in the case of alcohol dependency, dependency on other substances, psychoses and manic depression. This needs to be clarified [58].

3.2.7.3 Combination of caffeine and ethanol

Given the new trend amongst young people in various countries of consuming caffeinated alcohol (e.g. energy drinks mixed with vodka or caffeinated beers) [59], various research groups examined the question whether the popular belief is correct that the intake of energy drinks or caffeine can reduce the central nervous depressing effects of alcohol [59-68]. By way of summary from the study results, the conclusion can be drawn that the co-administration of caffeine, also as an ingredient in energy drinks, reduced the consumer's awareness of alcohol intoxication compared to awareness in conjunction with isolated alcohol intake. More particularly, the relevant alcohol-related impairments for safety at the workplace and when driving were not compensated by the effects of caffeine [e.g. 59, 60, 62, 64, 65]. The resulting estimations of the researchers that for instance "... the person is drunk but does not feel as drunk as he really is" [67-69] or the described misinterpretation of an alert state of mind despite alcohol consumption as being sober [61, 62] revealed the risk of misjudgements (e.g. of psychomotor skills) linked to the consumption of alcohol-containing energy drinks/caffeinated beers.

Ferreira *et al.* [59] examined for instance the effects of Red Bull (dose corresponded to one can of 250 ml/70 kg person) or vodka (dose of 2.5 or four standard drinks equivalent to 0.6 or 1.0 g ethanol/kg body weight) as isolated intake and as a mixture with the taste unchanged through fruit juice in 26 male test persons aged between 23 ± 3 years in a double-blind study. The test persons' awareness of headaches, weakness, dryness of the mouth and subjectively perceived motor co-ordination in conjunction with the intake of alcohol-containing energy drinks was reduced compared with isolated alcohol consumption. The objective measurements of motor co-ordination and visual reaction time revealed that the addition of energy drinks could not compensate for the worsening motor co-ordination and visual reaction time caused by alcohol.

The evaluation of a survey of 4,275 students at 10 universities in North Carolina revealed that students who consumed alcohol together with energy drinks, had a two-fold higher risk of alcohol-related damage and consequences (e.g. in respect of injuries, sexual exploitation and misjudgements of ability to drive) than those who drank alcohol without mixing this with energy drinks [66-68].

3.2.8 Reassessment of energy drinks by the European Food Safety Authority (EFSA)

EFSA is currently involved in updating its assessment of ingredients in energy drinks [3]. This was prompted by the new animal experiment data on taurine and glucuronolactone submitted by one of the leading market manufacturers of energy drinks. Based on the existing SCF assessments of energy drinks [3, 6], the European Commission asked EFSA to undertake a reassessment [3]. This request was made against the backdrop that following fatalities in Ireland and Sweden, energy drinks are currently banned in France, Denmark and Norway

(not an EU Member State) and that the French import ban has been upheld as being in conformity with Community law by the European Court of Justice [cf. 2].

3.3 Update of the risk assessment of energy drinks, also when mixed with alcoholic beverages

In view of the two fatalities and the adverse effects in connection with the consumption of energy drinks, the cause of which had not been established, the BfR expert opinion of 18 March 2002 [1] reported on the growing suspicion that the safety of energy drinks under the preconditions and circumstances under which they are possibly drunk mainly by young consumers should in principle be called into question. Against this background possible options were discussed for risk reducing measures which should be included in the deliberations on a uniform EU-wide approach. Besides the proposed additional information on product labels, reducing the concentration of the main ingredients in the energy drinks and the suspension of approval for energy drinks were also considered.

The recent fatalities that emerged from Sweden (3.2.1) and further reports about serious adverse effects (3.2.2 up to 3.2.4) substantiate the existing suspicion - where the causal relationship is still unclear - that under certain circumstances energy drinks could pose major health risks.

It is noticeable that further deaths have been reported in conjunction with combined energy drink and alcohol consumption. Also after the consumption of energy drinks in conjunction with physical activity a renewed case was observed of a severe acute disorder (rhabdomyolysis with renal failure, cf. 3.2.1). Indications of a possible interaction between the energy drink ingredient taurine and ethanol are also of interest (3.2.1 and 3.2.7.1).

Further research about the observed cardiac findings in healthy test persons is deemed to be necessary. There is also a need to clarify whether risk groups can be identified with specific clinical pictures. The question should be asked whether the consumption of energy drinks could pose a potential health risk for patients suffering from high blood pressure, arrhythmias or other heart disorders, (cf. 3.2.2., 3.2.3, 3.2.7.1.). Furthermore, there have been cases in which cerebral seizures were observed after the intake of larger amounts of energy drinks. Here the question should be raised whether, for instance, epileptics and diabetics could run a higher risk of adverse effects (cerebral seizures and lowered blood sugar, respectively) as a consequence of high energy drink consumption. There is also a need to elucidate the extent to which adverse effects, like central nervous seizures, are the result of hypoglycaemia caused by the action of taurine. This could play a part in the seizures suffered by a 14-year-old diabetic (3.2.4). In this context it should be pointed out that hypoglycaemia can be a symptom of elevated alcohol intake.

Finally, the question should be examined whether patients suffering from renal insufficiency (3.2.1), migraine (3.2.4) or mental disorders (3.2.4) must also be considered as highly sensitive risk groups for energy drinks.

The recommendation made in the BfR report of 18 March 2002 [1] about the need for research is upheld and should be supplemented with the topical questions presented above.

The updating of data reveals the importance of the recommended special information on the product label. In this context the results of the Swedish study (3.2.1) support the indications of possible adverse effects from the combination of the consumption of larger amounts of energy drinks together with extensive physical activity or alcoholic beverages. Concerning

the indications of not recommending these beverages, particularly in larger amounts, for children, pregnant women, lactating women and individuals who are sensitive to caffeine, reference is initially made to the statements in earlier BfR opinions, for example from 19 August 2003 [4]. In that opinion BfR in principle advised that caffeine intake should be restricted during pregnancy. Based on the available epidemiological data it had been recommended up to now that – with a view to the risks of spontaneous abortion, premature delivery and intrauterine growth retardation - the daily dose should be lower than 300 mg caffeine/person. Bearing in mind current findings (cf. 3.2.5) it is now recommended that the daily dose should be less than 200 mg caffeine/person. As already indicated in earlier expert reports, children are also seen as a risk group who could react highly sensitively to caffeine [4]. Findings are available which indicate that increased excitability, nervousness or anxiety were observed at a dose of 5 mg/kg body weight. Attention is drawn to the lack of information on the long-term effects of caffeine intake in children.

Given the cardiovascular effects of energy drinks described in Chapters 3.2.2, 3.2.3 and 3.2.7.1, BfR advises that until clarifying studies are available, patients with high blood pressure or cardiovascular diseases should be advised to exercise restraint when consuming energy drinks on the grounds of preventive health protection.

These recommendations reflect the situation that energy drinks are a special category of caffeine-containing beverages which not only contain caffeine but also other ingredients in high concentrations. Furthermore, the interaction between all the components has not been sufficiently researched.

The results of more recent studies (3.2.2) and new mechanistic findings on possible interactions between ethanol and taurine in the central nervous system (3.2.7.2) substantiate the concerns formulated in the report of 26 April 2000 [7] about the joint intake and joint marketing of energy drinks and alcoholic beverages. However, the available data are still not complete and do not permit any dose-related statements.

4 Recommended measures

Consumer information

In addition to the currently prescribed labelling requirements on high caffeine content (Directive 2002/67/EC) and given the updated data on the questionable safety of energy drinks, BfR reiterates its existing recommendation on the grounds of preventive health protection "that

- adverse effects cannot be ruled out when larger amounts of these beverages are consumed in conjunction with intensive physical activity or with the intake of alcoholic beverages,
- beverages of this kind, particularly when consumed in larger amounts, are not recommended for children, pregnant women, lactating women or individuals who are sensitive to caffeine."

Firstly, as a result of this consumers would be distinctly informed about the possible occurrence of "adverse effects" under the described conditions. Secondly, children, pregnant women and lactating mothers would also be advised about this. They are deemed to be groups who require special protection and for whom possible health risks as a consequence of exposure to caffeine and other energy drink components are relevant [e.g. 4, 54]. Finally,

individuals who are sensitive to caffeine would also be informed. This group also includes patients with arrhythmias or mental disorders. They must be considered as particularly sensitive risk groups for the effects of energy drinks.

Attention must be drawn to the risk of confusing the designation "energy drink" with carbohydrate-containing sports beverages. The latter supply calorific energy, are consumed in larger amounts in conjunction with intensive physical activity and are, therefore, associated with the consumer conditions which are specifically contra-indicated for energy drinks (3.2.1). The risk of misinterpreting the term "energy drink" is also highlighted by the categorisation used in the KIGGS Consumption Study on Children's and Adolescents' Health [70], in which "sports and energy beverages" are both included in the category "energy drinks".

As is the case for other foods with pharmacologically active ingredients, the question is also raised in conjunction with energy drinks about how to convey comprehensive risk relevant information which reflects the possible special health sensitivity of certain consumer groups. The additional mention of an official Internet address, telephone number and address on the food label could mean that the consumers could access in a targeted manner information pages cleared by authorised offices. This had already been mentioned in the BfR expert opinion of 17 February 2005 [71] using the example of quinine-containing bitter drinks.

Recommendation of an EU-wide harmonised approach

BfR believes there is a need for an EU-wide harmonised approach that reflects the current data situation. This could encourage EU-wide data matching and lead to the emergence of new findings about consumer groups who may be particularly sensitive to energy drinks. As far as exposure is concerned, it is pointed out that in the SCF expert report [6] which is still valid, reference was made to the unit of 250 ml cans for energy drinks which had been the norm up to then whereas far larger packs are now sold internationally.

Attention is also drawn to the ongoing need for research on the possible adverse effects of energy drinks in humans. In this context an EU-wide harmonised procedure is desirable.

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