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Children and adolescents: Excessive consumption of energy drinks increases health risk for cardiovascular system

BfR Opinion No. 018/2019 of 27 May 2019

In addition to other ingredients, energy drinks contain caffeine, usually in quantities of 80 milligrams (mg) per 250 millilitre (ml) can. In moderate quantities, caffeine can have a positive effect, such as enhancing attention levels. High doses, on the other hand, can have undesired effects, such as nervousness, insomnia, gastrointestinal complaints, palpitations and increased blood pressure.

The European Food Safety Authority (EFSA) derived safe caffeine quantities for healthy people in 2015. According to EFSA, individual caffeine doses of up to three mg caffeine per kilogram (kg) body weight, i.e. roughly 200 mg are still of no health concern for adults. For habitual consumption, up to 5.7 mg per kg body weight, or around 400 mg, are regarded as of no concern for healthy adults. According to EFSA, children and adolescents should in general not ingest any more than a total of three mg caffeine per kg body weight per day.

A study commissioned by the German Federal Institute for Risk Assessment (BfR) in 2013 on the consumption of energy drinks on special events showed that visitors to dance clubs, music and sports events, as well as participants in computer game parties, consume in part considerably more than one litre of pure energy drink or mixed with alcoholic beverages.

For this reason, using the latest studies as the basis, the BfR assessed the effects of energy drinks on the cardiovascular system depending on the dose. In order to estimate the health risk, studies with various influencing factors on the cardiovascular system (intervention studies) were observed along with studies on the consumption of energy drinks. Only intervention studies were included which focused on the acute effect of energy drinks, i.e. within up to three hours, in young, healthy adults. Intervention studies with children and adolescents or with the longer-term administration of energy drinks were not available.



The evaluation shows that acute, moderate consumption of energy drinks with caffeine intake levels still regarded as of no concern by EFSA does not lead to any undesired effects in healthy young adults. In the view of the BfR, the moderate consumption of energy drinks does not therefore pose a health risk to healthy adults.

When energy drink quantities of one litre or more were drunk, thereby exceeding the caffeine intake quantity still regarded as of no concern, moderate to severe undesired effects such as palpitations, shortness of breath, uncontrolled muscle tremors, severe nausea, anxiety, nervousness and changes in the electrocardiogram were observed in some young adults.

Surveys of energy drink consumption habits show that in particular a substantial percentage of children and adolescents in Germany consume large quantities of energy drinks of one litre or more on certain occasions. By doing so, this group exceeds the caffeine intake quantity still regarded as of no concern by EFSA. Consequently, in the view of the BfR, these children and adolescents should be seen as a risk group for which increased health risks can result, especially for the cardiovascular system. It is possible that accompanying factors, such as additional alcohol consumption and strenuous physical exercise, can intensify the

undesired effects of caffeine and that children and adolescents are probably not sufficiently aware of this.

The BfR therefore recommends to expand information and education in order to counteract the excessive consumption of energy drinks by children and adolescents.

 BfR Risk Profile: Excessive consumption of caffeine-containing energy drinks by children and adolescents increases the risk for the cardiovascular system (Opinion No. 018/2019)					
A Affected groups	Children and adolescents 				
B Probability of a health impairment through excessive intake of energy drinks	Practically excluded	Unlikely	Possible	Probable	Certain
C Severity of health impairment through excessive intake of energy drinks [1]	No impairment	Slight impairment [reversible]	Moderate impairment [reversible]	Severe impairment [reversible/irreversible]	
D Reliability of available data	High: The most important data are available and free of contradiction	Moderate: Several important data are missing or contradictory		Low: Numerous important data are missing or contradictory	
E Controllability by the consumer [2]	Control not necessary	Controllable through precautionary measures	Controllable through intake quantity	Not controllable	

Squares highlighted in dark blue indicate the properties of the risk assessed in this opinion (more detailed information on this is contained in BfR Opinion No. 018/2019 of 27 May 2019).

Explanations

The risk profile is intended to visualise the risk outlined in the BfR Opinion. It is not intended for the purpose of comparing risks. The risk profile should only be read in conjunction with the corresponding opinion.

[1] Line C – Severity of the health impairment:

The severity of the impairment can vary depending on the intake quantity and sensitivity in particular to caffeine.

[2] Line E – Controllability by the consumer:

The information given in the square “Controllability through intake quantity” should not be regarded as a recommendation from the BfR; it has a purely descriptive character.

1 Object of the assessment

On the basis of the latest available studies, the German Federal Institute for Risk Assessment (BfR) assessed the effects of energy drinks on the cardiovascular system depending on the dose. To assess the risk both human studies with cardiovascular endpoints (intervention studies), as well as studies on consumption behaviour with regard to energy drinks were taken into account.

The topic, including further research requirements, was already discussed by a panel of experts on 26 April 2017 and further processed once again. The BfR has already published a communication on the expert discussion itself on the BfR homepage (BfR, 2017).

2 Result

The BfR has evaluated the current study situation since the EFSA assessment on the safety of caffeine in 2015 (EFSA, 2015) with regard to the risk assessment of caffeine intake from energy drinks in Germany. The background to this was that, especially with energy drinks, there were still open questions relating to additional cardiovascular parameters that had to be considered, to exposure to these drinks in Germany and to the specification of risk groups. The BfR concludes as follows in this regard.

Effects of energy drinks on cardiovascular parameters

Under consideration of new literature and mode of actions that have not been evaluated by EFSA up to now (e.g. the potential inotropic effects of energy drinks and the effect of energy drinks on the QTc interval), the EFSA assessment from 2015 calculating that acute intake of up to 200 mg (milligrams) of caffeine – also in the form of energy drinks with other ingredients – does not pose a health risk to healthy adults, remains valid in the view of the BfR.

Moderate acute consumption of energy drinks

Under consideration of the current scientific data situation, the BfR concludes that acute moderate consumption of energy drinks with caffeine intake levels which do not exceed the intake quantity still regarded as safe by EFSA does not pose a health risk to healthy adults.

The BfR points out, however, that persons with a predisposition for e.g. certain heart diseases could react much more sensitively to caffeine intake (Gray et al., 2017).

In relation to moderate acute consumption by children and adolescents, there are no indications that the caffeine intake quantity regarded by EFSA as of no concern for healthy children and adolescents poses a health risk as an ingredient in energy drinks, but there are some knowledge gaps here which prevent a conclusive assessment at the moment. According to Regulation (EU) No. 1169/2011, energy drink products containing more than 150 mg of caffeine per litre must bear the warning: “*High caffeine content. Not recommended for children or pregnant or breast-feeding women*” in the same field of vision as the name of the beverage, followed by an indication in brackets of the caffeine content expressed in mg per 100 millilitres (ml).

High acute consumption of energy drinks

Health risks can result from acute excessive consumption of energy drinks. In intervention studies with healthy young adults in which energy drink quantities were administered as an acute single dose which led to the exceedance of the caffeine intake quantity still regarded as of no concern by EFSA, moderate to severe undesired effects such as palpitations, shortness of breath, severe tremors, severe nausea, anxiety and nervousness were observed in some participants (Section 3.5.2). Moreover, significant extensions of the QTc interval were observed in some intervention studies in healthy young adults who had been given energy drink quantities of 1 litre (Section 3.5.1.3).

In the view of the BfR, in particular children and adolescents who ingest caffeine quantities of health concern due to acute energy drink consumption on certain occasions could be defined as a risk group.

It can be seen from surveys that a substantial proportion of children and adolescents in Germany (17% of the consumers of energy drinks and 10% of all respondents) stated that they consume excessively high quantities of energy drinks (one litre and more) during a single session with an exceedance of the caffeine intake quantity that is still regarded as safe. Therefore, for this group of children and adolescents health risks for adverse effects can result, especially with focus on the cardiovascular system.

Some adults also drink such high quantities (1 litre and more) during a single session, but the percentage of adults with these consumption habits is lower (5% of all respondents).

The BfR study on the event-related consumption of energy drinks showed that awareness of the problem of the possible health risks posed by acute, excessive consumption of energy drinks, especially in combination with intensive physical exercise or alcohol consumption, was low or not sufficiently well pronounced among adolescents and young adults. The BfR is therefore assuming that also children and adolescents in general are unaware of the risks of excessive consumption of these drinks – especially in combination with intensive physical activity and/or high alcohol consumption – or that these population groups have not been adequately informed about the potential risks of excessive energy drink consumption.

As already reported in the results of the experts' discussion of 26 April 2017 (BfR, 2017), the BfR recommends the minimisation of the possible risk of acute excessive consumption identified for children and adolescents. Awareness of the risks of the excessive consumption of energy drinks by children and adolescents could be enhanced by target group-specific measures in the area of health education and health promotion, in order to prevent health risks and support independent actions towards a health-promoting lifestyle. Educational programmes could be developed to sensitise children, adolescents, teachers and parents with regard to the potential risks connected with this kind of consumption behaviour. Social media in particular could be used here, as these are used more intensively by children and adolescents than traditional media. In addition to the educational measures already provided (information flyers, videos, website with caffeine counter) on the Federal Centre for Nutrition (BZfE) homepage, it is recommended that sensitisation campaigns of this kind be intensified and expanded, especially in schools where the actual risk groups can be reached, in order to achieve a more sustainable effect.

With a view towards the identified undesired effects of high intake quantities of caffeine or energy drinks (sections 3.1.3, 3.5.1.3 and 3.5.2) which can occur even in healthy young adults, further-reaching measures with the goal of preventing the possible excessive consumption of energy drinks by children and adolescents in particular could also be considered if necessary.

Chronic consumption of energy drinks

The experts who participated in the panel discussion at the BfR on 26.04.2017 agreed that it cannot be excluded that a chronically very high caffeine intake e.g. through the consumption of more than 1 litre of energy drinks per day, could favour the development of cardiovascular disorders among children and adolescents in the long term too. It was established here,

however, that no studies have been conducted up to now which examine interrelationships of this kind in detail, with the result that no sound scientific knowledge is available in this regard. As can be seen from the BfR report (BfR, 2017), ideas on the significance of future studies which could contribute more information to this subject have been discussed. As intervention studies on this involving children and adolescents could not be justified from an ethical point of view, human observation studies, animal studies and *in-vitro* studies with cardiomyocytes were discussed. With regard to human observation studies, one participant suggested that the extent of caffeine and/ or energy drink consumption should be recorded together with cardiological parameters, such as blood pressure and left ventricular myocardium thickness, in a students' collective in order to examine whether habitually high caffeine or energy drink consumption could be associated with the corresponding cardiological changes. There was controversial discussion about the expense and effort required here, especially under consideration of the number of study participants required to conduct human observational studies of this kind with the goal of obtaining reliable results. It was noted that it is difficult to make causal relationships in studies of this kind but that they could nevertheless contribute towards the examination of possible connections.

With regard to the risk to children and adolescents that could be induced by the chronic high consumption of caffeine from energy drinks, the BfR concludes that this risk is not currently quantifiable. There is no reliable exposure data which shows how high the percentage of the German population or possible risk groups could be which chronically consumes such high quantities of energy drinks that the caffeine quantity still regarded as of no concern by EFSA is exceeded. National representative data collected over 10 years ago is better suited for determining chronic caffeine intake from traditional caffeine-containing foods such as coffee, tea and chocolate, in the view of the BfR, as it is not to be assumed that the presence of these products in the German market and their consumption over the last 10 years has changed to any great extent. With energy drinks, however, it has to be assumed that they currently have a stronger market presence than they did 10 years ago (Statista, 2017). In addition to this, other possible circumstances in several consumption studies (recovery of energy drinks in the NVS II survey, age group considered in the *Comprehensive European Food Consumption Database* on the basis of the EsKiMo study) could lead to the underestimation of caffeine intake from energy drinks.

When planning the case numbers in a study to examine the risks of chronically high caffeine intake from energy drinks, however, it would be of great importance to know how large the percentage of the population is which regularly consumes caffeine in quantities which are possibly of health concern. Valid case number planning is necessary to obtain statistically sound results on the one hand and to plan resources in the proper manner on the other. For reasons of proportionality, the BfR therefore recommends that valid exposure data on chronic caffeine intake quantities from energy drinks should be collected initially. This could be done on the basis of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS Welle 2) for example (RKI, 2017). On the basis of the exposure data some thought could then be given to other possible studies.

3 Justification

Energy drinks are caffeinated soft drinks, which in Germany according to § 4 (2) of the Fruit Juice and Soft Drink Regulation (FrSaftErfrischGetrV) may contain one or more of the substances listed in Appendix 8 Part B, in addition to caffeine with a maximum content of 320 mg/l in ready-to-eat food. Accordingly, ready-to-eat food may contain taurine up to a maxi-

mum of 4,000 mg/l, glucuronolactone up to a maximum of 2,400 mg/l and inositol up to a maximum of 200 mg/l.

In the following, potential ingredients are evaluated individually followed by the energy drinks as a whole.

3.1 Caffeine

Caffeine (1,3,7-trimethylxanthine) is a natural alkaloid found naturally in coffee beans, tea leaves, cocoa beans, and many other plants (Nawrot et al., 2003). In addition, caffeine is added to a variety of different foods, e.g. baked goods, ice cream, sweets, cola drinks and energy drinks. The European Food Safety Authority (EFSA) views the following positive effects of caffeine as being proven: "Caffeine helps improve alertness and concentration and contributes to increased performance endurance" (EFSA, 2011a; EFSA, 2011b)¹. The fulfilment of so-called health claims (Regulation (EC) No. 1924/2006), which EFSA assessed as positive, refers to the intake of a certain amount of caffeine by persons of a defined target group. For example, the data for increased alertness and concentration are linked to an intake of at least 75 mg of caffeine, with the target group being healthy adults.

3.1.1 Mode of action

The effects of caffeine are mainly based on antagonistic activity at the adenosine A₁ and A₂ receptors (Fisone et al., 2004, Ferre, 2008). The neuromodulator adenosine is said to have a sleep-promoting effect, i.a. it inhibits the release of glutamate and dopamine, which are thought to contribute to increased cortical activity or motor neuron activity (Ferre, 2010). The alertness-inducing effect of caffeine is mainly due to the fact that by binding to the adenosine receptor, caffeine prevents the interaction of adenosine with its receptor, which in turn causes an increased release of glutamate and dopamine and a stimulating effect can develop (Ferre, 2010; Nieber K., 2007). Caffeine thus acts differently than cocaine, which directly inhibits the re-uptake of dopamine (Lane et al., 2014). Caffeine is also thought to increase plasma concentration of adrenaline and norepinephrine (Riksen et al., 2009). Caffeine tolerance may develop after repeated intake, but this is not the case for all caffeine effects. Tolerance to caffeine effects on blood pressure and heart rate develops within days, and is associated with decreased caffeine-induced adrenaline, noradrenaline and renin release (Fredholm et al., 1999). The mechanism of tolerance development is not yet fully understood, but it is argued that this may be due to increased expression of adenosine receptors (Ammon, 1991; Fredholm et al., 1999).

Withdrawal symptoms that may occur with caffeine abstinence after regular high caffeine intake include headaches, fatigue, decreased activity/energy, decreased attention, drowsiness, decreased satisfaction, depressed mood, difficulty concentrating, irritability, and a "fogged" condition (Juliano and Griffiths, 2004).

¹ To date, these *health claims* that have been positively assessed by EFSA have not yet been approved by the EU Commission (as of June 2018).

3.1.2 Bioavailability, Distribution and Elimination

According to EFSA, studies show that caffeine is quickly and completely absorbed after ingestion (Blanchard and Sawers, 1983) and then freely crosses the blood-brain, placental and blood-testes barriers (Weathersbee and Lodge, 1977; Arnaud, 1993). In the human liver, caffeine is metabolised mainly to paraxanthin (70-80%), which is then further degraded and excreted via the kidneys. Paraxanthin is metabolised by the cytochrome P450 monooxygenase CYP1A2, which contributes to 95% of caffeine clearance (Berthou et al. 1991; Miners and Birkett, 1996).

In adults, caffeine has a plasma half-life of 2 to 8 hours (Knutti et al. 1981; Abernethy and Todd, 1985; Abernethy et al., 1985; Balogh et al., 1995).

Pregnant women have an increased plasma half-life for caffeine, which can reach up to 18 hours at the end of pregnancy in non-smoking women (Aldridge et al., 1981). The increased caffeine half-life in pregnant women is explained by the ability of estrogens and progestins to inhibit CYP1A2 activity (Rietfield et al., 1984; Abernethy et al., 1985; Balogh et al., 1995).

Since neither the foetus nor the placenta can metabolise caffeine, foetuses from women who consume caffeine are exposed to caffeine for a longer period (Grosso et al., 2006).

Even neonates still have no relevant CYP1A2 activity and therefore show a caffeine half-life of 50 to 103 hours (Ginsberg et al., 2004; Grosso et al., 2006). The half-life for caffeine, however, decreases drastically with increasing months of life. It drops to 14 hours in the third to fourth months and to 2 to 3 hours in the fifth to sixth months (Aranda et al., 1979). During childhood, the caffeine half-life remains stable at 2 to 3 hours, then increases again in adolescents and adults (NNT, 2008).

3.1.3 Adverse Effects

The hazard potential of caffeine has been intensively and extensively studied and illustrated in numerous publications (EFSA, 2015; Nawrot et al., 2003; Wikoff et al., 2017).

Accordingly, the known undesirable effects of caffeine, which may potentially occur depending on the dose absorbed or the individual sensitivity, are i.a. nervousness, increased anxiety, excitability, insomnia, gastrointestinal distress, increased diuresis, increased respiration, elevation of body temperature, arrhythmias, tachycardia, increased blood pressure, reduction of myocardial blood flow and reduced foetal growth in pregnant women (EFSA, 2015, Nawrot et al., 2003; Wikoff et al., 2017).

3.1.4 Caffeine Intake of no health concern

The most important evaluations of international expert committees and the relevant aspects addressed therein are summarised below.

EFSA (2015)

The EFSA Opinion on the safety of caffeine was published in 2015 (EFSA, 2015). The Opinion addressed possible adverse health effects of acute and habitual consumption of caffeine from all sources within the healthy, general population. The possible undesirable effects of caffeine on the health of particularly sensitive populations, e.g. people with certain pre-existing medical conditions or people who take certain medicines and/or drugs in combination with caffeine or consume large amounts of alcohol, were not considered.

The EFSA concluded that for healthy adults, single doses of caffeine of up to 200 mg or the same amount within a short time (equivalent to 3 mg/kg bodyweight (bw)) from all sources do not give rise to safety concerns, even if the caffeine intake occurs less than two hours before intensive physical activity under normal (environmental) conditions. According to EFSA, intake up to this amount is unlikely to produce clinically relevant changes in blood pressure, myocardial blood flow, hydration status or body temperature (EFSA, 2015).

For habitual caffeine intake, EFSA provided a healthy intake of up to 400 mg (equivalent to 5.7 mg/kg bw) throughout the day for healthy adults.

According to the EFSA Opinion, a habitual caffeine intake of up to 200 mg throughout the day is harmless for the foetus and breastfed child in pregnant women and nursing mothers respectively. For nursing women, a single dose of 200 mg is also harmless for the child (EFSA, 2015).

In its Opinion, EFSA points out that the data available for children and adolescents regarding the relationship between caffeine intake and health effects are insufficient to derive a safe intake level (as an acute single dose or for habitual consumption throughout the day). However, EFSA concludes that a single-dose acute caffeine intake of 3 mg/kg bw, which is of no health concern for adults, can also be considered harmless for children and adolescents since the rate at which children and adolescents metabolise caffeine is at least equal to that of adults. For the habitual caffeine intake of children and adolescents, EFSA also suggests a safety level of 3 mg/kg bw per day.

Health Canada (2003)

In 2003, *Health Canada* published derived safe caffeine intake levels (Nawrot et al., 2003). *Health Canada* concluded that a moderate daily caffeine intake of up to 400 mg per day for the healthy adult population is not associated with adverse effects such as general toxicity, cardiovascular effects, effects on bone status and calcium balance, changes in adult behaviour, increased incidence of cancer and effects on male fertility. According to *Health Canada*, the data also showed that women of reproductive age and children are "at risk" groups, for which specific recommendations for reducing caffeine intake should possibly apply. It was recommended that women of childbearing age should not consume more than 300 mg caffeine per day and children not more than 2.5 mg/kg bw per day. In a recent systematic review (Wikoff et al., 2017) on the adverse effects of caffeine which compares the results with those that *Health Canada* still considers to be safe caffeine doses, the authors conclude that those values derived by *Health Canada* for healthy adults continue to be valid. According to the authors, there is also evidence that up to 300 mg of caffeine per day is not associated with adverse reproductive and developmental effects in healthy pregnant women. For children and adolescents, the authors point out that there are either no data or insufficient data for the various endpoints to draw conclusions, but there is no evidence to suggest that *Health Canada's* recommendation (2.5 mg/kg bw per day) needs to be changed.

US-American Dietary Guidelines Advisory Committee (DGAC) (2015)

In its 2015 caffeine and coffee consumption assessment, the DGAC concluded that there is strong evidence that moderate coffee consumption (3 to 5 cups per day, or 400 mg of caffeine per day) is not associated with an increased risk of the most important chronic diseases, e.g. cardiovascular disease, cancer or premature death in healthy adults (DGAC, 2015). In addition, there is consistent empirical evidence that moderate coffee consumption is associated with a reduced risk of type 2 diabetes, cardiovascular disease, liver and endometrial cancer. The estimation of harmless caffeine levels with regard to cardiovascular diseases, e.g. stroke, heart failure, and hypertension were assessed by meta-analyses, which were mainly based on prospective cohort studies with heterogeneous caffeine sources. Intermediate endpoints, e.g. blood pressure, blood lipids and blood glucose was assessed by meta-analyses using randomised controlled trials.

According to DGAC, there is little evidence for health effects of very high caffeine intake (>400 mg per day in adults, not defined in children and adolescents). The Committee notes, however, that initial signs based on case reports of adverse effects associated with the consumption of high-caffeine beverages point to a potential risk. As long as safety has not been established, the DGAC (as well as the *American Academy of Pediatrics* and the *American Medical Association*) advocates limited or no consumption of beverages or other products with a high caffeine content for vulnerable population groups, including children and adolescents (DGAC, 2015).

3.2 Taurine

Taurine (2-aminoethanesulfonic acid) is a nutrient found naturally in foods, particularly in seafood and meat, and also occurs as an endogenous metabolite in humans. In the human body, taurine is produced as a metabolic end product mainly from the amino acid cysteine in the liver. Normal dietary intake varies between 10 and 400 mg per day (EFSA, 2009). Taurine occurs in particularly high concentrations in the heart and skeletal muscle (Schaffer et al., 2010).

3.2.1 Health Effects of Taurine

3.2.1.1 Effect on Blood Pressure

In several studies, taurine has demonstrated hypotensive activity in hypertensive animal models (Abebe and Mozaffari, 2011; Hano et al., 2009; Nara et al., 1978; Sato et al., 1987; Trachtman et al., 1989). A randomised, double-blind, placebo-controlled human trial also showed similar results (Sun et al., 2016). In this study, 120 pre-hypertensive individuals (ages 18 to 75) received either 1.6 g taurine per day or a placebo for 12 weeks. Taurine significantly reduced ambulatory 24-hour blood pressure, especially in those with normally high blood pressure. Outpatient systolic blood pressure was reduced by 3.8 mmHg in the taurine group, whereas only 0.3 mmHg was measured in the placebo group. Outpatient diastolic blood pressure decreased by 3.5 mmHg in the taurine group and only by 0.6 mmHg in the placebo group.

3.2.1.2 Effect on Calcium Homeostasis and Muscle Contraction

In particular, it is discussed that taurine participates in calcium homeostasis in muscles. Therefore, it has been shown that physiological taurine concentrations increase the isometric force in skinned muscle fibre preparations from porcine atrial and ventricular myocardial cells, as well as in crustacean slow abdominal musculature. It was assumed that this is due to an increased Ca^{2+} sensitivity of contractile myofilaments (Galler et al., 1990). Furthermore, based on studies on skinned tissue samples from rat hearts, it has been suggested that taurine interacts directly with the sarcoplasmic reticulum and that taurine enhances caffeine-induced contraction (Steele et al., 1990). In human skinned *vastus lateralis* muscle fibre preparations biopsied from 11 healthy individuals, taurine increased the uptake of Ca^{2+} into the sarcoplasmic reticulum in both type 1 and type 2 fibres (Dutka et al., 2014). In another study, taurine treatment of skinned muscle fibres of the *extensor digitorum longus* of rats significantly increased the depolarisation-induced response strength. Increased Ca^{2+} accumulation in the sarcoplasmic reticulum as well as enhanced taurine-induced Ca^{2+} release were also reported, suggesting that taurine interacts with the Ca^{2+} release channels. Furthermore, taurine was shown to increase both the peak and rate of caffeine-induced response strength (Bakker and Berg, 2002).

3.2.1.3 Effect on Myocardial Contractility

In a double-blind *cross-over* study, 13 trained endurance athletes received either (a) a 500 ml placebo drink 40 minutes before training (energy drink without taurine, without glucuronolactone, without caffeine, with glucose (10.5 g), with sucrose (43 g)) or (b) a 500 ml control drink (energy drink without taurine, without glucuronolactone, with caffeine (160 mg), with glucose (10.5 g), with sucrose (43 g)) or (c) the 500 ml Verum drink (original energy drink with taurine (2,000 mg), with glucuronolactone (1.2 g), with caffeine (160 mg), with glucose (10.5 g), with sucrose (43 g)) (Baum and Weiss, 2001). The placebo and control drinks were made by the energy drink manufacturer similarly to the original drink, but without the above components. Echocardiographic examinations were performed before consumption of the beverage, 40 minutes after consumption of the drink, immediately before the exercise (cycling) and in the regeneration phase after cycling.

Heart rate increased significantly in all three intervention groups after workout, likely due to athletic activity. However, after "drink and training", only the verum group exhibited a significant increase in *fractional shortening* as well as a significant reduction in left ventricular end-systolic diameter (LVESD) was observed. Because these ventricular effects were not observed in the placebo and caffeine groups, the authors believe that the combination of taurine and caffeine in the original energy drink increases left ventricular contractility of the heart (Baum and Weiss, 2001). It should be noted, however, that a drink with taurine, but without added caffeine was not tested, so that it cannot be clarified to what extent taurine could be responsible for these ventricular effects alone. In addition, the energy drink still contains glucuronolactone, but it is unlikely to contribute to these effects.

In a study of 32 healthy volunteers (20 men, 12 women, average age: 28 years) all drank a body surface area adjusted amount of a commercially available energy drink (168 ml/m²) with a usual level of caffeine (0.03%) and taurine (0.4%) (Doerner et al., 2015). According to the authors, for a typical participant this corresponded to 105 mg caffeine and 1,304 mg taurine in a volume of 326 ml. Ten of the participants were selected as a control group who on another day (more than 1 week apart) ingested a commercially available caffeine drink (34 mg/100 ml) without taurine. The participants were examined before consumption of the drink and one hour later by means of cardiac magnetic resonance spectroscopy. Energy drink consumption resulted in a small but significant increase in the *peak systolic strain rate*, which is a parameter for regional contractility (Sinning, 2009). This effect was not observed in the caffeine group. In contrast, global left ventricular function was unchanged (Doerner et al., 2015). It should be noted, however, that no information was provided as to what components, besides caffeine and taurine, were present in the commercial energy drink or alongside caffeine in the commercial caffeine drink and to what extent they are otherwise comparable. Therefore, it cannot be ruled out that other ingredients could have influenced the observed effect. However, due to the effects of glucuronolactone and inositol described above, they are unlikely to show such effects.

The studies presented indicate that taurine may have a hypotensive effect in prehypertensive individuals and increase myocardial contractility, although this could be achieved via a Ca²⁺-dependent mechanism.

3.2.1.4 Taurine Deficiency and Heart Function

In animal studies, Ito et al. show that taurine transporter knockout mice (TauTKO) - with a deficit of taurine content in the heart and skeletal muscle compared to the wild type - exhibit structural and functional changes in the cardiac ventricles: dilated ventricles with a reduction in wall thickness, cardiac muscle atrophy associated with smaller cardiomyocytes and a reduced cardiac output. The skeletal muscle cells of the TauTKO mice have reduced cell volume and structural damage (Ito et al., 2008; Ito et al., 2010).

In another study, male Wistar rats were given a taurine transporter antagonist (3% beta-alanine) for 30 days (T(-); n = 17) while the control group (C; n = 17) did not receive this antagonist (Pansani et al., 2012). In the treated rats, there was a clear decrease in the taurine concentration in the left ventricle compared to the control group (C = 1.8 ± 0.8 $\mu\text{mol}/\text{mg}$ tissue, T(-) = 0.4 ± 0.1 $\mu\text{mol}/\text{mg}$ tissue). The authors found a decrease in ventricular wall thickness, posterior left ventricular wall thickness, and weight of the left ventricle in the taurine-deficient rats. Based on the function of the heart, the ejection fraction, the *fractional shortening* and the cardiac output are decreased. Overall, Pansani et al. concluded that taurine deficiency in rats led to cardiac atrophy, especially of the left ventricle, but the exact mechanisms were unknown.

3.2.1.5 Adverse Effects of Taurine

The published human studies on taurine are primarily concerned with the possible positive effects of taurine, such that adverse effects are hardly considered. However, the *Norwegian Scientific Committee for Food Safety* (VKM) (VKM, 2015a) has identified a few studies that reported adverse effects of taurine supplementation as part of a risk assessment of taurine.

In an open-label study, the effects of taurine on adaptive behaviour and tolerability in succinate-semialdehyde dehydrogenase deficiency disease (an inborn metabolic disorder of GABA degradation) were tested (Pearl et al., 2014). The taurine doses were continuously increased from 50 mg/kg bw to 200 mg/kg bw. The 18 participants were aged between 0.5 and 28 years old. A total of 16 subjects participated in the study for 3 to 50 months. The taurine doses showed no clinically relevant improvements. In contrast, a patient (30 years) with a dose of 200 mg/kg bw (16 g/day) had a severe adverse effect, a hypersomnia that had to be treated in the hospital. As a result, the maximum dose of taurine was limited to 10 g per day. Other adverse effects reported were severe fatigue and somnolence, as well as mild to moderate effects on the occurrence of cognitive changes, ataxia, and insomnia (Pearl et al., 2014). In this study, however, it should be noted that the subjects had a disease and, in some cases, were still infants, so that based on this study no conclusions can be drawn regarding the general healthy population.

In a *crossover* study (two periods over 7 days) with eight healthy men (22 ± 0 years) in which the aim was to investigate whether taurine supplementation can increase the taurine content in the muscle or change the substrate metabolism during prolonged exercise, a subject complained of muscle cramps during the taurine period (2 capsules 3 times daily with 0.83 g taurine = ~ 5 g daily) (Galloway et al., 2008). These mild undesirable effects could be explained by the potential effects of taurine on muscular contractility described above.

Brons et al. (2004) investigated the effect of taurine on insulin secretion in 20 obese men with a predisposition to type 2 *diabetes mellitus* in a double-blind randomised *crossover* study (Brons et al., 2004). Subjects were treated either with taurine for 8 weeks or a placebo for 8 weeks. Taurine was given in a daily dose of 1,500 mg. Eighteen subjects completed the study. The participants exhibited no evidence of adverse effects.

In a double-blind randomised study of 51 women (18-22 years old) who had iron deficiency anaemia, the aim was to investigate if a supplement of oral taurine increased the efficacy of oral iron sulphate in the treatment of iron deficiency (Sirdah et al., 2002). The subjects were treated with iron sulphate for 20 weeks. In addition, one group (n = 26) received one capsule containing 1,000 mg taurine daily, while another group received a placebo (n = 25). The authors reported that no adverse effects of taurine were detected.

3.2.2 Taurine Intake of no health concern

The Norwegian VKM refers to the human studies (Brons et al., 2004; Sirdah et al., 2002), which did not show any adverse effects after taurine administration of up to 1,500 mg per day.

On the basis of these studies, the VKM considers it unlikely that a taurine intake of up to 21 mg/kg bw per day (equivalent to about 1,500 mg per day in a 70 kg adult) would cause adverse health effects (VKM, 2015a).

Based on a 13-week (subchronic) neurotoxicity study in rats, EFSA derived a NOAEL of 1,000 mg/kg bw per day for pathological changes and 1,500 mg/kg bw for behavioural changes. The panel concluded that there are no health concerns against daily intakes of up to 1,400 mg taurine/day (the intake rate in the 95th percentile of chronic energy drink consumption, equivalent to 350 ml per day according to EFSA) (EFSA, 2009; SCF, 2003).

There are currently no published data on the acute toxicity of taurine (VKM, 2015a).

The BfR points out that taurine was evaluated as a single substance and possible interactions of taurine with other ingredients from energy drinks, e.g. caffeine, apart from those on diuretic effects that were considered unlikely (EFSA, 2009), were not considered. In the opinion on the safety of caffeine, EFSA concluded that taurine at commercial energy drink concentrations (4,000 mg per litre) does not affect the safety of single caffeine doses up to 200 mg (EFSA, 2015). Possible interactions with higher caffeine or taurine intake levels were not evaluated. In addition, there are no data available on long-term high taurine levels (> 12 months) that would allow an estimation of possible chronic effects.

3.3 Glucuronolactone

Glucuronolactone is also naturally produced in the body as a metabolite of glucose (EFSA, 2009; McLellan and Lieberman, 2012) and is also a component of fibrous connective tissue. With food, glucuronolactone is absorbed only in small amounts (1 to 2 mg per day) (EFSA, 2009). Uptake of glucuronolactone is completely absorbed, hydrolysed, and excreted in urine as glucuronic acid, xylitol, and L-xylulose (Dowben, 1956; EFSA, 2009).

3.3.1 Health Effects of Glucuronolactone

Hardly any studies have been conducted to study glucuronolactone as a single substance. In an older study in which 100 mg per kg bw of glucuronolactone or other sugars were injected into rats three times a day, positive effects on swimming performance, blood sugar and liver glycogen levels were observed after glucuronolactone administration, which was not observed as with the other sugars (Tamura et al., 1968). However, similar observations have been made in other studies after injection of glucose and galactose (Coyle et al., 1986; Coyle

et al., 1983), so it can be assumed that these effects are based on the known ergogenic effects of carbohydrates in general (McLellan and Lieberman, 2012).

No human studies could be identified in which the toxicity of glucuronolactone as a single substance was investigated.

3.3.2 Glucuronolactone Intake of no health concern

According to EFSA, a 13-week (subchronic) study in rats with intake levels of up to 1,000 mg glucuronolactone/kg bw per day did not show any harmful effects, with particular regard to kidney toxicity (EFSA, 2009).

In contrast to primates, including humans, rodents can endogenously synthesise vitamin C from glucuronic acid and thus can also produce vitamin C from exogenously added glucuronolactone. However, it has been reported that, according to the literature, glucuronolactone is primarily metabolised via the pentose pathway, while the vitamin C pathway plays only a minor role, so the rat model appeared to be applicable (EFSA, 2009).

The EFSA panel concluded that there are no health concerns against daily intakes of up to 840 mg glucuronolactone per day (the intake in the 95th percentile of chronic energy drink consumption, equivalent to 350 ml per day according to EFSA) (EFSA, 2009; SCF, 2003).

There are currently no published data on the acute toxicity of glucuronolactone (VKM, 2015b)

3.4 Inositol

The sugar alcohol inositol is a white crystalline odourless powder with a slightly sweet taste (EFSA, 2014). The molecular formula of inositol is C₆H₁₂O₆ (CAS number :87-89-8). Naturally, inositol is synthesised by almost all plants and animals. It exists in nine possible stereoisomers, four of which are physiologically active. It mainly occurs in the form of *myo*-inositol. In nature, inositol is both bound and unbound. Free inositol is over 90% absorbed in the small intestine.

The bioavailability of *myo*-inositol from phytic acid (inositol hexaphosphate) is very limited and depends on a variety of factors such as phytate solubility and the presence of minerals, plant phytases, microbial intestinal phytases, delivered phytases and food processing (EFSA, 2016).

Endogenous inositol is mainly synthesised in the kidneys and the concentration of free inositol in the renal medulla cells is 1000 times higher than in the blood. It is estimated that about 4 g per day are produced in humans. The plasma levels in the kidneys are regulated by glomerular filtration, reabsorption and catabolism or excretion.

3.4.1 Health Effects of Inositol

The *Norwegian Scientific Committee on Food Safety* (VKM) (VKM, 2015c) identified various human studies that reported adverse effects after inositol administration as part of its inositol risk assessment.

One review considered 12 controlled clinical trials involving a total of 250 adults who received 4 to 30 g of inositol per day (equivalent to 57 to 429 mg per kg of bw per day for a 70

kg individual) over 1 to 12 months (Carlomagno and Unfer, 2011). The most commonly reported and dose-related adverse events were nausea, flatulence, loose bowel movements, and diarrhoea. At a dose of 4 g of inositol per day, mild adverse effects such as mild insomnia and flatulence were reported.

In an open-label study, the safety and maximum tolerated dose of *myo*-inositol in smokers (24 men, 2 women) with bronchial dysplasia was investigated (Lam et al., 2006). In order to determine the maximum tolerated dose, the administered dose of *myo*-inositol was first increased in 16 subjects from 12 to 30 g per day during one month. Adverse effects included flatulence, loose bowel movements or diarrhoea. A NOAEL of 18 g per day was determined. In a second phase, 10 subjects were then given this dose for three months. Mild gastrointestinal symptoms were listed as adverse effects during the first month of treatment. There was also a statistically significant, albeit clinically insignificant, increase in haemoglobin after taking 18 g / day *myo*-inositol for more than 4 weeks (Lam et al., 2006).

In a clinical trial in Israel comparing inositol versus fluvoxamine to treat panic disorder in otherwise healthy individuals (N = 21, 9 men, 12 women, average age 39 years) (Palatnik et al., 2001), the following adverse effects have been reported during administration of 12 g inositol per day (1st week) to 18 g inositol per day (2nd to 4th week): Nausea (8 people) and fatigue (1 person).

3.4.2 Inositol Intake of no health concern

The quality of the available human studies is not sufficient to derive safe intake levels. However, studies with 4 g of inositol per day (equivalent to 57 mg per kg bw per day) showed either no undesirable effects or only in very few participants, which then showed mild symptoms (Carlomagno and Unfer, 2011).

In respect to animal studies no conventional toxicology studies were available, but the results of studies in rodent models with chronic diseases suggest, according to EFSA, that the toxicity of inositol is low (EFSA, 2014). In mice in which tumours had been induced with other substances, no adverse effects were observed over a dose range of 450-9,000 mg per kg bw per day. Only one study in diabetic and non-diabetic rats showed an adverse effect at 1,800 mg per kg bw per day (thickening of the basal membrane of retinal capillaries and glomeruli in non-diabetic rats) (EFSA, 2014).

Similarly, no data are available on the acute toxicity of inositol (VKM, 2015c).

3.5 Energy Drinks as a "Uniform Product"

In addition to the presentation of individual ingredients in energy drinks in 3.1 to 3.4, consideration is given below to energy drinks as "uniform products". Energy drinks are caffeinated soft drinks, which in Germany according to § 4 (2) of the Fruit Juice and Soft Drink Regulation (FrSaftErfrischGetrV) may contain one or more of the substances listed in Appendix 8 Part B, in addition to caffeine with a maximum content of 320 mg/l in ready-to-eat food. Accordingly, ready-to-eat food may contain taurine up to a maximum of 4,000 mg/l, glucuronolactone up to a maximum of 2,400 mg/l and inositol up to a maximum of 200 mg/l.

3.5.1 Effects of Energy Drinks on the Cardiovascular System

The BfR has performed a comprehensive literature search on published intervention studies with energy drinks in which cardiovascular parameters were examined (non-systematic search up to January 2018).

Based on the "cardiovascular system" end point, a total of 29 intervention studies were identified (with the exception of a meta-analysis, four studies were performed with Energy Shots). These are listed in Table 1 in the Appendix with the respective study design. In these studies, only acute effects of energy drink consumption were analysed in almost exclusively young healthy adults (18 to 45 years). Only one study also included 15-year-old children (Hajsadeghi et al., 2016), but they did not stratify by age. A single study was conducted with patients who had a familial-related prolonged QTc syndrome (Gray et al., 2016). The subjects consumed the energy drinks mostly as a single dose within a short period of time (maximum within three hours), i.e. only acute effects were investigated. In two studies, the acute energy drink dose was administered twice to several times a day (Franks et al., 2012; Shah et al., 2016b). As a rule, the observation time ranged from 0.5 hours to 24 hours. Two studies extended energy drink exposure and observation time over seven days, but measured acute effects on certain days within that time period (Shah et al., 2016b; Steinke et al., 2015). When stated, the caffeine dosages given by energy drinks were mainly between 80 mg and 320 mg per day, and the taurine dosages, if given, were between 1,000 mg and 4,000 mg per day (one study with 100 mg taurine). Little information was available on glucuronolactone levels (84 and 1200 mg per day) and almost none on inositol.

There were no intervention studies on children or adolescents (except (Hajsadeghi et al., 2016)), and generally no intervention studies (whether for children, adolescents or adults) were identified on longer-term chronic use and on excessive consumption of more than one litre of energy drink. It should be noted that clinical trials on this topic could also not be justified for ethical reasons.

Regarding the research on studies containing data on the consumption behaviour of children, adolescents and young adults, 16 studies were identified (non-systematic search up to January 2018 and infrequent subsequently identified studies).

3.5.1.1 Effects of Energy Drinks on Blood Pressure

Certain fluctuations in blood pressure are normal and are seen as an adaptation response to exogenous and endogenous requirements. Hypertension is a disease of the vascular system where the blood pressure levels are permanently too high (Hochdruckliga, 2015). Thresholds for hypertension diagnostics are given in Germany for adults by the German Society of Cardiology (DGK, 2013) and in the German S2k-Guideline on paediatric arterial hypertension for

children and adolescents (German Society of Paediatric Cardiology (DGPK), 2013), where the thresholds for the group of children and adolescents are based on age- and size-dependent reference values (Wühl et al.; 2002, RKI, 2013).

According to the European Society of Hypertension and the European Society of Cardiology, an acute and severe increase in systolic or diastolic blood pressure (> 180 mmHg systolic or > 120 mmHg diastolic) is defined as a "hypertensive emergency" if it is associated with impending or progressive organ damage, or as "hypertensive urgency" without organ damage (Mancia et al., 2013; Salvetti et al., 2018). There are no clear thresholds for children and adolescents (DGPK, 2013).

In the intervention studies identified here, which examined blood pressure as the end point after energy drink consumption, only acute effects were analysed (maximum over 7 days as an acute single dose) and not the possible chronic consequences of long-term energy drink consumption.

In an acute caffeine dose of not more than 200 mg administered via energy drinks, systolic blood pressure changes were approximately +3 mmHg to +9 mmHg relative to baseline (Elitok et al., 2015; Franks et al., 2012; Grasser et al. 2015; Grasser et al., 2014; Majeed et al., 2017; Marczynski et al., 2014; Miles-Chan et al., 2015; Ragsdale et al., 2010; Steinke et al., 2009) and diastolic approximately +2 to +5 mmHg (Steinke et al., 2009; Elitok et al., 2015; Grasser et al., 2014; Majeed et al., 2017; Marczynski et al., 2014; Miles-Chan et al., 2015; Hajsadeghi et al., 2016). Even in acute caffeine doses of up to 320 mg, no changes above 9 mmHg were measured (Basrai, 2019; Fletcher et al., 2017; Kurtz et al., 2013; Phan and Shah, 2014; Rashti et al., 2009; Shah et al., 2016c; Svatikova et al., 2015). An open-label, uncontrolled study showed no significant changes in SBP at caffeine levels above 200 mg (240 mg) (Higgins et al., 2017). Serious blood pressure changes were observed in an open-label study from the US in which 960 ml of an energy drink were consumed (Kozik et al., 2016). Here, the systolic blood pressure increased by nearly 20 mmHg after consumption (from 132 ± 7.83 to 151 ± 11.21 mm Hg, $p = 0.001$). However, no control group was included and no caffeine levels were reported. The BfR points out that the US has not set any legal maximum levels for caffeine and other ingredients in energy drinks.

Identified studies with administered caffeine doses around 100 mg and below did not show any significant changes in blood pressure (Al-Fares et al., 2015; Alford et al., 2001; Doerner et al., 2015).

Overall, it can be stated that the consumption of energy drinks can significantly increase blood pressure. The blood pressure increase is probably based on the ingredient caffeine, whereby taurine could mitigate this increase. Based on the identified intervention studies, a moderate² energy drink³ consumption (acute single dose up to 200 mg caffeine and taurine (in the studies here: not more than 2,000 mg, if indicated)) resulted in maximal blood pressure changes of approximately 10 mmHg systolic and 5 mmHg diastolic. These induced acute changes in blood pressure in healthy adults may be considered physiologically and sanitarily safe, if they occur occasionally and under normal (environmental) conditions. Caffeine doses of more than 200 mg up to 320 mg via energy drinks did also not lead to a clinically-significant increase in blood pressure within the identified studies in young, healthy

² The term "moderate" is defined as the consumption of energy drinks that does not exceed the amount of caffeine that EFSA considers safe. These are based on the maximum permitted levels in Germany for caffeine in energy drinks and based on acute consumption (single dose) for healthy adults up to 625 ml maximum (depending on weight, correspondingly less for children for which 3 mg of caffeine per kg bw is considered to be safe).

³ The term "acute" is defined as a time period of up to three hours.

adults. However, it should be noted that such an amount may be critical for more sensitive individuals (e.g. children or those with high blood pressure), especially in combination with high levels of consumed alcohol or intense physical activity. For higher intake levels (more than 1 litre of energy drinks), for children and adolescents and for chronic consumption, no conclusions can be drawn because no data are available in this regard.

3.5.1.2 Effects of Energy Drinks on Heart Rate

Increased heart rate at rest is associated with a higher risk of cardiovascular disease and mortality (Cooney et al., 2010). So far, however, there are no reference values for heart rate so it is not possible to clearly state which threshold level may lead to an increased risk to health (Stoschitzky, 2011). In the US, heart rate > 100 beats per minute (bpm) at rest is defined as tachycardia and < 60 bpm is defined as bradycardia, as determined by “clinical consensus”. A revised clinical guideline based on an analysis of current cardiac practice and epidemiological data defines a heart rate > 90 bpm at rest as tachycardia and < 50 bpm as bradycardia (Ostchega et al., 2011).

In the studies in which no more than 200 mg of caffeine were acutely absorbed through energy drinks, both heart rate increases (between +2 and 8 bpm, +16 bpm with exercise) (Alford et al., 2001; Baum et al., 2001; Elitok et al., 2015; Franks et al., 2012; Grasser et al., 2014; Grasser et al., 2015; Steinke et al., 2009), no change (Al-Fares et al. Doerner et al., 2015; Menci et al., 2013) as well as heart rate decline (Hajsadeghi et al., 2016, Ragsdale et al., 2010) were observed. For caffeine doses of more than 200 mg up to 320 mg, the studies of Basrai et al. and Fletcher et al. demonstrated an increase in heart rate (although not significant in Fletcher) by approximately 3 to 4 bpm (Basrai, 2019; Fletcher et al., 2017), while heart rate was scarcely affected in other studies (Higgins et al., 2017; Kurtz et al., 2013; Phan et al., 2014; Rashti et al., 2009; Shah et al., 2016b; Shah et al., 2016c; Svatikova et al., 2015). Meta-analysis also showed no significant heart rate changes after energy drink consumption (Shah et al., 2016a).

The data on the extent to which an acute consumption of energy drinks of up to one litre affects heart rate is contradictory, so that no clear statements can be made in this regard. For higher intake levels (more than 1 litre of energy drinks), for children and adolescents and for chronic consumption, no conclusions can be drawn because no data are available in this regard.

3.5.1.3 Effects of Energy Drinks on the QTc Interval

The QT interval is a measure in the evaluation of the electrocardiogram and represents the duration of the ventricular systole, i.e. the time interval required to complete both ventricular depolarisation and repolarisation (Kauzner et al., 2002). A significant prolongation of the QT interval indicates a delayed cardioventricular repolarisation, which may be the cause of life-threatening ventricular tachycardia, e.g. in the worst case torsade de pointes, which can develop into ventricular fibrillation and therefore end with sudden cardiac death (FDA, 2005). Extensions of the QT interval may be innate (genetically) or acquired, and could have many causes, e.g. ion channel diseases, myocarditis, medication, etc. (Lazzerini et al 2015; Yap et al., 2003; Thomas et al., 2016). As the duration of ventricular repolarisation decreases with increasing heart rate, a frequency correction of the QT interval (QTc) must be made for which a correction formula is used (FDA, 2005; Haverkamp et al., 2002). According to the German Society of Paediatric Cardiology, the following thresholds represent a prolonged

QTc interval: > 460 ms for children (1 to 15 years), > 450 ms for male adolescents and men (> 15 years) and > 470 ms for female adolescents and women (> 15 years) (DGPK, 2011).

This parameter was not significantly affected in the intervention studies in Table 1 in the Appendix, which examined the QTc interval and did not include more than 200 mg of caffeine via energy drinks (Brothers et al., 2016; Elitok et al., 2015; Hajsadeghi et al., 2016; Ragsdale et al., 2010; Steinke et al., 2009). QTc prolongation was observed at these doses in only one study of overweight subjects, but the overweight subjects had already higher QTc intervals at baseline than normal subjects (Alsunni et al., 2015). In the studies in which 320 mg of caffeine were administered via energy drinks, two showed a significant prolongation of the QTc interval compared to before consumption (+ 3 to 8 ms) (Basrai, 2019; Shah et al., 2016c). In the study by Fletcher et al., although a significant difference was observed in the QTc interval 2 h after consumption compared to the caffeine group (960 ml of energy drink with 320 mg caffeine), this was due to the reduction of the QTc interval in the caffeine arm, while the QTc interval within the energy drink arm demonstrated little difference with respect to before consumption.

A significant increase in the QTc interval was demonstrated in the open-label study by Kozik et al. (USA), where 14 participants consumed 960 ml of an energy drink. Here, the QTc interval increased by approximately 80 ms from 423 ± 22.74 ms to 503 ± 24.56 ms ($p < 0.001$), which by definition corresponds to a prolonged QTc interval and may therefore involve a risk. However, as previously mentioned, no control group was included here and no caffeine levels were reported. The BfR points out that the US has not set any legal maximum levels for caffeine and other ingredients in energy drinks.

In an intervention study with patients with pre-existing familial prolonged QT syndrome, moderate energy drink consumption (with caffeine and taurine levels of 160 mg and 2,000 mg, respectively) already resulted in severe QTc prolongation in some subjects (> 50 ms) up to a maximum value of 557 ms. However, the increase in QTc interval was not significant for the entire energy drink group (Gray et al., 2017).

Overall, moderate acute energy drink consumption with caffeine intake of up to 200 mg does not appear to affect the QTc interval in young healthy adults, except in a study of overweight individuals, but even then not to alarming levels (Alsunni et al., 2015). Therefore, occasional moderate intake of energy drinks under normal (environmental) conditions cannot be expected to pose a health risk to healthy adults in terms of changes in the QTc interval. In conjunction with one litre of energy drink consumption, three out of four studies showed a significant increase in the QTc interval. In one of these studies, serious QTc prolongations, which could pose a potential health risk, were induced in young healthy adults by the high consumption of energy drinks (caffeine levels were not cited). In addition, QTc interval increases with a potential serious health risk could occur even with moderate consumption in patients with a pre-existing prolonged QTc syndrome (Gray et al., 2017).

For even higher intake levels (more than 1 litre of energy drinks), for children and adolescents or for chronic consumption, no conclusions can be drawn because no data are available in this regard.

3.5.1.4 Effects of Energy Drinks on Cardiac Output (e.g. Inotropic Effects)

Cardiac function is affected by myocardial contractility (Authenrieth et al., 1984). An increase in contractility leads to increased cardiac output or minute output. Cardiac output (l/min) is the amount of blood pumped by the heart in one minute and represents the product of stroke volume and heart rate (*beats per minute* = bpm) (Vincent et al., 2008). Certain changes in

cardiac output may be considered as a transient adaptation response to the different oxygen demand of the heart muscle and skeletal muscle as a function of different exogenous and endogenous stimuli (e.g. exercise) (Duncker et al, 2008; Evans et al., 1985).

Other parameters for recording the contractility of the myocardium are i.a. *fractional shortening* (FS), *peak systolic strain rate*, left ventricular end-systolic diameter (LVESD), etc.

For some intervention studies listed in Table 1 in the Appendix, parameters for recording cardiac output after energy drink consumption have been collected. In all of these studies, at least some of the measured parameters suggest that myocardial contractility or cardiac output was increased after energy drink consumption (Baum and Weiss, 2001; Doerner et al., 2015, Grasser et al., 2015; Grasser et al., 2014; Menci et al., 2013; Miles-Chan et al., 2015).

The studies that included a caffeine control indicated that these effects could be due in particular to the composition of the energy drinks, as the caffeine control had no effect on these parameters. Therefore, the intervention studies with caffeine controls are listed again in the following.

The study design of Baum and Weiß has already been explained under Point 3.2.1.3 (Baum and Weiss, 2001). In contrast to the control drink with caffeine (160 mg) (but without taurine) and the placebo, consumption of 500 ml of the original energy drink (with 160 mg caffeine and 2,000 mg taurine) demonstrated a significant increase in stroke volume and *fractional shortening* after training, as well as a significant reduction in left ventricular end-systolic diameter (LVESD). The authors conclude that the combination of taurine and caffeine in the original Red Bull beverage could increase left ventricular contractility of the heart (Baum and Weiss, 2001).

The study design of Doerner et al. has also been explained in Point 3.2.1.3 (Doerner et al., 2015). Energy drink consumption (equivalent to 105 mg caffeine and 1,304 mg taurine for a typical participant) resulted in a small but significant increase in the *peak systolic strain rate*, which is a parameter for regional contractility (Sinning, 2009). This effect was not observed in the caffeine group, so the authors conclude that caffeine and taurine-containing energy drinks may affect myocardial contractility (Doerner et al., 2015). However, it cannot be ruled out whether other ingredients in the energy drink could have influenced the observed effect.

The study by Miles-Chan et al. considers how caffeine drinks or Red Bull energy drinks affect blood pressure or cardiac output (Miles-Chan et al., 2015). In this controlled randomised *cross-over* study, 18 healthy young men (25.4 ± 1.3 years) received, blind and on four separate days, either 355 ml (1) energy drink (containing 114 mg caffeine, 1,420 mg taurine, 85 mg glucuronolactone, 39 g sugar) + placebo capsule (not further defined); (2) sugar free energy drink + placebo capsule; (3) water + 120 mg caffeine or (4) water + placebo capsule within 4 minutes. The amount of caffeine in the Red Bull drink was comparable, but slightly less. Cardiovascular monitoring was performed at baseline for 30 minutes and after consumption of the drink for 120 minutes. The Red Bull drink, the sugar-free Red Bull drink as well as the "caffeine + water" drink resulted in a comparable increase in blood pressure (3-4 mmHg) compared to the "water + placebo" drink ($p < 0.001$) with only negligible changes. However, different effects were found on parameters of cardiac function. In contrast to the other three beverages, only the sugar-containing Red Bull drink significantly increased heart rate, stroke volume (SV), cardiac output (heart rate x stroke volume), contractility index (represents the aortic *peak flow*) and the double product (systolic blood pressure x heart rate; surrogate marker for myocardial oxygen demand) ($p < 0.01$ for all parameters). The *total peripheral resistance* (TPR) was reduced for the Red Bull drink, while the sugar-free Red Bull

drink and the "water + caffeine" drink caused an increase in peripheral resistance compared to the placebo. The authors conclude that the observed blood pressure changes may have been triggered by different haemodynamic pathways: through the energy drink via changes in myocardial performance and through caffeine as a single substance via vascular effects. Since the sugar-free Red Bull drink did not affect cardiac parameters, the authors discuss that this could be an effect of the combination of caffeine and sugar mediated by insulin, to which inotropic effects are attributed (Klein et al., 2010; Klein and Visser, 2010). In contrast to the two previous studies, it is not believed that taurine or the combination of taurine and caffeine could be responsible for the effects on cardiac output, as the sugar-free Red Bull drink also contained the appropriate amounts of taurine and caffeine as the sugar-containing Red Bull, however, it did not have the same effect on cardiac output.

Overall, the BfR notes that there are possible initial indications that energy drinks can influence contractility and therefore cardiac output. The three studies with caffeine controls suggest that energy drinks may be different in that respect than other caffeine-containing foods without typical energy drink ingredients. However, with regard to the question of which ingredients or which combination of ingredients (sugar, taurine) could be responsible for these potential effects, the data are contradictory.

With regard to the outcome "myocardial contractility", the identified intervention studies investigated only the acute moderate consumption of energy drinks (105 to 160 mg caffeine) by healthy young adults. With these intakes, the observed changes in these parameters, which reflect contractility, appear to be physiologically insignificant and harmless, as long as they occur occasionally and under normal (environmental) conditions in healthy adults. It remains unclear whether effects on human health can be expected in the event of possible long-term high energy drink consumption and the potential inducible long-term increase in myocardial contractility.

For high acute exposures, as well as for children and adolescents, no conclusions can be drawn because no data are available.

3.5.2 Adverse Effects of Energy Drinks

3.5.2.1 Human Studies

In the intervention studies with energy drinks focusing on cardiovascular parameters (Table 1 in Appendix), a maximum of 1 litre of energy drink was given and only the acute effects of energy drink consumption were considered. Intervention studies with chronic energy drink consumption over several months are not available, so that no statements can be made in this regard.

In two studies on caffeine intake of 80 mg acutely administered through energy drinks, participants reported no adverse effects (Franks et al., 2012; Hajsadeghi et al., 2016).

In the study by Steinke et al. (N = 15), 200 mg of caffeine and 2,000 mg of taurine were administered for seven days via energy drinks (Steinke et al., 2009). Mild adverse effects were reported, e.g. agitation (n = 4), gastrointestinal discomfort or abdominal cramps (n = 3), increased urination (n = 1), disturbed sleep (n = 1) and stronger heartbeats (n = 1). A control group was not included.

In the study by Kurtz et al. (N = 20), about 215 mg of caffeine was administered via an Energy Shot (Kurtz et al., 2013). The following adverse effects were reported: Agitation (n = 2),

nausea (n = 1), palpitations (n = 1), sweating (n = 1) and abdominal pain (n = 1). However, the participants in the control group (decaffeinated Energy Shot) reported headache (n = 1), agitation (n = 1), palpitations (n = 1), drowsiness (n = 3) and abdominal pain (n = 1), too.

Phan et al. administered Energy Shots which also contained 215 mg caffeine to 10 participants. One participant complained of dizziness and another about palpitations. But a participant who had consumed a decaffeinated Energy Shot also reported headaches (Phan et al., 2014).

In the study by Basrai and co-workers, the acute intake of 750 or 1,000 ml of control product, an energy drink (320 mg/l caffeine, 4,000 mg/l taurine, 308 mg/l glucuronolactone, 92 mg/l inositol), control product plus caffeine or control product plus taurine caused moderate to more severe symptoms in all four interventions in some participants (Basrai et al., 2019). However, the largest proportion of participants (7 out of 19) was affected by the consumption of energy drinks after 1,000 ml was administered, while after administering 750 ml, the largest proportion of participants was affected after consuming the control product plus caffeine (6 out of 19). Severe symptoms, which occurred in five out of 38 people, were caused only after the administering of energy drinks (severe tremor, severe nausea) or control product plus caffeine (severe tremor, severe agitation).

In the study by Fletcher et al. 15 participants (N = 18) reported the following adverse effects after acute consumption of 960 ml of energy drink (320 mg caffeine, taurine and glucuronolactone unknown): Anxiety (n = 3), difficulty in falling asleep (n = 4), dizziness (n = 3), dyspepsia/upset stomach (n = 4), nosebleeds (n = 1), headache (n = 2), nervousness (n = 8), nausea (n = 2), palpitations (n = 4) and shortness of breath (n = 1). However, 13 participants in the caffeine group (N = 18) also reported similar adverse effects (Fletcher et al., 2017).

The other researched intervention studies (see Table 1 in Appendix) did not address adverse effects, i.e. it is unclear to what extent they were even queried.

Overall, moderate acute energy drink consumption with ingested caffeine levels of up to 200 mg by young healthy adults resulted in hardly any adverse effects being reported. Ingestion of higher amounts (up to one litre) caused moderate to severe adverse effects in some subjects. However, some subjects also had effects after taking higher levels of caffeine via an accompanying control drink without other typical energy drink ingredients. This suggests that caffeine could be mainly responsible for the adverse effects. In some studies, some people reported adverse effects even after ingesting a caffeine-free beverage. It is not clear if this is due to other ingredients in this drink or possibly induced excitement about participating in the study.

For even higher intake levels (more than 1 litre of energy drinks), for children and adolescents or for chronic consumption, no conclusions can be drawn because no data are available in this regard.

3.5.2.2 Case Reports

The BfR has researched a large number of published case reports in connection with the consumption of energy drinks in PubMed (search until mid-October 2017, as well as case reports added occasionally on later dates) (see Table 2 in Appendix). The main symptoms observed were mostly cardiovascular (chest pain, tachycardia, infarction, cardiac arrhythmia and cardiac arrest etc.), psychiatric disorders (anxiety, psychosis, hallucinations) and epilepsy.

In healthy adults, adverse effects were observed in a temporal context with a particularly high/excessive energy drink consumption. Causal relationships were not derived from these case reports.

Similarly, the *Food and Drug Administration* (FDA) collects a variety of voluntary reports (physicians, family members, consumers) about adverse effects associated with energy drink consumption in a database. The FDA points out that these event reports on specific products do not represent an FDA conclusion on a causal relationship (<http://wayback.archive-it.org/7993/20171114232636/https://www.fda.gov/Food/RecallsOutbreaksEmergencies/SafetyAlertsAdvisories/ucm328536.htm>) (FDA, 2012).

The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) has also reported adverse health effects following the consumption of energy drinks as part of its Nutrivigilance system (<https://www.anses.fr/en/system/files/NUT2012sa0212EN.pdf>) (ANSES, 2013). The ANSES has, with the aid of various criteria (e.g. two reporters, temporal relationships, *rechallenge*, exclusion of other possible causes), derived causal relationships such as e.g. very likely, likely, possible, unlikely or excluded. For example, in 95 cases examined, cardiovascular manifestations were reported. According to ANSES, the causality analysis yielded the following result: very likely for 5 cases; likely for 9 cases; possible for 25 cases; unlikely for 55 cases; excluded for 1 case.

Although causality relationships have not been established in most cases, the large number of case reports on adverse effects after consuming energy drinks, especially after excessive consumption in healthy adults, gives cause for concern that over-consumption of such beverages may be associated with adverse health effects.

3.6 Exposure

The BfR has assessed the following studies on exposure data for caffeine intake in Germany, in particular to what extent the intake of caffeine from energy drinks was adequately recorded. Both chronic and acute exposure were considered, as EFSA also derived safe levels of caffeine intake for both exposure scenarios.

Since, in the view of BfR, potential risks from high energy drink consumption are to be taken into consideration, especially among the sensitive group of children and adolescents, the aim was primarily to present comprehensive data on the consumption of energy drinks for children and adolescents.

3.6.1 Data on the Consumption of Energy Drinks for Children and Adolescents in Germany

Survey study in 16 EU member states (Zucconi et al., 2013)

In an EFSA-commissioned survey conducted in 16 European Union member states in 2012 (Zucconi, 2013), 60% of 1,068 children and adolescents surveyed (10 to 18 years old, male 49.9%, female 47.5%) in Germany stated that they had been drinking energy drinks in the previous year (at the time of the survey). These were defined as energy drink consumers⁴. Of these energy drink consumers, 17% stated that they drink energy drinks in quantities of 1 litre and more on certain occasions (in a "single session"⁵). Based on the total number of children and adolescents surveyed in Germany⁶, 10% indicated that they had drunk such amounts in a "single session".

Furthermore, of the German children and adolescents, 9% of energy drink consumers stated that they consume energy drinks 4 to 5 days per week or more frequently. Based on the total number of children and adolescents surveyed in Germany, this figure was around 5%, which stated that they regularly consume energy drinks in this way. However, in respect to the presented frequency of energy drink consumption the consumed amount was not reported.

Other data from another study show that high levels of energy drinks are consumed by adolescents and young adults, especially on certain occasions/ events (BfR, 2013). From the point of view of the BfR, persons with high energy drink consumption upon certain occasions represent the actual risk group with regard to the acute intake of caffeine from energy drinks. This acute risk can be quantified using the Zucconi study.

The Zucconi study is not suitable for quantifying the chronic risk of caffeine intake from energy drinks, as no consumed energy drink quantities were recorded in terms of regular consumption and therefore it is unknown what proportion of the regular energy drink consumers exceed the safe intake of caffeine intake according to EFSA.

A publication from 2018 pointed to limitations of the Zucconi study (Verster et al., 2018). One limitation is given by the circumstance that this study is not representative for Europe, as Italian children are over-represented. Also from the point of view of the BfR, this study is not representative for Europe, in particular because data were only collected from 16 EU member states. However, in the opinion of the BfR the data can be considered in relation to the individual Member States. It is also noted that male participants are over-represented. This is not the case with regard to the data from Germany. Moreover, an overlap between the group of children (3 to 10 years) and adolescents (10 to 18 years) is indicated. From the point of view of the BfR, this overlap seems negligible, as long as both groups are considered separately. In addition, from the point of view of the BfR, the number of participants of German children aged between 3 and 10 is too low (N = 30) to obtain meaningful results, which is why this group was not taken into account by the BfR. A possible bias regarding the recalled consumption up to one year prior, as well as the support of teachers in answering the questions, was also pointed out. A certain bias regarding the surveying of consumption behaviour is unavoidable in dietary surveys. However, the estimation that a proportion of adolescents and adults in Germany consumed, to some degree, high amounts of energy drinks in a "single session" was reinforced by the results of the BfR study concerning event-related consumption (BfR, 2013), in which the retrospective survey period was 24 hours.

⁴ Energy drink consumers have been defined as subjects who have been drinking Energy Drinks at least once over the last year.

⁵ A "single session" is defined as a period of a few hours, e.g. a night out, a study or exercise session.

⁶ In the 75th percentile based on the data, acute intake of caffeine from energy drinks during a *single session* among the total number of children and adolescents surveyed in Germany was 3.05 mg/kg bw.

The EFSA opinion on the safety of caffeine also refers to data on energy drink consumption from the Zucconi study (EFSA, 2015). For example, Table 4 on page 29 states that based on the Zucconi study, 24% of children and adolescents consuming energy drinks (10 to 18 years) consume three or more doses of energy drinks during a “*single session*” (summarised from 16 EU member states). Among the total number of children surveyed, 16.3% drink such amounts, according to EFSA. Furthermore, Table 4 shows that caffeine intake from energy drinks during a “*single session*”, amongst children and adolescents, totals 7.2 mg/kg body weight (bw) in the 95th percentile.

However, EFSA makes no statements as to which sections of the population are at risk from exceeding the caffeine intake levels that it considers to be safe, which, according to EFSA's interpretation of the “*Terms of References*”, was not the goal in drafting the Opinion on Caffeine either.

EFSA Opinion on the Safety of Caffeine (2015)

EFSA compiled the “*Comprehensive European Food Consumption Database*” (hereinafter referred to as the EFSA database) to estimate caffeine intake in the individual member states. This database, which includes consumption data from many national surveys in the European Union (EU), only considers 24-hour or 48-hour *recalls* or dietary protocols over three to seven days (EFSA, 2015; page 23). This means that food consumed irregularly is probably not detected adequately, i.e. the acute intake of caffeine from a potentially high energy drink consumption on certain days could be underestimated. However, as mentioned above, from the point of view of the BfR, persons with such a consumption behaviour represent the actual risk group with regard to acute energy drink consumption.

Furthermore, from the point of view of the BfR regarding the implementation of the German national surveys - Eating Study as KiGGS module (EsKiMo) (Mensink et al., 2007) and National Nutrition Survey (NVS) II (MRI, 2008) - in the EFSA database, limitations may possibly exist with respect to the estimation of caffeine intake from energy drinks. For example from the EsKiMo study, only 11-year-olds adolescents (10 to <18 years) were recorded in the EFSA database (EFSA, 2015, Appendix A, page 96), as only for this age group the dietary protocols used by EFSA were available. However, the group of 11-year-olds cannot be used as a representative group for 10- to 18-year-old adolescents, especially with regard to energy drink consumption, since it can be assumed that older adolescents are likely to consume larger amounts. From the point of view of the BfR, it can therefore be assumed that the data in the EFSA database, which are based on the EsKiMo study, are likely underestimating the daily intake of caffeine from energy drinks among 10 to 18-year-old adolescents. This should be taken into consideration when looking at the value of the percentage contribution of caffeine from energy drinks to the total daily intake of caffeine (0.9%) based on the EsKiMo study (EFSA, 2015, Appendix E, page 106).

Furthermore, the BfR points out that when the NVS II was implemented in the first version of the EFSA database (2010), no unique Energy Drink Code was used (EFSA, 2015, Appendix A, pages 96 and 97 footnote a, and page 23). For surveys that have been integrated into this database, codes such as “*Carbohydrate-rich energy food products for sports people*” or “*carbohydrate electrolyte solutions for sports people*” have been used to calculate the intake of caffeine from energy drinks. The NVS II also did not have a clear energy drink code yet, which could have led to difficulties in recovery. This assumption is supported by the fact that, based on the NVS II data in the EFSA database, the percentage contribution of caffeine from energy drinks to total caffeine intake is 0% for both adolescents and adults (EFSA, 2015,

Appendix E, page 106 and 107). From the point of view of the BfR, this does not seem realistic.

In addition, the BfR points out that the consumption data from the EsKiMo and NVS II study were collected more than 10 years ago, i.e. at a time when energy drinks were much less present on the market (Statista, 2017).

Overall, it can therefore be assumed that on the basis of the EFSA database, the daily intake of caffeine from energy drinks of German children and adolescents as well as adults is underestimated. In estimating caffeine intake levels from other traditional caffeine-containing foods, such as chocolate, coffee or tea, it can be assumed that these can be estimated more realistically on the basis of the NVS II data in the EFSA database, since clear coding is present and it is not likely that the presence of these products in the German market has changed dramatically over the last 10 years. Based on the EsKiMo data, estimates of caffeine intake from these products can only be representative of 11-year-olds, which is also reflected by the fact that based on EsKiMo data it is estimated that 42.7% of total caffeine intake in adolescents comes from chocolate, while using NVS II this amount is only 16.3% (EFSA, 2015, Appendix E, page 106).

Data from the DONALD and NVS II study (Lachenmeier et al., 2013)

Lachenmeier and colleagues used both the “*Dortmund Nutritional and Anthropometric Longitudinally Designed*” study (DONALD) and the NVS II to estimate caffeine intake from beverages.

On the basis of the non-representative DONALD study (study period 2007 and 2011) with 316 children and adolescents aged 9 to 19 years, 941 nutritional protocols (*3-day-weighing protocols*) were available. Based on these data, caffeine intake per day via energy drinks plays a rather minor role (0.7 g/day on average). However, 3-day weighing protocols can underestimate the consumption of foods that are consumed irregularly, which means that potentially high energy drink consumption on certain days is not necessarily recorded. In addition, long-term studies place high demands on the participants. Following this, the group from the DONALD study has an above-average social status (Kroke et al., 2004), which could possibly influence energy drink consumption behaviour.

Lachenmeier and colleagues used NVS II (14 to 80 years) to determine the intake of caffeine from drinks for certain age groups. Data on beverage consumption was based on 15,371 individual *diet history interviews* covering food intake over the past four weeks (54% female, 46% male, survey period November 2005 to November 2006). Only mean intake data was collected separately for coffee and tea for each age group and for the total soft drink intake (without specification of caffeinated soft drinks and energy drinks). As there were no clear consumption data on energy drinks in NVS II, it was estimated that they represented 5% of total soft drink consumption. This estimate is based on a consumer analysis from the years 2010 to 2012 (VuMA, 2013), which covers the entire German-speaking population over the age of 14, in which no stratification by age was made.

Lachenmeier and colleagues calculated a caffeine intake of 0.9 mg/kg bw per day for the age group of 14 to 18-year-old male participants and a caffeine intake of 0.6 mg/kg bw per day for the female participants. The highest intake of caffeine from beverages was reported by the 35 to 50-year-olds (2.5 mg/kg bw per day for women and men). It should be noted, however, that by recording average intakes, potentially high levels of energy drink consumption are “watered down” on certain days. With regard to the estimation of the daily intake of caffeine from energy drinks, certain limitations must also be stated. These include the lack of

coding for energy drinks, the estimate that energy drinks make up 5% of total soft drink consumption, which also could not be stratified by age, meaning that, with respect to energy drinks, 14 to 18 year olds were not considered separately and, as already mentioned, the survey period was over 10 years ago.

DAK Report (2017)

During the 2016/17 school year, the DAK health insurance company performed a survey in schools in six German states amongst grades 5 to 10 (ages 10 to 18) (N=6,902) in which the consumption of energy drinks was queried (DAK, 2017). However, the survey on energy drinks was not very detailed, as this was not the primary goal of the study. Of the students who had ever drunk energy drinks, 74% said they currently consumed them, of which 60% occasionally (less than once per week) and 14% frequently (at least weekly). The most common use was reported by male respondents in grades 9 and 10 (13 to 18 years), for which the rate of minimum weekly consumption was 20%. Regarding the amount consumed, 21% of students in grades 9 and 10 (ages 13 to 18) and 11% of students in grades 7 and 8 (11 to 16 years) reported drinking more than 1 can at a time. No information was given on how many cans were consumed when more than one can was consumed. When asked at what occasions they drank energy drinks in the past 30 days, 20% of the students said "before" or "during school" and 28% "when gaming" (DAK, 2017).

3.6.2 Data on the Consumption of Energy Drinks by Adults from Germany

Survey study in 16 EU member states (Zucconi et al., 2013)

In the EFSA-commissioned survey conducted in 16 European Union member states in 2012 (Zucconi, 2013), 30% of 1,553 adults surveyed in Germany (18 to 65 years old, male 49.6%, female 50.4%) stated that they had been drinking energy drinks in the previous year (at the time of the survey). Of these energy drink consumers, 19% stated that they drink energy drinks in quantities of 1 litre and more on certain occasions (in a "single session"). Based on the total number of adults surveyed in Germany, 5% indicated that they had drunk such amounts in a "single session".

Furthermore, of the German adults surveyed, 11% of energy drink consumers used to consume energy drinks 4 to 5 days a week or more frequently. Based on the total number of adults surveyed in Germany, this figure was around 3%, which stated that they regularly consume energy drinks in this way. However, in the study, the amount consumed was not reported together with the frequency of energy drink consumption, therefore chronic caffeine intake from energy drinks cannot be qualified.

BfR Study on the event-related Consumption of Energy Drinks

A study initiated by the BfR on the event-related consumption of energy drinks in 2013 provided indications that energy drinks are consumed in large amounts by some people on certain occasions (BfR, 2013). The survey interviewed attendees at LAN parties, sports events, music festivals and clubs who had consumed more than 500ml of energy drinks or more than 60ml of Energy Shots over the past 24 hours at the time of the survey. A total of 508 interviews were conducted (with 489 interviews for evaluation after data cleansing). The majority of respondents were between 15 and 30 years old, due to the selected events. Few respondents were 31 years or older except for sports events where the average age of respondents was 33 years. Therefore, the results relate primarily to young adults and only partially to adolescents.

On average, those interviewed stated that they had consumed approximately 1 litre of pure energy drinks or 1.5 litres mixed with alcoholic beverages. In particular, according to the data, substantial amounts of energy drinks were drunk at LAN parties due to long waking times of the participants: here the surveyed participants stated that they consumed on average about 1.5 litres of pure energy drinks or about 2.5 litres mixed with alcohol.

The survey also showed that the awareness of the potential health risks of excessive consumption of energy drinks, especially in relation to intense exercise or the consumption of alcohol, was low among those who consumed it.

Further Studies on Energy Drink Consumption of Children and Adolescents in Europe

Most studies on energy drink consumption have been collected in North America, but only studies from Europe are considered below (Visram et al., 2016).

A 2012 to 2013 study conducted in Poland interviewed 2,629 students (12 to 20 years) (junior school 55%, senior school 45%) (Nowak and Jasionowski, 2015). Of the students, 67% said that they consume energy drinks, with more boys consuming energy drinks (75%). About 2% of the young people surveyed consumed energy drinks on a daily basis; corresponding to 3.1% of energy drink consumers, and 8% several times a week; corresponding to 12% of energy drink consumers. The authors said that the subgroup of adolescents who consume energy drinks on a daily basis consumed 205mg of caffeine per day only from energy drinks.

A smaller Polish study (N = 329) with younger children (11 to 13 years), conducted at Warsaw schools in 2009 to 2010, found that 24% of students consumed energy drinks (Wierzejska et al., 2016). Four percent said they consume such drinks several times a week (median: 500ml/week).

Another survey study conducted in Veneto (northern Italy) between 2011 and 2012 involved 916 students with a mean age of 12.2 ± 1.1 years (Gallimberti et al., 2013). Amongst older students (8th grade), 16.5% of boys said that they drink energy drinks at least once a week, compared to about half of that for girls (8.6%). No quantities were listed.

Kristjansson et al. used data from the "2013 Youth in Iceland" study (N = 11267), which collected health-related data from children (10 to 12 years) from all primary schools in Iceland (Kristjansson et al., 2014). Of the boys, 7.1% said that they drink one energy drink or more each day; of the girls it was 2.8%.

In Lithuania in 2012, 1,747 schoolchildren from 10 secondary schools (8th grade, age is not mentioned) took part in a survey in the city of Kaunas on the consumption of certain foods considered "unhealthy" (Vilija and Romualdas, 2014). Of the children surveyed, 21% said they consumed energy drinks on a daily basis. Quantities were not listed.

In a Dutch study, 509 students (11 to 16 years, median 13 years) were interviewed for their caffeine (e.g. coffee) and energy drink consumption (Van Batenburg-Eddes et al., 2014). Of the young people surveyed, 6% drank one or more energy drinks per day. A survey period is not listed.

In Greece, the Greek Food Authority conducted a survey (September 2011 to February 2012) on drink consumption by adolescents (N = 4,562) between the ages of 16-18 (55.4% male) with a focus on energy drinks (Knowledge of Energy Drinks and Consumption Patterns) (EFET, 2012). The study showed that 43.9% of adolescents consumed energy drinks at least once a month. Approximately seven out of ten energy drink consumers (or 30.4% of all participants) said that they consumed energy drinks at least once a week. Of those who consume energy drinks, 17.0% indicated that they had consumed energy drinks for the first time in primary school (6-12 years old), 47.9% in secondary school (13-15 years old) and 23.7% in secondary school (16-18 years old). Of the energy drink users, 8.1% said that the maximum number of energy drinks they consumed in one day was more than 5 drinks (5 cans).

A UK study used data from the “*National Diet and Nutrition Survey (NDNS) 2008-10*” (N = 2,126) to study caffeine intake from various caffeinated beverages (Fitt et al., 2013). For adolescents aged 11 to 18 years, caffeine intake from energy drinks and soft drinks (boys: n = 155, girls: n = 145) was in the same range as caffeine intake from tea (boys: n = 91, girls: n = 90) and coffee (boys: n = 27, girls: n = 27). The average daily intake of caffeine from energy drinks and soft drinks was between 40.8 ± 24.0 (boys) and 36.0 ± 21.6 (girls) mg per day for 11 to 18-year-old consumers. A 95th percentile stratified by age is not specified. Consumption data were collected on the basis of a four-day dietary protocol, which may have led to underestimation of foods that are consumed infrequently.

In order to determine the intake of caffeine, an Austrian study surveyed 700 persons between the ages of 14 and 39 using a semi-quantitative questionnaire (Rudolph et al., 2014). The caffeine intake of all users averaged 357.4 ± 400.4 mg per day and 957.2 mg per day in the 95th percentile. Coffee (60.8%), energy drinks (11.9%) and cola drinks (9.5%) mainly contributed to the caffeine intake. For adolescents aged 14 to 17 years, the average daily intake of caffeine from energy drinks was 46.6 ± 95.7 mg per day. A survey period is not listed.

In an Italian study, 1,213 adolescents aged 12 to 19 were interviewed for caffeine intake from different sources during the 2013/2014 school year (Santangelo et al., 2018). Of the participants, 2.6% (only boys 4.5%) indicated daily consumption of energy drinks. The daily energy drink consumers had a daily intake of 105.8 ± 52.5 mg of caffeine per day from energy drinks.

Verster and Koenig published a review on caffeine intake and caffeine sources in 2018 (Verster et al., 2018). Only studies that were nationally representative and that had recorded caffeine intake from all sources were included in this review. Caffeine intakes were estimated for the US, Canada, Europe, Australia, New Zealand and Asia. Of the five listed works from Europe, three contain data on caffeine intake in Germany. The European studies assessed by the authors are already mentioned in this opinion (see above) (EFSA, 2015; Zucconi et al., 2013; Lachenmeier et al., 2013; Fitt et al., 2013; Rudolph et al., 2014). The authors concluded that across all age groups, energy drinks contribute little to the overall caffeine intake.

Overall, with regard to the acute consumption of energy drinks, it can be assumed that consumption on certain specific days (occasions) in particular can lead to very high intake levels of energy drinks, which is why, from the perspective of the BfR, the individuals with this consumption behaviour represent the actual risk group with regard to the acute risk. National representative studies, which might lead to an underestimation of irregularly consumed foods due to the design of the study, are therefore not suitable for adequately quantifying this risk group. This also applies to other studies that do not query such consumption behaviour.

From the point of view of the BfR, however, the Zucconi study covers this risk group (Zucconi, 2013). The results of the Zucconi study are confirmed by surveys that also query such consumption behaviour (BfR, 2013, EFET, 2012).

The Zucconi study shows that acute high energy drink consumption on certain occasions is widespread in Germany. A substantial proportion of children and adolescents surveyed in Germany using energy drinks (17% of consumers, 10% in total) stated that they consumed these drinks in excessive quantities (1 litre or more) on certain occasions (Zucconi, 2013). This results in caffeine intake levels above what EFSA considers safe intake and therefore poses a risk of possible acute adverse effects from energy drinks.

Regarding regular consumption, about 9% of the energy drink consuming German children and adolescents and 5% of the children and adolescents surveyed in total indicated that they consumed energy drinks 4 to 5 days a week or more, according to the Zucconi study. This consumption behaviour roughly matches the consumption behaviour of children and adolescents from other European countries, where studies have shown that about 2% to 7% of the children and adolescents surveyed consume energy drinks on a daily basis (with the exception of Lithuania, 21%).

From the BfR's point of view, however, the current published data does not adequately capture the chronic intake amount of caffeine from energy drinks among the German population, which means that the proportion of the German population which may be consuming more than what is considered safe according to EFSA, cannot be quantified. Therefore, the risk that could arise from a possible chronic high intake of caffeine from energy drinks is currently not quantifiable.

3.7 Risk Characterisation

In the research (non-systematic search up to January 2018, and occasional studies published later) on intervention studies with energy drinks focusing on cardiovascular parameters, only studies that investigated acute effects in healthy young adults (up to 40 years) could be identified. There was only one study (Hajsadeghi et al., 2016) in which the participants were 15 to 30 years old, but they were not stratified by age. In another study, patients with QT syndrome were studied (Gray et al., 2017). However, this study was not used for the final risk assessment.

3.7.1 Moderate Acute Consumption of Energy Drinks

In summary, the acute moderate consumption of energy drinks in amounts that do not exceed the safe intake of caffeine according to EFSA (200 mg caffeine for healthy adults) does not pose a health risk to the cardiovascular system of healthy adults. This also applies to the other potential ingredients in energy drinks such as taurine, glucuronolactone and inositol in the amounts currently added. The observed changes in blood pressure, QTc interval, heart rate, or myocardial contractility in combination with moderate energy drink consumption appear to be of no health concern if consumption occurs occasionally and under normal (environmental) conditions. In addition, in association with moderate energy drink consumption in young healthy adults, adverse effects have been reported only rarely.

Therefore, taking into account recent literature and mechanisms of action not yet assessed by EFSA (e.g. the potentially inotropic effects of energy drinks and the impact of energy drinks on the QTc interval), the panel's assessment is confirmed that acute intake of up to

200 mg of caffeine - even in the form of energy drinks with other ingredients - does not pose a health risk to healthy adults.

No studies have been published that have investigated a dose-response relationship between acute exposure to energy drinks and possible adverse effects on the cardiovascular system in children and adolescents (BfR, 2017). EFSA concludes that a single-dose acute caffeine intake of 3 mg/kg bw, which is of no health concern for adults, can also be considered safe for children and adolescents since the rate at which children and adolescents metabolise caffeine is at least equal to that of adults (EFSA, 2015). So far, there is no evidence that caffeine levels which are still considered safe for healthy children and adolescents by EFSA are unsafe as an ingredient in energy drinks.

However, a final assessment is not possible due to missing data.

3.7.2 High Acute Consumption of Energy Drinks

In the identified intervention studies with cardiovascular outcomes in combination with energy drink consumption, the maximum intake was one litre, which generally corresponds to a maximum caffeine intake of about 320 mg (possibly higher energy caffeine was used in an open-label study). Intervention studies with a higher energy drink consumption of more than one litre have not been identified. However, such studies with excessive amounts are also unacceptable for ethical reasons.

No conclusions can be drawn on the extent to which a high acute energy drink consumption affects heart rate or myocardial contractility, as the data was either conflicting (heart rate) or the studies were not conducted with energy drink levels greater than 200mg caffeine (myocardial contractility). It should be noted, however, that there are indications that energy drinks have a greater impact on myocardial contractility than other caffeinated beverages without typical energy drink ingredients (Baum et al., 2001; Doerner et al, 2015; Chan et al., 2015).

Caffeine doses of more than 200 mg up to a maximum of 320 mg from energy drinks significantly increased blood pressure, although the changes were only moderate in young healthy adults. However, such amounts of energy drinks consumed (or more) could possibly lead to a higher blood pressure increase when consumed by sensitive individuals, especially in combination with intense physical activity and/or very high alcohol consumption. EFSA also assumes caffeine has an additive effect on blood pressure when taken in combination with exercise (EFSA, 2015). Most importantly, children or adolescents, who are generally less used to caffeine, may be more sensitive to high levels of energy drink exposure.

One litre of energy drink consumption resulted in significant prolongations of the QTc interval in healthy young adults in three out of four studies analysing this endpoint (Basrai et al., 2019; Shah et al., 2016c; Kozik et al., 2016). This effect was not observed in combination with moderate energy drink consumption. In one of these studies, conducted in the US, the induced QTc interval prolongations in healthy young adults were so significant that they could pose a potential health risk (Kozik et al., 2016). However, the intake of caffeine was not reported in this study. The BfR points out that there are no statutory maximum levels for ingredients in energy drinks in the USA. It can therefore be assumed that excessive acute energy drink consumption could trigger harmful QTc prolongations even in some healthy young adults. Since a caffeine dose of 320 mg from energy drinks has already been shown to significantly increase the QTc interval in healthy adults, it can be assumed that more sensitive

individuals, such as children and adolescents, may respond with greater changes in the QTc interval.

In addition, the identified studies with caffeine intake levels exceeding 200 mg from energy drinks reported moderate to severe adverse effects such as palpitations, shortness of breath, severe tremor, severe nausea, anxiety and nervousness in some participants (Basrai et al., 2019; Fletcher et al., 2017; Kurtz et al., 2013; Phan et al., 2014). These undesirable effects seem to become more frequent and stronger as the amount of energy drink consumed increases. However, similar adverse effects were also observed when consuming the caffeine control (if used), suggesting that caffeine may be responsible for most of these undesirable effects. Some people also reported adverse effects after consuming a control drink without caffeine. It is not clear if this is due to other ingredients in this drink or possibly induced excitement about participating in the study.

Since high energy drink consumption (with a caffeine intake exceeding 200mg) was already associated with adverse effects in some young healthy adults, it can be assumed that a similar consumption behaviour, especially among more sensitive groups such as children and adolescents may result in similar, if not stronger, effects, as this group is generally less accustomed to caffeine.

According to EFSA, acute single doses of caffeine of 3 mg per kg bw are safe for children and adolescents. The acute intake of caffeine for a 13-year-old boy with a weight of about 50 kg (RKI, 2013) which is still considered safe therefore corresponds to a maximum of 150 mg. Consumption of two commercially available energy drinks, each 250 ml with 80 mg of caffeine, corresponds to consumption of 160 mg of caffeine, which exceeds the value considered safe by EFSA. With consumption of 1 litre (e.g. four cans each of 250 ml), the intake of caffeine would be 320 mg, which would be more than twice as high as the safe level of caffeine for boys with this corresponding body weight.

Since caffeine appears to be responsible for most of the undesirable effects of energy drinks, ingesting other caffeinated foods, if taken in such amounts and within a correspondingly short time, that they give rise to similar high caffeine concentrations in the body, may also produce undesirable effects. However, children's and adolescents' consumption behaviour towards caffeine-containing beverages, such as coffee, is different from their consumption behaviour towards energy drinks (Zucconi et al., 2013; MRI, 2008). Although some adolescents drink coffee, there is currently no evidence that they (or a relevant number of them) consume such drinks in excessive quantities within a short time. On the other hand, energy drinks are consumed in high amounts within a few hours by a substantial proportion of children and adolescents as well as young adults on certain occasions (Zucconi et al., 2013, BfR, 2013), especially at certain events such as LAN parties, music festivals and discotheques (BfR, 2013). In the survey on energy drink consumption in 16 member states of the EU, 17% of children and adolescents consuming energy drinks in Germany said they drink energy drinks in quantities of 1 litre or more during a "*single session*". Based on the total number of children and adolescents surveyed in Germany, 10% indicated that they had drunk such amounts in a "*single session*" (Zucconi et al., 2013). It should be noted that, depending on body weight, as described above, consumption of less than one litre of energy drink may already exceed the safe level of acute caffeine intake according to EFSA, therefore this would increase the proportion of children and adolescents for whom a risk to health exists.

The stated motivation for consuming energy drinks amongst the majority of energy drink consuming children, adolescents and young adults is the flavour, the conviction that energy drinks provide them with energy, the belief that they lead to increased performance, improved concentration and alertness, as well as the visual design and influence of idols and celebrities (Zucconi et al., 2013; EFET, 2012; BfR, 2013; Maschkowski, 2016).

In summary, a potential health risk from excessive acute consumption of energy drinks has been identified for a substantial proportion of children and adolescents. The same is true for adults with a similar consumer behaviour, however the proportion of adults who drink excessive amounts of energy drinks (5% of total respondents) is lower than among children and adolescents (10% of total respondents).

The potential health risks may depend on personal sensitivity to the effects of caffeine. It can therefore be assumed that, in particular, some of the children could have been only slightly exposed to caffeine and could therefore be particularly sensitive to caffeine intake. In addition, individual sensitivity may be influenced by caffeine intake from other sources of caffeine, and possibly by concomitant factors such as alcohol consumption or strenuous physical or athletic activity.

In addition, it was shown for adolescents and young adults that awareness of the potential health risks from excessive consumption of energy drinks, especially in relation to intense exercise or alcohol consumption, was low or insufficient (BfR, 2013). The BfR therefore assumes that children and adolescents generally do not always possess sufficient risk awareness of excessive consumption of these drinks.

3.7.3 Chronic Consumption of Energy Drinks

There are no published studies investigating a dose-effect relationship between chronic exposure to energy drinks and possible adverse health effects in adults or children and adolescents, meaning that the effects of long-term high intake are unclear.

In the expert discussion within BfR "*The Potential Effects of Caffeine on the Cardiovascular System of Children and Adolescents*" from 26 April 2017, some cases from a paediatric cardiology practice were reported, in which cardiac wall thickening had been observed, which should have occurred with a long-term excessive consumption of energy drinks and a correspondingly high intake of caffeine. It was therefore discussed whether children and adolescents who habitually consume energy drinks in amounts that exceed the range of caffeine intake defined by EFSA as safe over a longer period of time may be expected to have long-term effects on the cardiovascular system. The experts present stated that it could not be ruled out that very high, chronic caffeine intake, including in the form of energy drinks, may favour the development of cardiovascular diseases in children and adolescents in the long-term (BfR, 2017). So far, however, no documentation or publications exist regarding the cases mentioned. The BfR notes that for sound and appropriate conclusions based on clinical data, detailed documentation or publication of cases in accordance with scientific standards is considered necessary and important.

So far, no studies exist that have examined such relationships in detail, so that there is no sound scientific information in this regard (BfR, 2017). However, studies on this topic that produce clear results, e.g. a causal relationship, are difficult. Long-term human intervention studies would not be ethically acceptable, especially among children and adolescents. Human observational studies with chronic high consumers compared to a control group would

be conceivable, but associated with a relatively high effort. Since the endpoints to be examined often have multi-factorial causes with regard to the cardiovascular system, numerous other possible causes would have to be ruled out and a correspondingly large number of subjects would need to be examined both with regard to the cardiovascular parameters and dietary habits in order to obtain meaningful results.

According to the study by Zucconi et al. (2013), 9% of the energy drink consuming German children and adolescents and 5% of the total surveyed children and adolescents indicated that they consumed energy drinks 4 to 5 days a week or more, whereby no details about amounts were given. It is therefore unclear whether those German children and adolescents with chronic energy drink consumption exceed the safe levels of caffeine intake set by EFSA and whether a potential health risk exists for 9% of the children and adolescents consuming them. However, a number of cases were reported in which adolescents in Germany consumed excessive amounts of energy drinks in the long-term (BfR, 2017). However, quantification of the risk with regard to chronic energy drink consumption in German children and adolescents is not possible on the basis of the current data.

4 Framework and Recommendation of Measures

Moderate Acute Consumption of Energy Drinks

Taking into account the current scientific data, the BfR concludes that the acute moderate consumption of energy drinks with a caffeine intake that does not exceed the safe levels according to EFSA does not pose a health risk for healthy adults.

The BfR points out, however, that persons with predispositions i.a. for certain heart diseases could be much more sensitive to caffeine intake (Gray et al., 2017).

With regard to moderate acute consumption in children and adolescents, there are no hints that caffeine intake amounts considered safe by EFSA for healthy children and adolescents, also as an ingredient in energy drinks, poses a risk to health, however there are currently gaps in our knowledge concerning this matter in order to perform a final assessment. .

According to Regulation (EU) No. 1169/2011, energy drink products containing more than 150 mg of caffeine per litre must bear the warning: "*High caffeine content. Not recommended for children or pregnant or breast-feeding women*" in the same field of vision as the name of the beverage, followed by an indication in brackets of the caffeine content expressed in mg per 100 ml.

High Acute Consumption of Energy Drinks

Health risks can result from acute overconsumption of energy drinks. In intervention studies with healthy young adults who received energy drink quantities as acute single doses which exceeded EFSA's safe intake levels for caffeine, moderate to more severe adverse effects such as, e.g. palpitations, shortness of breath, severe tremor, severe nausea, anxiety and nervousness were observed in some subjects (Section 3.5.2). In addition, significant prolongations of the QTc interval were observed at given energy drink quantities of 1 L in some intervention studies in healthy young adults (Section 3.5.1.3).

From the BfR's point of view, in particular children and adolescents who ingest high amounts of caffeine that may be of health concern, due to acute high energy drink consumption on certain occasions, can be defined as an at-risk group.

Surveys on consumption behaviour show that a substantial proportion of children and adolescents in Germany (17% of consumers of energy drinks and 10% of total respondents) have indicated that they have consumed excessive amounts of energy drinks (1 litre or more) on certain occasions during a *single session* - which exceeds the caffeine intake level considered safe. For this group of children and adolescents, there may therefore be risks of adverse health effects, in particular with regard to the cardiovascular system.

Adults also drink similar high levels (1 litre and more) during a *single session* to some extent, but the proportion of adults with such a consumption behaviour is lower (5% of the total respondents).

The BfR study on the event-related consumption of energy drinks showed that awareness of the problem of the possible health risks posed by acute, excessive consumption of energy drinks, especially in combination with intensive physical exercise or alcohol consumption, was low or not sufficiently well pronounced among adolescents and young adults. The BfR therefore assumes that children and adolescents in general also have a low awareness of the risk of excessive consumption of these drinks, especially in connection with intensive physical activity and/or high alcohol consumption, or that these population groups are not sufficiently informed about the potential risks of excessive consumption of energy drinks.

As already noted in the report of the experts' discussion of 26/04/2017 (BfR, 2017), the BfR recommends the minimisation of the possible risk of acute excessive consumption identified for children and adolescents. Awareness of the risks of overconsumption of energy drinks amongst children and adolescents could be strengthened through target-group specific measures in the scope of health education and health promotion to prevent health risks and promote an independently healthy lifestyle. Educational programs could be developed to raise awareness amongst children, adolescents, teachers and parents to the potential risks associated with such consumption patterns. In particular, social media could be used as they are used by children and adolescents more intensively than traditional media. In addition to the already existing measures for raising awareness (information leaflet, videos, website with caffeine counter) that are available (Federal Centre for Nutrition (BZfE) homepage), it is recommended that such campaigns to raise awareness should be intensified and expanded in order to achieve a more sustainable impact, especially in schools where the actual risk groups may be reached.

In view of the identified adverse effects associated with high intakes of caffeine or energy drinks (Sections 3.1.3 and 3.5.1.3 and 3.5.2), which may already be present in young healthy adults, further measures might also be considered to counteract potential over-consumption of energy drinks, especially in children and adolescents.

Chronic Consumption of Energy Drinks

The experts who participated in the panel discussion at the BfR on 26 April 2017 agreed that it cannot be excluded that a chronic very high caffeine intake e.g. through the consumption of more than 1 litre of energy drinks per day, could also encourage the development of cardiovascular disorders among children and adolescents in the long term. However, it was found that no studies have examined such relationships in detail, so no sound scientific information is available regarding this. As can be extracted from the BfR result report (BfR, 2017), con-

sideration was given to the importance of future studies, which could contribute to further information on this topic. As intervention studies regarding this which involve children and adolescents could not be justified from an ethical point of view, human observation studies, animal studies and *in-vitro* studies with cardiomyocytes were discussed. With regard to human observational studies, one participant suggested that the extent of caffeine or energy drink consumption should be recorded, together with cardiac parameters, e.g. blood pressure and left ventricular myocardial thickness, within a student group to investigate whether habitual high caffeine or energy drink consumption could be associated with corresponding cardiac changes. The necessary effort, even taking into account the required number of study participants in carrying out such human observational studies in order to obtain meaningful results, has been the subject of controversial discussion. It has been noted that it is difficult to identify causal relationships in such studies, but that such studies could contribute to investigating possible associations.

With regard to the risk to children and adolescents that could be caused by the chronic high consumption of caffeine from energy drinks, the BfR concludes that this risk is not currently quantifiable. There is no reliable exposure data which shows how high the percentage of the German population or possible risk groups, which chronically consume such high quantities of energy drinks that the caffeine quantity still regarded as of no concern by EFSA is exceeded, could be. National representative data collected over 10 years ago is better suited for determining chronic caffeine intake from traditional caffeine-containing foods such as coffee, tea and chocolate in the view of the BfR, as it is not to be assumed that the presence of these products in the German market and their consumption over the last 10 years has changed to any great extent. With energy drinks, however, it has to be assumed that they currently have a stronger market presence than they did 10 years ago (Statista, 2017). In addition, potential additional circumstances within some consumption surveys (recovery of energy drinks in NVS II, age group considered in the *Comprehensive European Food Consumption Database* on basis of the EsKiMo study) could lead to underestimation of caffeine intake from energy drinks.

However, for the purpose of sample size planning within a study to investigate the risks of chronic high caffeine levels from energy drinks, it would be very important to know how high that proportion of the population which regularly consumes potentially harmful levels of caffeine is. Valid sample size planning is necessary in order to obtain statistically sound results on the one hand and to perform appropriate resource planning on the other hand. For reasons of proportionality, the BfR therefore recommends initially collecting valid exposure data regarding chronic caffeine intake amount from energy drinks. This could be done on the basis of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS Welle 2) for example (RKI, 2017). Consideration could then be given for possible further studies on the basis of the exposure data.

German Federal Institute for Risk Assessment (BfR)

Appendix

Table 1: Intervention Studies with Energy Drinks Focusing on Cardiovascular Parameters
(Status: January 2018, individual studies added later)

Reference	Study design	Participant number(n)	Control(n) Caffeine=C Placebo=P	Age (years)	ED amount, Dose of: Caffeine, Taurine, glucuronolactone (GL), inositol	Main endpoint	Time interval between ED consumption and measurement	Effect
(Al-Fares et al., 2015) Saudi Arabia	controlled, single blind, <i>cross-over</i>	32	P (32) Juice	19.93 ± 0.8	ED: 4 ml per kg bw Caffeine: Amount ?	BP, HR	45 minutes	No significant differences were observed between ED and placebo groups with respect to BP or HR before or after exercise.
(Alford et al., 2001) United Kingdom	Randomised, controlled, double blind, <i>cross-over</i>	10	P (10)	18 to 30	ED (250 ml) Caffeine: 80 mg Taurine: 1000 mg GL: 600 mg	BP, HR	0.5 h	No significant changes in BP were measured. The HR was not significantly increased in an initial study, but increased in a second study from 75.9 bpm before ED consumption to 83.3 bpm after consumption.
(Alsunni et al., 2015) Saudi Arabia	Cross-sectional study	31 (18 with overweight and 13 with normal weight)		18-22	ED: 5 ml per kg bw ED-content per 250 ml Caffeine: 80 mg	QTc, HRV	0.5 to 1 h	Compared to the normal weight group, the overweight group showed a significant increase in the QTc interval 2 h after ED consumption ($p = 0.006$). QTc from graph: before ED consumption: Overweight group approx. 347 ms and normal weight group approx. 327 ms; 60 minutes after ED consumption: Overweight group approx. 367 ms and normal weight group approx. 333 ms), whereby the overweight group already had a higher QTc value at time point 0. HRV in the overweight group significantly lower compared to normal weight group.
(Baum and Weiss, 2001) Germany	Controlled, double-blind, <i>cross-over</i>	13 Endurance athletes	C (13), P (13) Juice	26 ± 4	500 ml ED: Caffeine: 160 mg Taurine: 2000 mg GL: 1200 mg	Cardiac contractility: HR, FS, LVESD	40 min after drinking before <i>cycling</i> and after <i>cycling</i> in the regeneration phase	After "drink and exercise", a significant reduction of LVESD was only observed in the original Red Bull group (from 33.3 ± 4.2 to 31.6 ± 4.9 mm) and an increased stroke volume (of 80.4 ± 21.4 ml to 97.5 ± 26.2 ml). This effect was not observed in the placebo group and not in the caffeine group. Combination of taurine and caffeine possibly responsible for increasing the left ventricular contractility of the heart.

Reference	Study design	Participant number(n)	Control(n) Caffeine=C Placebo=P	Age (years)	ED amount, Dose of: Caffeine, Taurine, glucuronolactone (GL), inositol	Main endpoint	Time interval between ED consumption and measurement	Effect
(Basrai, 2019) Germany	Controlled, randomised, double-blind, cross-over	38	C (19) Control drink + caffeine P (19) Control drink	18 to 25	Within one hour: ED up to 1000 ml: Caffeine: 320 mg Taurine: 4000 mg GL: 308 mg Inositol: 92 mg	BP, HR, QTc and others	Up to 11 h	Individual substances (control drink (CD), CD + caffeine, CD + taurine, CD + caffeine + taurine, CD + GL and ED) were also tested. Only consumption of ED after 1 h showed significant prolongation of QTc interval compared to baseline (from 393.3 ± 20.6 ms to 400.8 ± 24.1 ms). CD + caffeine + taurine and CD + GL showed a significant decrease in the QTc interval. HR and the SBP increased significantly after consumption of ED (from 61.5 (56.0 - 67.8) bpm to 64.5 (58.3 - 68.8) bpm and from 116.9 ± 10.4 mmHg, to 120.7 ± 10.7 mmHg). SDB increased significantly with CD + caffeine (from 115.8 ± 11.8 mmHg to 123.3 ± 8.7 mmHg). DBP increased significantly after CD + caffeine and CD + caffeine + taurine. Serious adverse symptoms, in 5 out of 38 participants, were only seen after the administration of EDs (severe tremor, severe nausea) or CD plus caffeine (severe tremor, severe agitation). Adverse symptoms also occurred in other interventions.
(Brothers et al., 2016) USA	randomised, double-blind, controlled, cross-over	15	C (15) Coffee: 2 mg caffeine/ kg bw P (15) Water	27 ± 4	Within 20 minutes ED: 3 mg caffeine/ kg bw 2 mg caffeine/ kg bw max: up to 720 ml ED Taurine, GL, inositol	QTc, BP, HR	Up to 6.5 h	No change in QTc interval, HR and SBP. Only minor changes to the DBP.
(Doerner et al., 2015) Germany	Controlled, open label, cross-over	32	C (10) coffee drink 340 mg caffeine/l	28 (MV)	Within 5 minutes: 168 ml ED / m ² body surface area ED content per L Caffeine 320 mg Taurine: 4000 mg Administered on average: Caffeine: 105 mg Taurine: 1304 mg GL: approx. 800 mg?	Cardiac contractility: HR; PSS; PSSR; LVEDV, LVSV, LVEF, Blood pressure: SBP and DBP	1 h	ED consumption led to significant increases in PSS and PSSR (parameters for cardiac contractility) 1 h after ED consumption. This effect was not observed in the caffeine group. The LVSV (ml) increased slightly in both the ED and caffeine groups, but the effect was not significant in the caffeine group. Before and after ED consumption, there were no significant changes in SBP, DBP and HR. The caffeine drink also did not demonstrate any significant changes in SBP, DBP and HR.
Reference	Study design	Partici-	Control(n)	Age	ED amount,	Main end-	Time interval	Effect

		pant number(n)	Caffeine=C Placebo=P	(years)	Dose of: Caffeine, Taurine, glucuronolactone (GL), inositol	point	between ED consumption and measurement	
(Elitok et al., 2015) Turkey	Open-label	52		25 ± 2.3	355 ml ED Caffeine: 114 mg Taurine: 1420 mg, GL: 84.2 mg	QTc; Tp-e interval; Tp-e/QTc, HR, SBP, DBP	Up to 2 h	Significant increase in HR (77.96 ± 14.94 bpm versus 84.8 ± 10.7 bpm) and SBP (112 ± 6.1 versus 121 ± 7.4 mmHg) and DBP (73 ± 5.3 versus 76.3 ± 6.2 mmHg) were measured relative to baseline at 2 h after consumption of ED. The other parameters such as QTc interval were not changed significantly.
(Fletcher et al., 2017) USA	Randomised, controlled, double blind, cross-over	18	C (18) juice + 320 mg caffeine)	26.7 ± 4	Within 45 minutes: 946 ml ED Caffeine: 320 mg Taurine: Amount ? GL: Amount ? Inositol: Amount ?	QTc, BP	1 to 24 h	Within the ED arm, the QTc interval was barely changed compared to baseline. Compared to the caffeine group, there was a significant difference in the QTc interval after 2 h, but this was due to the reduction of the QTc interval in the caffeine arm. Higher SBP increase in the energy drink arm compared to the caffeine arm (4.72 ± 4.67 versus 0.83 ± 6.09 mmHg, p = 0.01). No changes in DBP. With regard to ED consumption, the greatest BP changes were observed after 1 h compared to baseline (SBP: 6 ± 6.64 and DBP: 4.25 ± 4.01 mmHg). The HR increased by 3.39 ± 11.04 bpm from baseline after 2 h, but not significantly. Both PT of the ED group (83%) and PT of the caffeine group (72%) complained of adverse effects (dizziness, nausea, nervousness, etc.)
(Franks et al., 2012) USA	Controlled, randomised, open-label, cross-over	9	C (9) water + 80 mg caffeine	18 to 45	Every 3 to 4 hours over 24 hours: Each 8.3 oz ED (approx. 250 ml) with Caffeine: 80 mg Taurine: 1000 mg	24-hour blood pressure	Up to 24 h	Compared to caffeine supplementation, the mean 24-hour SBP (123.2 versus 117.4 mmHg, p = 0.04), DBP (73.6 versus 68.2 mmHg, p = 0.02) as well as the 24-hour mean arterial BP (90.1 versus 84.8 mmHg, p = 0.03) were significantly higher during ED supplementation. Compared to baseline, SBP increased from 120.9 to 127.0 mmHg during the day after ED consumption, DBP decreased from 78.3 to 77.0 mmHg during the day, and HR increased from 73.1 bpm to 75.9 bpm during the day. No adverse effects were observed.
Reference	Study design	Partici-	Control(n)	Age	ED amount,	Main end-	Time interval	Effect

		pant number(n)	Caffeine=C Placebo=P	(years)	Dose of: Caffeine, Taurine, glucuronolactone (GL), inositol	point	between ED consumption and measurement	
(Grasser et al., 2014) Switzerland	Controlled, randomised, open-label, cross-over	25	P (25) Water	22.5 ± 0.6	Within 4 minutes: 355 ml ED Caffeine: 114 mg Taurine: 1420 mg GL: 84.2 mg	BP, HR, CO Respiratory rate, cerebral blood flow	Up to 2 h	Significantly higher SBP increase after ED consumption compared to water control (3.3 ± 1.0 mmHg versus 0.3 ± 0.7 mmHg, p = 0.005) and DBP compared to water control (4.1 ± 0.7 mmHg versus 1.3 ± 0.4 mmHg, p = 0.005). Likewise, the HR (from graph: approx. + 3 bpm after approx. 1.5 h) and the cardiac output were significantly increased (p < 0.05). ED consumption resulted in increased respiratory rate and reduced cerebral blood flow velocity. The energy drink significantly increased CO.
(Grasser et al., 2015) Switzerland	Controlled, randomised, open-label, cross-over	20	P (20) Water	22.1 ± 0.5	Within 4 minutes: 355 ml ED Caffeine: 114 mg Taurine: 1420 mg GL: 84.2 mg	BP, cerebral blood flow, CO, SV	1.5 h	Consumption of the energy drink led to significant increases in SBP (+ 7 mmHg) and DBP (+ 4 mmHg) and HR (+ 7 bpm). Cerebral blood flow decreased significantly more after the energy drink than after water (- 9 versus - 3 cm/s, p < 0.005). Additional mental stress significantly increased SBP and DBP by + 3 mmHg and HR by + 13 bpm. Energy drink consumption led to significant increase in CO.
Gray et al., 2017 Australia	Randomised, double-blind, cross-over	24 Patients with QT syndrome	P (24)	16 to 50	Within 30 minutes: 2 x sugar-free ED with total: Caffeine: 160 mg Taurine: 2000 mg	QTc, BP	1.5 h	QTc: Three patients showed a QTc prolongation of ≥ 50 ms to 480 to 550 ms after ED consumption. But no significant difference was found between the ED and control group. Significant differences in BP between groups (SBP: + 7 ± 16 mmHg vs + 1 ± 16 mmHg, p = 0.046); DBP: + 8 ± 10 mmHg vs + 2 ± 9 mmHg; p = 0.01).
(Hajsadeghi et al., 2016) Iran	Open-label	44		15 to 30	250 ml ED Caffeine: 80 mg Taurine: Amount ? GL: Amount ?	HR, QTc, ST-T, SBP, DBP	Up to 4 h	Compared to baseline, significant drop in HR from 79.9 bpm to 74.8 bpm 2 h after ED consumption. No significant changes in the QTc interval. There were hardly any changes in the SBP (from 113.4 mmHg before consumption to 113.9 mmHg 30 min after ED consumption) and DBP (from 76.3 mmHg before consumption to 78.6 mmHg 4 h after ED consumption). Significant ST-T changes after consumption of ED (p = 0.004). No adverse effects were observed.
Reference	Study design	Partici-	Control(n)	Age	ED amount,	Main end-	Time interval	Effect

		pant number(n)	Caffeine=C Placebo=P	(years)	Dose of: Caffeine, Taurine, glucuronolactone (GL), inositol	point	between ED consumption and measurement	
(Higgins et al., 2017) USA	Open-label	11		24.5 ± 1.5	Within about 1 minute: 24 oz (approx. 720 ml) ED: Caffeine: 240 mg Taurine: 2000 mg GL: Amount ? Ginseng extract: 400 mg	HR, SBP, DBP, Endothelial function	1.5 h	Compared to baseline, HR, SBP and DBP did not differ significantly. But significant difference in endothelial function.
(Kozik et al., 2016) USA	Open-label	14		18 to 40	Within one hour: 32 oz (960 ml) ED: Caffeine: Amount ? Taurine: Amount ? GL: Amount ?	SBP, QTc	Up to 4 h	SBP significantly increased compared to baseline (132 ± 7.83 versus 151 ± 11.21 mmHg, p = 0.001), QTc interval significantly increased compared to baseline (423 ± 22.74 versus 503 ± 24.56 ms, p < 0.001)
(Kurtz et al., 2013) USA	Controlled, randomised, double-blind, cross-over	20	P (20) decaffeinated Energy Shot	18 to 40	Energy Shot Caffeine: 138 to 215 mg Taurine: Amount? GL: Amount ?	BP, HR	1 to 5 h	When comparing caffeinated and decaffeinated Energy Shots, BP increased greater after consuming the caffeinated Energy Shot. The difference between the two groups for the SBP was 6.08 ± 7.71 mmHg after one hour, p = 0.001. The difference in DBP was 5.18 ± 8.38 mmHg after one hour, p = 0.007. HR did not differ between the two groups. No indication to what extent consumption of ED increases BP in relation to baseline only. Both Energy Shot and control group reported adverse reactions (restlessness, abdominal pain, etc.)
(Majeed et al., 2017) Saudi Arabia	Open-label	50		18 to 22	5 ml/kg bw ED 1 can energy drink: Caffeine: 80 mg Taurine: 100 mg GL: 600 mg	BP, VR	1 h	Compared to baseline, SBP increased 1 h after ED consumption within the NW group from 122.3 to 131.9 mmHg and within OW group from 120.3 to 129.1 mmHg and DBG with NW from 74.9 to 79.0 mmHg and with OW from 71.6 to 77.2 mmHg. One hour after consumption, a significant decrease in the Valsava ratio was observed in overweight/obese subjects and in normal and overweight/obese women.
Reference	Study design	Partici-	Control(n)	Age	ED amount,	Main end-	Time interval	Effect

		pant number(n)	Caffeine=C Placebo=P	(years)	Dose of: Caffeine, Taurine, glucuronolactone (GL), inositol	point	between ED consumption and measurement	
(Marczinski et al., 2014) USA	Controlled, double-blind, cross-over	14	P (14)	18 to 29	Within one minute: Energy Shot (57 ml) Caffeine: 200 mg Taurine: Amount? GL: Amount?	(Emotional state), BP, pulse rate	0.5 to 6 h	Energy Shot consumption increased SBP compared to baseline (from graph: from approx. 115 to 121 mmHg after 1 h) and DBP (from graph: from approx. 72 to 74 mmHg after 2 h).
(Menci et al., 2013) Italy	Controlled, single-blind, cross-over	35	P (35)	25 ± 2	Within 5 minutes: 168 ml ED / m ² body surface area ED content per L Caffeine: 320 mg Taurine: 4000 mg GL: 2400 mg	Cardiac contractility: MAPSE, GLS, LV-twisting, TAPSE, global RVLS free wall RVLS Blood pressure: SBP and DBP	1 h	Parameters related to left ventricular function were significantly elevated compared to baseline and suggest an increased contractility after ED consumption: MAPSE (from 15.6 ± 1.6 mm to 17.2 ± 1.8 mm, p < 0.001), GLS (from -20.5 ± 2.2% to -22.5 ± 3.2%, p = 0.004), LV twisting (from 10.9 ± 4.1 to 13.5 ± 6.3 degree, p < 0.0001). The right ventricular function was also increased: TAPSE (from 21.7 ± 2.9 mm to 25 ± 3.5 mm, p < 0.0001), global RVLS (from -23.2 ± 3.8% to -24.9 ± 3.9%, p = 0.001) and free wall RVLS (from -28.7 ± 5.9% to -30.3 ± 6.1%, p = 0.1). SBP, DBP and HR did not differ significantly after ED compared to baseline.
(Miles-Chan et al., 2015) Switzerland	Controlled, randomised, cross-over	18	C (18) Energy drink (sugar-free) or Water + 120 mg caffeine P (18) Water	25.4 ± 1.3	Within 4 minutes: 355 ml ED: Caffeine: 114 mg Taurine: 1420 mg GL: 85 mg Inositol: Amount ? 39 g sugar	Blood pressure: SBP and DBP Cardiac parameters: SV, CO contractility index, double product	0.5 to 2 h	With respect to cardiac function (contractility), only the sugary Red Bull drink had significant effects on HR, SV, CO, contractility index and double product (p < 0.01). However, both ED with sugar and ED with no sugar and the "caffeine-only" drink increased BP significantly compared to the "water-only" control (3-4 mmHg, p < 0.001). From graph: 70 minutes after "RB + sugar" consumption, SBP increased by about 7 mmHg and DBP by about 4 mmHg compared to baseline.
Reference	Study design	Partici-	Control(n)	Age	ED amount,	Main end-	Time interval	Effect

		pant number(n)	Caffeine=C Placebo=P	(years)	Dose of: Caffeine, Taurine, glucuronolactone (GL), inositol	point	between ED consumption and measurement	
(Phan and Shah, 2014) USA	Controlled, randomised, double-blind, cross-over	10	P (10) decaffeinated Energy Shot	18 to 40	Energy Shot Caffeine: 215 mg	BP, HR, ejection time	1 to 3 h	After 3 h peripheral SBP increased significantly more in the caffeine-containing shot compared to the decaffeinated shot (8.30 ± 4.19 mmHg versus -0.20 ± 5.55 mmHg, $p = 0.009$) compared to baseline. Similarly true for central SBP (8.00 ± 4.03 mmHg versus 1.50 ± 6.57 mmHg, $p = 0.045$) and peripheral pulse pressure (4.00 ± 4.57 mmHg versus -1.50 ± 3.5 mmHg, $p = 0.009$). A stronger increase was also observed in DBP, but was not significant. Other cardiac parameters, e.g. HR and ejection time did not differ between groups. In the Energy Shot group, 2 participants reported tachycardia and 1 participant reported dizziness. In addition, 1 control group participant reported headaches.
(Ragsdale et al., 2010) USA	Double-blind, controlled	68	P (?) Water + dextrose	19.8 ± 1.6	250 ml ED Caffeine: Amount ?	BP, HR, QTc	1 to 2 h	1 h after consumption of normal caloric energy drink, SBP increased from 117 ± 10.9 mmHg to 124.5 ± 10.1 mmHg, DBP from 76.8 ± 8.6 mmHg to 77.9 ± 8.6 mmHg and HR decreased from 75.1 ± 16.2 to 72.8 ± 16.0 bpm. QTc unchanged.
(Rashti et al., 2009) USA	Controlled, randomised, double-blind, cross-over	10	P (10) Juice	$20.4 \pm 0,7$	Within 30 minutes: 140 ml ED Caffeine: 230 mg	BP, HR	1 to 3 h	2 h after ED consumption, mean SBP increased from 110.0 ± 3.9 mmHg to 112.2 ± 4.9 mmHg compared to baseline. However, a significant difference between the ED and placebo group already existed at the starting point, prior to consumption of the drinks. DBP and HR did not differ between the two groups.
(Shah et al., 2016a) USA	Meta-analysis (prospective clinical trials)	322-340		18 to 40 (One study of 15)	Caffeine: 80 to 240 mg and possibly more (946 ml ED)	SBP, DBP, HR	0.5 to 6 h	SBP and DBP increased significantly by 4.44 mmHg (95% CI: 2.71 - 6.17) and 2.73 mmHg (95% CI: 1.52 - 3.95) after ED consumption, while HR did not change significantly. With regard to SBP, the greatest changes were observed after intake of ≥ 200 mg caffeine (6.44 mmHg (95% CI: 4.62 - 8.27)).
Reference	Study design	Partici-	Control(n)	Age	ED amount,	Main end-	Time interval	Effect

		pant number(n)	Caffeine=C Placebo=P	(years)	Dose of: Caffeine, Taurine, glucuronolactone (GL), inositol	point	between ED consumption and measurement	
(Shah et al., 2016b) USA	Controlled, randomised, double-blind, cross-over	26	P (26) Juice	18 to 40	2 x daily over 7 days: Energy Shot (2 oz) Caffeine: Amount ?	BP, QTc	1, 3, 5 h on 1 st and 7 th day	On the first day after ED consumption, SBP increased: from 120 ± 9 mmHg to 128 ± 10; DBP increased from 77 ± 6 to a maximum of 83.8 ± 8; HR increased from 65 ± 8 to 70 ± 10; QTc was extended from 414 ± 17 ms to 422 ± 15 ms, but not significantly. On the 7 th day: Differences in BP before and after consumption were less.
(Shah et al., 2016c) USA	Controlled, randomised, double-blind, cross-over	30	P (30) Juice + ginseng or juice	18 to 40	ED (2 x 16 oz = approx. 480 ml) Caffeine: 320 mg Taurine: 4000 mg GL: Amount ? Ginseng: 800 mg	BP, QTc, HR	1 to 5.5 h	2h after consumption, SBP increased significantly more in the ED than in placebo group (2.00 ± 6.37 mmHg versus - 2.67 ± 5.83 mmHg, p = 0.014) compared to baseline. The maximum change in SBP from baseline was 6.80 ± 6.9 mmHg. At 2 h after consumption, the QTc interval prolonged significantly more after ED than after placebo (3.37 ± 10.7 ms versus - 3.19 ± 11.8 ms, p = 0.03) (no absolute data listed) compared to baseline. HR and DBP remained unaffected. The ginseng beverage showed no significant effects on the measured parameters.
(Steinke et al., 2009) USA	Prospective open-label study	15		18 to 40	Within 30 minutes 500 ml ED daily over 7 days: Caffeine: 200 mg/day Taurine: 2000 mg/day GL: Amount ?	BP, HR; QTc	0.5 to 4 h Measurement on 1 st and 7 th day	After ED consumption, SBP increased significantly compared to baseline both on the 1 st day (from 109.9 ± 12.4 mmHg to 118.6 ± 16.1 mmHg, p = 0.006) and after 7 days of ED consumption (from 108.9 ± 12.9 mmHg to 119.4 ± 17.6 mmHg, p < 0.001). DBP increased significantly on the 1 st day (from 68.3 ± 11.6 mmHg to 73.1 ± 11 mmHg, p = 0.046) and not significantly after 7 days. HR increased significantly on the 1st day 4 h after consumption (from 65.4 ± 12.4 bpm to 73.5 ± 12.5 bpm, p = 0.009) and after 7 days (from 66.2 ± 14.0 bpm to 70, 5 ± 14.4 bpm, p < 0.001). The QTc interval did not change significantly. Mild adverse effects, e.g. restlessness, gastrointestinal complaints, etc. were reported.
Reference	Study design	Partici-	Control(n)	Age	ED amount,	Main end-	Time interval	Effect

		part number(n)	Caffeine=C Placebo=P	(years)	Dose of: Caffeine, Taurine, glucuronolactone (GL), inositol	point	between ED consumption and measurement	
(Svatikova et al., 2015) USA	Controlled, randomised, cross-over	25	P (25) Juice	18 and older?	Within 5 minutes 480 ml ED: 240 mg caffeine, 2000 mg taurine	BP, HR	0.5 h	After ED consumption, SBP increase was significantly higher compared to the placebo with regards to the baseline SBP (6.2% versus 3.1%; from 108.4 to 115 mmHg versus 108.3 to 111.6 mm Hg, $p = 0.01$), as well as DBP (6.8% versus 0%, $p = 0.001$), and mean BP (6.4% versus 1%, $p < 0.001$). HR did not differ between the two treatment periods.

Table 2: Case Reports in Temporal Context with Energy Drink Consumption. Causal relationships were not determined. (Status: October 2017, with individual case reports added subsequently).

Reference	Person	Quantity of energy drinks (ED)	Effects	Known pre-existing medical conditions (PEMC)	Additional parameters
(Avci et al., 2013) Turkey	m 28 years	3 cans ED each 250 ml 240 mg caffeine	Ventricular tachycardia. Death by sudden cardiac arrest on 3 rd day after hospitalisation. Tachycardia and nausea before; unconsciousness during exercise	No PEMC, no family history (interview)	During basketball game 5 h after ED consumption, with regular ED consumption for 7 months (1 ED per day)
(Babu et al., 2011) USA	m 15 years	2 cans in quick succession (Energy Shot)	Observed tonic-clonic epileptic seizure, lasting 1 minute, 2 hours after consumption of ED, frequent vomiting in hospital Follow-up: no further seizures after 2 months of ED abstinence	So far, no epileptic seizures, no PEMC mentioned	Consumption before school plus 1 cup of coffee, occasional ED drinker, but so far no effects
(Benjo et al., 2012) USA	m 24 years	3 cans ED with vodka	Acute thrombosis in main coronary vessel, beforehand 10 hours nausea, vomiting, palpitations, chest pain	No PEMC, no family history (interview)	+ alcohol, marijuana consumption 1 week beforehand, no more than 5 cigarettes per week
(Berger and Alford, 2009) Australia	m 28 years	7 to 8 cans of ED	ST segment elevation myocardial infarction (STEMI), therapy, discharged after 6 days, Follow-up: no further complaints after 2 months with therapy	No PEMC, no family history	At motocross races
(Berigan, 2005) USA	m 25 years	6 to 8 oz ED daily (240 ml) 800 mg of caffeine per day	Anxiety disorder Follow-up: symptom-free after 3 months ED abstinence	No PEMC	
(Calabro et al., 2012) Italy	m 20 years	4 to 6 cans of ED daily	Observed tonic-clonic epileptic seizure. Follow-up after 2 years: no more seizures	No epileptic PEMC	4 to 6 cans of energy drink daily for five months, otherwise no drugs
(Cannon et al., 2001) Australia	f 25 years	55 ml bottle of Energy Shot Analysis: 10 g of caffeine per litre -> 550 mg caffeine / 55 ml	Death by ventricular fibrillation	Mitral valve prolapse	

Reference	Person	Quantity of energy drinks (ED)	Effects	Known pre-existing medical conditions (PEMC)	Additional parameters
(Cruzado et al., 2014) Peru	f 31 years	7 to 8 ED (per bottle 81 mg caffeine, 202 mg taurine)	Mania. No further symptoms after 1 month ED abstinence. After 8 months, again ED consumption (2 bottles) and symptoms. Follow-up: over one year of ED abstinence and asymptomatic	No PEMC, sister with bipolar disorder	2 to 5 cups of coffee daily
(Dikici et al., 2013) Turkey	m 37 years	3 cans ED each 250 ml + vodka	Observed tonic-clonic epileptic seizure over 10 minutes, ischemic stroke	So far, no epileptic seizures, no PEMC mentioned	+ Alcohol (regular consumption, occasionally with ED), two packs of cigarettes daily
(Di Rocco et al., 2011) USA	m 14 years	Unknown amount of a caffeine-containing drink	Atrial fibrillation, previous cardiac flutters after race competition. Therapy: Digoxin. Follow-up after 1 month: Symptom-free	No PEMC	Racing competition, Drunk energy drink 5 days beforehand and also noticed cardiac flutter
(Di Rocco et al., 2011) USA	m 16 years	Unknown amount ED at party with vodka	Atrial fibrillation. Previous symptoms of intoxication and vomiting after minor head trauma. Therapy: intravenous fluid intake. Follow-up after 1 week: asymptomatic	Known attention deficit / hyperactivity disorder (ADHD)	+ alcohol
(Dufendach et al., 2012) USA	f 13 years	16 oz ED (480 ml) 160 mg of caffeine almost daily for 2 weeks	Extended QTs (622 ms). Previously tachycardia, chest pain, dizziness. Therapy: Beta blockers	Previously undiagnosed ion channel disease with <i>long</i> QTc syndrome (mutation: G179S-KCNQ1). Father and a sibling also turned out to be positive.	
(Enriquez and Frankel, 2017) USA	m 19 years	8 oz (approx. 240 ml) ED in 2 h	Cardiac arrest after ventricular fibrillation. Release with implanted cardioverter-defibrillator	?	

Reference	Person	Quantity of energy drinks (ED)	Effects	Known pre-existing medical conditions (PEMC)	Additional parameters
(Enriquez and Frankel, 2017) USA	f 23 years	1 can of ED	Ventricular fibrillation. Therapy: Implanted cardioverter defibrillator and a recommendation to refrain from ED and other caffeine sources Follow-up: no complaints after three months	Peripartum cardiomyopathy during the 3 rd pregnancy	
(Gharacholou et al., 2017) USA	m 27 years	Sometimes up to 4 to 5 EDs within 12 hours	Acute ST segment elevation myocardial infarction (STEMI), but normal coronary arteries. Beforehand left-sided chest pain, shortness of breath, diaphoresis, increased blood pressure. Therapy with nitrates and calcium channel blockers	No PEMC, uncle with coronary heart disease	
(Gonzalez et al., 2015) Puerto Rico	m 44 years	One ED before exercise	Dissection of the coeliac artery. Previous epigastric pain, dizziness.	No PEMC	Intense exercise over several hours
(Gorgulu et al., 2014) Turkey	m 21 years	1 to 2 ED daily. 150 mg caffeine, 800 mg taurine, 100 mg inositol and 20 mg glucuronolactone per bottle	Psychosis. Follow-up: with therapy (amisulpride) asymptomatic	No PEMC	Sometimes with some vodka
(Hanan Israelit et al., 2012) Israel	m 24 years	20 cans of ED (XL)	Death by ST elevation myocardial infarction. Previous chest pain, nausea, vomiting	Overweight and slightly elevated blood pressure.	+ 3,4-methylenedioxymethamphetamine (MDMA)
(Harb et al., 2016) USA	m 50 years	4 to 5 ED daily for three weeks	Acute hepatitis. Previously for 2 weeks feeling unwell, loss of appetite, abdominal pain, nausea, vomiting, jaundice, dark urine Follow-up: adjuvantly treated . No transaminitis after 2 weeks of ED abstinence	Chronic HCV infection	
(Hernandez-Huerta et al., 2017) Spain	m 18 years	Last 7 days 6 ED per day (80 mg caffeine / can)	Psychosis. Follow-up: Therapy. Asymptomatic after 2 years of ED and cannabis abstinence	No PEMC	20 cigarettes daily, 3 cannabis cigarettes per day, occasionally alcohol on weekends

Reference	Person	Quantity of energy drinks (ED)	Effects	Known pre-existing medical conditions (PEMC)	Additional parameters
(Iyadurai and Chung, 2007) USA	m 25 years	2 bottles of 24 oz ED (2 x 720 ml)	Observed tonic-clonic epileptic seizure for 2 minutes one hour after consumption of ED. Follow-up: in 6 months of ED abstinence no more seizures	No PEMC, no family history of epilepsy	
(Iyadurai and Chung, 2007) USA	m 19 years	Several 24 oz (720 ml) EDs	Observed tonic-clonic epileptic seizure for 1 minute after two hours of ED consumption. Follow-up: in 6 months of ED abstinence no more seizures	Migraine, no family history	
(Iyadurai and Chung, 2007) USA	m 26 years	> 2 x 24 oz (720 ml) EDs	Observed tonic-clonic epileptic seizure, previous seizures related in time to ED consumption Follow-up: in 2 months of ED abstinence no more seizures.	Migraine,	
(Iyer et al., 2016) USA	m 35 years	2 bottles of ED	Rhabdomyolysis. Previous dark urine and muscle pain. Therapy: Intravenous fluid intake. After three days in the hospital creatine kinase levels dropped Follow-UP: asymptomatic after 2 weeks	No PEMC	
(Jonjev and Bala, 2013) Serbia	m 54 years	Occasional 4 to 5 ED (mostly same energy drink)	Subacute aortic dissection. Chest pain, tiredness, shortness of breath. Surgery. Follow-up: after one year without symptoms	?	
(Jonjev and Bala, 2013) Serbia	m 26 years	5 to 6 ED at a party	Subacute aortic dissection. Previously chest pain	Dilatation of the ascending aorta, bicuspid aortic valve	
(Jonjev and Bala, 2013) Serbia	m 48 years	ED consumption	Subacute aortic dissection.	Familial hypertension	

Reference	Person	Quantity of energy drinks (ED)	Effects	Known pre-existing medical conditions (PEMC)	Additional parameters
(Kaoukis et al., 2012) Greece	m 24 years	ED consumption (with caffeine and 1,3-dimethylamylamine (DMAA))	Reverse Takotsubo cardiomyopathy. Previously chest pain, respiratory arrest, tachycardia. Follow-up: 2 months after treatment with lisinopril and carvedilol normal ventricular function	?	+ 1,3-dimethylamylamine (DMAA)
(Mattioli et al., 2016) Italy	m 22, 23, 26 years	ED consumption 2 x 125 mg caffeine 1 x 80 mg caffeine + alcohol	Atrial fibrillation 8 h after ED consumption. Spontaneous disappearance of atrial fibrillation. Follow-up: in 2 years of ED abstinence no further atrial fibrillation	Anamnesis?, no other clinical symptoms, toxicological screening negative	in one patient + alcohol
(Mounir et al., 2015) Morocco	m 28 years	4 cans (1000 ml) of ED in three hours	Hypokalemia. Previously thirst, sweating, nausea	No PEMC	
(Nagajothi et al., 2008) USA	f 23 years	ED consumption: one Energy Shot and one ED	Supraventricular tachycardia. Previously tightness in the chest, tachycardia. Adenosine therapy.	No PEMC	
(Peake et al., 2007) United Kingdom	m 58 years	1 bottle per week (1000 ml) with 4000 mg caffeine/L for 6 months	Tachycardia-induced dilated cardiomyopathy. Therapy: Digoxin, ramipril and warfarin. Follow-up: asymptomatic with normal ventricular size at 6 months and ED abstinence	No PEMC	
(Polat et al., 2013) Turkey	m 13 years	First time ED consumption	Spontaneous coronary artery dissection (SCAD) and ST elevation myocardial infarction (STEMI). Previous chest pain 8 h after ED consumption. Treatment Follow-up: no more chest pain after 1 month with therapy	No PEMC, no family history	

Reference	Person	Quantity of energy drinks (ED)	Effects	Known pre-existing medical conditions (PEMC)	Additional parameters
(Rottlaender et al., 2012) Germany	f 22 years	6 cans of ED within 4 hours	Cardiac arrest due to prolonged QT syndrome. Resuscitation after adrenaline and electric shock successful. QTc normalised after three days. Discharge with cardioverter-defibrillator and beta-blocker therapy Follow-up: after 1.5 years without symptoms and normal QTc interval	No PEMC, no family history Genetic testing revealed Long-QT syndrome	Discotheque
(Rutledge et al., 2012) USA	m 24 years	First time ED consumption (80 mg caffeine, 1000 mg taurine) + vodka	Ventricular fibrillation after a few swallows. Therapy: Automatic Intracardiac Defibrillator (AICD)	Previously undiagnosed Brugada syndrome (malfunction of the sodium channel), before occasional palpitations, no family history	+ alcohol
(Schoffl et al., 2011) Germany	m 17 years	3 litres of ED in combination with 1 litre of vodka (780 mg caffeine, 4600 mg taurine, 380 g alcohol)	Acute kidney failure. Delivered to the hospital because vomiting and dizziness after two 100-metre runs at school, after the amount of ED was consumed the day before. Therapy with Enalapril. Follow-up after three weeks showed no more pathological findings.	No PEMC reported.	With 380 g of alcohol. Consumed ED bottle with a pack size of 1 litre.
(Scott et al., 2011) United Kingdom	m 19 years	2 to 3 ED daily for a week	ST segment elevation myocardial infarction (STEMI). Previously chest pain, shortness of breath. Therapy for acute coronary syndrome and aspirin, ACE inhibitors and beta-blockers Follow-up: after 2 months with therapy and ED abstinence no further chest pain	Gastroesophageal reflux, otherwise no, no family history	Domperidone

Reference	Person	Quantity of energy drinks (ED)	Effects	Known pre-existing medical conditions (PEMC)	Additional parameters
(Solomin et al., 2015) USA	m 26 years	Usually about 4 litres of ED	ST segment elevation myocardial infarction (STEMI). Previously chest pain, sweating, nausea, vomiting Therapy: Platelet aggregation inhibitor, ACE inhibitor, beta-blocker, statin	Anamnesis?, toxicological screening negative	20 cigarettes a day
(Szpak and Allen, 2012) United Kingdom	m 28 years	14 cans of ED (each 250 ml) in one day	Impulsive suicide. Previously 72 hours without sleep. Previously, no thoughts of suicide and no memory of the suicide incident.	No PEMC, brother committed suicide, another brother died of alcohol and drug overdose, father alcoholic incident.	
(Terlizzi et al., 2008) Italy	f 16 years	4 to 5 cans of ED daily	Postdural Tachycardia Syndrome (POTS). Previously 3 months beforehand orthostatic intolerance and transient unconsciousness, unconsciousness, occurred one week after start of ED consumption Follow-up: one week after ED abstinence asymptomatic, even after 1 year	No PEMC	Professional volleyball player
(Trabulo et al., 2011) Portugal	m 28 years	6 cans of ED	Observed tonic-clonic epileptic seizure for 10 minutes. Initial treatment. Follow-up: no further seizures in 3 months after ED abstinence	No PEMC with regard to epilepsy, but chronic hepatitis C, mitral regurgitation, postinfectious endocarditis	+ coffee Earlier consumption of heroin and cocaine
(Unal et al., 2015) Turkey	m 32 years	5 bottles of ED	Coronary arterial thrombosis, acute anterior myocardial infarction. Previously chest pain, palpitations, vomiting 5 to 6 h after ED consumption	No PEMC, no family history	

Reference	Person	Quantity of energy drinks (ED)	Effects	Known pre-existing medical conditions (PEMC)	Additional parameters
(Unal et al., 2015) Turkey	m 32 years	5 bottles of ED	Coronary arterial thrombosis, acute anterior myocardial infarction. Previously chest pain, palpitations, vomiting 5 to 6 h after ED consumption	No PEMC, no family history	
(Usman and Jawaid, 2012) Pakistan	m 16	About 3 cans of ED daily in the previous two weeks	Tachycardia, hypertension (140-160 / 80-100 mm Hg) Follow-up: after 2 weeks ED abstinence asymptomatic	Not mentioned	
(Vivekanandarajah et al., 2011) USA	f 22 years	10 cans of ED daily two weeks prior	Acute hepatitis. Previously nausea, vomiting, epigastric pain. Intravenous fluid therapy. Follow-up: after 1 month liver parameters decreased	?	
(Ward et al., 2014) USA	m 45 years	3 cans of ED within 3 to 4 h	Ventricular tachycardia, but automatic implanted cardiac defibrillator (AICD), AICD shock 30 minutes after ED consumption	Known heart defect, treated Fallot tetralogy, implanted defibrillator	
(Wilson et al., 2012) USA	m 17 years	3 to 4 cans of ED (80 mg caffeine/can) and 2 to 3 cans of ED (160 mg caffeine/can) the evening before	Acute coronary artery vasospasm. Previously severe chest pain Follow-up: symptom-free within one month of therapy with diltiazem and ED abstinence	Doubtful postinfectious myopericarditis, no family history	
(Zacher et al. 2018) Germany	m 25 years	> 8 cans of ED with strong alcohol	Coronary artery dissection. Previous persistent vomiting and chest pain. Stent therapy.	Hypertension treated with ACE inhibitor.	With alcohol. Average nicotine consumption.

5 List of Abbreviations

BP	Blood pressure
bpm	<i>Beats per minute</i>
ED	Energy drink
DBP	Diastolic blood pressure
FS	<i>Fractional shortening</i>
GLS	<i>Global longitudinal strain</i>
HR	Heart rate
HRV	Heart rate variability
CO	Cardiac output
LV	Left ventricular
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
LVESV	Left ventricular end systolic volume
LVSV	Left ventricular stroke volume
MAPSE	Mitral annular systolic plane systolic excursion
MV	Mean value
NW	Normal weight
PSS	<i>Peak systolic strain</i>
PSSR	<i>Peak systolic strain rate</i>
RV	Right ventricular
RVLS	<i>Right ventricular longitudinal strain</i>
SBP	Systolic blood pressure
SV	Stroke volume
TAPSE	<i>Tricuspid annular plane systolic excursion</i>
PT	Participant
Tp-e	<i>Electrocardiographic T wave</i>
OW	Overweight
VR	<i>Valsava ratio</i>

Further information on the topic Energy Drinks at the BfR website:

A-Z Index on the topic of Caffeine

https://www.bfr.bund.de/en/a-z_index/caffeine-129927.html#fragment-2

„Makes the Heart Beat faster – Caffeine“, Science magazine „BfR2GO“, Issue 2/2018

https://www.bfr.bund.de/cm/429/bfr2go_issue_2_2018_en_caffeine-in-food.pdf

„Frequently asked questions on Caffeine and Foods Containing Caffeine, including Energy Drinks“, BfR FAQ 23 July 2015

<https://www.bfr.bund.de/cm/349/frequently-asked-questions-on-caffeine-and-foods-containing-caffeine-including-energy-drinks.pdf>

BfR Communication No 018/2017 of 9 August 2017 on outcomes of the expert discussion “Potential Effects of Caffeine on the Cardiovascular System of Children and Adolescents”

<https://www.bfr.bund.de/cm/349/outcomes-of-the-expert-discussion-potential-effects-of-caffeine-on-the-cardiovascular-system-of-children-and-adolescents.pdf>



„Stellungnahmen-App“ des BfR / BfR „Opinions app“

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