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Review

Risk assessment of energy drinks with focus on cardiovascular parameters and energy drink consumption in Europe

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A B S T R A C T

To assess the possible cardiovascular risks associated with energy drink (ED) consumption in Europe, a comprehensive literature research was performed in regard to (i) possible ED-induced dose-dependent cardiovascular outcomes, (ii) ED consumption patterns in Europe and (iii) the risks of EDs in combination with alcohol.

The identified intervention studies primarily investigated acute ED effects in young healthy adults. Moderate consumption of EDs corresponding to an acute caffeine intake of up to 200 mg did not result in clinically relevant cardiovascular changes in young healthy adults. However, high intake of EDs (about 1 L) was associated with moderate to severe adverse effects in some participants (i.a. prolonged QTc interval, palpitations).

Studies have indicated that on some occasions, a substantial proportion of ED consuming children and adolescents (12% in 16 EU Member States) drink EDs in high quantities (≥ 1 L). This could pose a possible health risk to this group since adverse effects by such high ED consumption have been observed already in young healthy adults.

Among further measures that might be considered to minimize this identified risk, policy makers could develop information and educational programs with the aim of raising public awareness.

1. Introduction

Energy drinks (ED) are caffeinated soft drinks that contain in addition to caffeine one or more other ingredients such as taurine, glucuronolactone and inositol (AendVO2_FruchtsaftVO, 2012). They were first introduced in Austria in 1987 and are now available in more than 140 countries (Ali et al., 2015). EDs are very popular especially among young adults and adolescents (BfR, 2013; EFET, 2012; Zucconi et al., 2013). The motives behind their consumption have been mainly related to taste, the stimulating effect, the intention to increase physical performance, but also to marketing-related attributes such as the brand design or the influence of the celebrities who advertise them (BfR, 2013; EFET, 2012; Maschkowski, 2016; Zucconi et al., 2013).

Caffeine is the main active ingredient in EDs, which is known to have positive effects on endurance performance and alertness (EFSA, 2011a, b). Generally, it is well tolerated by healthy adults, if consumed in moderation. However, heavy caffeine consumption may increase the risk of adverse effects, including, among others, nervousness, anxiety, insomnia, heart palpitations, tachycardia, increased diuresis, arrhythmia, elevated respiration and gastrointestinal disturbances (EFSA, 2015; Nawrot et al., 2003; Wikoff et al., 2017).

According to the *Food Information to Consumers Regulation* (EU) No 1169/2011, in the European Union beverages containing more than 150 mg/L of caffeine have to be labelled with the indication *"High caffeine content. Not recommended for children or pregnant or breast feeding women"* followed by a quantitative indication of the caffeine content (Regulation (EU) No 1169/2011, 2014).

Moreover, since 2013, national statutory limits for EDs regarding caffeine (320 mg/L), taurine (4000 mg/L), inositol (200 mg/L) and glucuronolactone (2400 mg/L) have been established in Germany (AendVO2_FruchtsaftVO, 2012).

Over the last years a growing body of scientific literature regarding the health effects of EDs and their consumption patterns has been published. Therefore, the aim of the present study was to assess the cardiovascular risk of ED consumption in Europe by reviewing the literature in regard to (i) possible ED induced dose-dependent cardiovascular outcomes (ii) the exposure to such beverages in Europe and (iii) the risks of EDs in combination with alcohol.

Abbreviations: ED, Energy drink; BW, body weight; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; HR, heart rate; HRV, HR variability; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; bpm, beats per minute; QTc, corrected QT interval

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2. Caffeine

Caffeine (1,3,7-trimethylxanthine) is a natural alkaloid found in coffee beans, tea leaves, cocoa beans, yerba mate and many other plants (Nawrot et al., 2003). In addition, caffeine may in certain cases be added to a variety of different foods, such as bakery products, ice cream, sweets, soft drinks and also EDs. The European Food Safety Authority (EFSA) has published positive scientific opinions on the substantiation of health claims related to caffeine in association with mental and physical performance (EFSA, 2011a, b), whereby the positively assessed effect depends on the ingested dose of caffeine. However, due to safety concerns expressed by some EU Member States these claims are currently not authorized in the EU Register of nutrition and health claims and remain “on hold” until final clarification.

2.1. Mode of action of caffeine

The stimulating effects of caffeine are mainly based on its antagonistic activity at adenosine A1 and A2 receptors (Ferre, 2008). Adenosine exhibits a sleep-inducing effect by inhibiting the release of glutamate and dopamine, which are thought to contribute to increased cortical or motoneuron activity. Caffeine binding to adenosine receptors prevents the interaction of adenosine with its receptors, resulting in increased release of glutamate and dopamine with their activating potential (Ferre, 2010). Moreover, caffeine has been shown to increase the plasma concentrations of epinephrine and norepinephrine (Riksen et al., 2009). Repeated administration can lead to tolerance development against many but not all caffeine effects. In regard to blood pressure (BP) and heart rate (HR), such tolerance may develop within days. 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 (Fredholm et al., 1999).

Withdrawal syndromes that may occur after caffeine abstinence include weariness, apathy, weakness and drowsiness, headaches, anxiety, decreased motor behaviour, increased heart rate, and increased muscle tension and, occasionally, tremor, nausea, vomiting, and flu-like symptoms (Fredholm et al., 1999).

2.2. Bioavailability of caffeine

Caffeine is rapidly and completely absorbed after ingestion and easily passes through the blood-brain, placental and blood-testes barriers (EFSA, 2015). In the human liver, caffeine is metabolized mainly to paraxanthine (70–80%), which is then further degraded and finally excreted via the kidney. Metabolism of caffeine to paraxanthine involves the cytochrome P450 monooxygenase isoform CYP1A2, which contributes to 95% of caffeine clearance (EFSA, 2015; Miners and Birkett, 1996).

In adults, caffeine has a plasma half-life of two to eight hours (EFSA, 2015). Pregnant women have an increased plasma half-life for caffeine, which can reach up to eighteen hours at the end of pregnancy in non-smoking women (Aldridge et al., 1981; EFSA, 2015). This observation can be explained by the interaction of caffeine with oestrogens and gestagens which have been shown to inhibit the activity of CYP1A2 (EFSA, 2015). Since neither the fetus nor the placenta can metabolize caffeine, fetuses from caffeine-consuming women are exposed to caffeine for a longer period of time (Grosso et al., 2006). During childhood, the caffeine half-life is stable at two to three hours and then increases again in adolescents and adults (EFSA, 2015; Meltzer et al., 2008).

2.3. Adverse effects of caffeine

The occurrence of adverse effects of caffeine consumption depends on the individual sensitivity to caffeine and on the level of daily consumption, e. g. of caffeinated drinks (EFSA, 2015; Fredholm et al., 1999). Acute adverse effects of caffeine include nervousness, irritability, insomnia, nausea, headache, tremor, increased anxiety, cognitive disorders, increased diuresis, arrhythmia, tachycardia, increased body temperature, elevated respiratory rate, gastrointestinal disorders and reduction of myocardial blood flow (EFSA, 2015; Nawrot et al., 2003; Wikoff et al., 2017). High repeated exposure over an extended period of time to caffeine has been associated with a range of dysfunctions involving the gastrointestinal system, liver, renal system, musculature, and also with a reduced fetal growth in pregnant women (EFSA, 2015; Nawrot et al., 2003).

Case reports of severe poisoning resulting in death due to extremely high caffeine intakes through pills have also been reported (Bonsignore et al., 2014). A life-threatening acute dose of caffeine has typically been estimated at being between 10 and 14 g, though a smaller amount can be life-threatening in children and sensitive populations (FDA, 2018).

2.4. Caffeine intake of no health concern - EFSA's opinion on caffeine

EFSA published an opinion on the safety of caffeine in 2015 (EFSA, 2015). The opinion provides advice on caffeine intakes from all dietary sources that do not give rise to concerns regarding health effects for the general healthy population and subgroups thereof. The EFSA opinion does not consider possible adverse effects of caffeine for people affected by disease or medical conditions, people who take certain medicines and/or drugs in combination with caffeine or individuals who consume large amounts of alcohol.

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 body weight (bw), based on a body weight of 70 kg) from all sources do not raise safety concerns for the general healthy adult population, even when consumed less than two hours prior to intensive physical exercise under normal environmental conditions. According to EFSA, up to this amount it is unlikely that clinically relevant changes in blood pressure (BP), myocardial blood flow, hydration status or body temperature might occur.

For habitual caffeine consumption, EFSA concluded that intakes of up to 400 mg/day (equivalent to 5.7 mg/kg bw/day) do not raise safety concerns for healthy adults in the general population.

For pregnant and lactating women, caffeine intakes from all sources of up to 200 mg throughout the day are, according to EFSA, safe for the fetus and breast-fed child. For breast-feeding women, 200 mg as a single dose is also considered to be safe for the child.

EFSA pointed out that the information available on the relationship between caffeine intakes and health outcomes was insufficient to derive a safe level of caffeine intake for children and adolescents. However, EFSA considered that singles doses of caffeine that were regarded to be of no concern for adults (3 mg/kg bw) may also apply to children, considering that caffeine clearance in children and adolescents is at least that of adults. Similarly, EFSA considered a daily habitual caffeine intake of 3 mg/kg bw/day as safe for children and adolescents (EFSA, 2015).

3. Taurine

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

3.1. Taurine effects on BP

In several studies, taurine has demonstrated hypotensive activity in hypertensive animal models (Abebe and Mozaffari, 2011). In addition, a randomized, double-blind, placebo-controlled human study showed

similar results (Sun et al., 2016). In this study, 120 pre-hypertensive subjects (18–75 years) received either 1.6 g of taurine per day or a placebo for 12 weeks. Taurine significantly reduced 24-h ambulatory BP, especially in those with high normal BP.

3.2. In vitro studies of taurine effects on calcium homeostasis and muscle contraction

Physiological taurine concentrations seem to increase the isometric force in skinned muscle fiber preparations from pig heart and crayfish skeletal muscles, possibly due to an increase of Ca^{2+} sensitivity of the force-generating myofilaments (Galler et al., 1990). Furthermore, in human skinned fibers of the human vastus lateralis muscle, biopsied from 11 healthy individuals, taurine increased the uptake of Ca^{2+} into the sarcoplasmic reticulum (Dutka et al., 2014). In another study, taurine enhanced significantly the depolarisation-induced force response in skinned skeletal muscle fibers of the rat. An augmented Ca^{2+} accumulation in the sarcoplasmic reticulum as well as an increased taurine-induced Ca^{2+} release was observed, indicating interaction of taurine with Ca^{2+} release channels. Furthermore, taurine was shown to increase both the peak and rate of rise of caffeine-induced force responses in the fibers (Bakker and Berg, 2002). Further human studies are discussed in the ED section.

In summary, there are indications that taurine may have a hypotensive activity in prehypertensive persons and might increase myocardial contractility via a Ca^{2+}-dependent mechanism.

3.3. Adverse effects of taurine

The published human studies on taurine are primarily concerned with beneficial effects of taurine ingestion, so that adverse effects are hardly considered. However, the Norwegian Scientific Committee (VKM) identified some studies that also reported adverse effects of taurine supplementation (VKM, 2015b). In succinate semialdehyde dehydrogenase deficiency patients (0.5–30 years) receiving 10 g of taurine per day, acute adverse effects such as fatigue, somnolence, mild ataxia, insomnia and cognitive changes occurred (Pearl et al., 2014). In healthy participants treated with about 5 g per day isolated muscle cramps were observed (Galloway et al., 2008).

3.4. Taurin intake amounts regarded as being of no health concern - opinions from national and international scientific bodies

In 2015, the Norwegian VKM (VKM, 2015b) derived taurine intake levels of no health concern, based on human studies that did not show adverse effects after taurine administration of up to 1500 mg/day (Brons et al., 2004; Sirdah et al., 2002).

Therefore, VKM considered it unlikely that an intake of taurine up to approximately 21 mg/kg bw/day (equivalent to about 1500 mg/day in a 70 kg adult) would cause adverse health effects (VKM, 2015b).

EFSA identified a "*No Observed Adverse Effect Level*" (NOAEL) of 1000 mg/kg bw/day for pathological changes and 1500 mg/kg bw/day for behavioural changes, based on a 13-week subchronic neurotoxicity study with rats. Therefore, EFSA concluded that daily intakes of up to 1400 mg taurine/day (according to EFSA: the intake amount in the 95th percentile of chronic ED consumption, corresponding to 350 ml/day) were of no health concern for humans (EFSA, 2009b; SCF, 2003).

With respect to these derived taurine intake amounts of no health concern, it has to be considered that taurine was assessed as a single substance. Possible interactions of taurine with other substances such as alcohol or with other ingredients in EDs, such as caffeine, were not considered, apart from those on diuretic effects that were thought to be unlikely (EFSA, 2009b).

Data in regard to possible acute toxicity of taurine are not available so far (VKM, 2015b). In addition, there are no data available on high oral long-term taurine intakes (≥12 months).

4. Glucuronolactone

Glucuronolactone is naturally produced in the body as a metabolite of glucose and is a component of fibrous connective tissue (EFSA, 2009b; McLellan and Lieberman, 2012). The glucuronolactone intake by normal food is small (1–2 mg/day). Orally administered glucuronolactone is completely absorbed, hydrolyzed and excreted in urine as glucuronic acid, xylitol and L-xylulose (EFSA, 2009b).

4.1. Studies on glucuronolactone effects

Hardly any studies have been found that examined glucuronolactone as a single substance. In an earlier study, 100 mg glucuronolactone per kg bw or other sugars were injected into rats three times a day. After glucuronolactone administration, positive effects on swimming performance, blood sugar and liver glycogen levels were observed, which were not observed after treatment with the other sugars (Tamura et al., 1968). However, similar observations have been made in other studies after injection of glucose and galactose, suggesting that these effects are based on the known ergogenic effects of carbohydrates in general (McLellan and Lieberman, 2012).

4.2. Adverse effects of glucuronolactone

Human studies investigating the toxicity of glucuronolactone as a single substance have not been identified.

4.3. Glucuronolactone intake regarded to be of no health concern - EFSA's opinion on glucuronolactone as constituent of EDs

EFSA identified a "*No Observed Adverse Effect Level*" (NOAEL) of 1000 mg/kg bw/day for pathological changes, based on a 13-week subchronic neurotoxicity study in rats (EFSA, 2009b).

The EFSA panel concluded that there were no health concerns with respect to daily intakes of up to 840 mg glucuronolactone per day (according to EFSA: the intake amount in the 95th percentile of chronic ED consumption, corresponding to 350 ml/day) (EFSA, 2009b; SCF, 2003).

Data with regard to possible acute toxicity of glucuronolactone are not available so far (VKM, 2015a).

5. Inositol

Inositol, a sugar alcohol ($C_6H_{12}O_6$ (CAS number: 87-89-8)), is a white crystalline odourless powder with a slightly sweet taste, naturally synthesized by almost all plants and animals (EFSA, 2014). It exists in nine possible stereoisomers, four of which are physiologically active. The main form is *myo*-inositol. In nature, inositol exists in a bound as well as in an unbound form. Absorption of free inositol in the small intestine is high, amounting to over 90%.

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 synthesized in the kidney and the level of free inositol in the renal medulla cells is 1000 times higher than in blood. It is estimated that in humans about 4 g of inositol are produced daily. The plasma levels in the kidneys are regulated by glomerular filtration, reabsorption and catabolism or excretion (EFSA, 2014).

5.1. Adverse effects of inositol

A review examined twelve controlled clinical trials involving a total of 250 adults receiving 4–30 g of inositol per day (equivalent to

57–429 mg/kg bw/day for a 70 kg person) over 1–12 months (Carlomagno and Unfer, 2011; VKM, 2015c). The most frequently reported events were nausea (7–12%), flatulence (1–7%), loose stool and diarrhea (number of affected persons not indicated). At a dose of 4 g of inositol per day, mild adverse effects such as mild insomnia and flatulence were reported by only a few participants. Similar adverse effects were also reported in other studies (Lam et al., 2006; Palatnik et al., 2001; VKM, 2015c).

5.2. Inositol intake of no health concern

The quality of the available human studies is not sufficient to derive safe intake quantities. However, in studies with 4 g of inositol per day (equivalent to 57 mg/kg bw/day for a 70 kg person) only a few participants reported mild symptoms such as mild insomnia or flatulence (Carlomagno and Unfer, 2011).

Data in regard to a possible acute toxicity of inositol are not available so far (VKM, 2015c).

6. Energy drink consumption and cardiovascular risk

6.1. Search method

In order to identify intervention studies investigating cardiovascular endpoints after ED administration we performed a non-systematic search in PubMed. We used terms like “energy drink”, “cardiovascular”, “blood pressure”, “heart” and “QT” alone or in combination by concurrently using the PubMed filter “clinical trial”. Titles and abstracts of identified publications were screened so that publications not covering the aim of the search were excluded. In order to identify consumption data of EDs, in particular regarding children and adolescents in Europe, we performed an additional non-systematic search in PubMed using the terms “energy drink” and “consumption” in combination with the term “adolescents” or “students” or “children”. Identified publications were thoroughly evaluated in order to identify relevant European food consumption surveys. For both search approaches, references within relevant papers as well as scientific reports/opinions identified by internet search were also examined. Only articles in English or German were selected for further analysis. Articles were excluded when essential parameters (e.g. lack of baseline values) had not been determined. The searches were completed in January 2018 and selected articles were reviewed. In some cases, studies found later were also taken into account. Additionally, we screened PubMed for case reports, potential adverse effects of EDs combined with alcohol (in both human and animal studies) and for single ingredients of EDs.

6.2. Results

Twenty-eight intervention studies and one meta-analysis with intervention studies assessing the relationship between ED consumption (four were performed with energy shots) and cardiovascular endpoints were identified and thoroughly evaluated (Supplementary Table 1). In these studies only acute effects of ED consumption in almost exclusively young healthy adults (18 and 45 years) were analysed; only one study was performed with patients.

According to the studies examined, the participants consumed the EDs within a short period of time (within a time interval of not more than three hours). In two studies the acute ED dose was administered two to several times daily (Franks et al., 2012; Shah et al., 2016b). In general, the observation time ranged from 0.5 h to 24 h. Two studies expanded the ED intake and observation time over seven days, but measured acute effects on specific days within this period (Shah et al., 2016b; Steinke et al., 2009). When indicated, the caffeine doses administered by EDs ranged mainly from 80 mg to 320 mg/day and the taurine doses, if indicated at all, between 1000 mg and 4000 mg/day (one study with 100 mg taurine). Little information was given for ingested glucuronolactone amounts (84 and 1200 mg/day) and nearly none for inositol.

No intervention study data are available for children and adolescents or for chronic or excessive high (more than 1 L EDs) ED consumption in general.

Regarding the ED consumption behaviour in Europe, we identified fifteen studies containing data involving children, adolescents and/or adults. With regard to case reports, we identified 41 studies from Europe and elsewhere (Supplementary Table 2).

6.2.1. Effects of ED consumption on BP

Certain fluctuations in BP are normal and can be considered as an adaptation response to exogenous and endogenous stimuli. Hypertension is a disease of the vascular system with permanently elevated BP levels (Deutsche Hochdruckliga e.V. DHL, 2015). An acute and severe increase in systolic or diastolic BP ($>$ 180 mmHg systolic or $>$ 120 mmHg diastolic, respectively) is, according to the European Society of Hypertension and the European Society of Cardiology, defined as “hypertensive emergency”, when it is associated with impending or progressive organ damage, or without organ damage as “hypertensive urgency” (Salvetti et al., 2018). There are no clear limits for children and adolescents (DGPK, 2013).

Intervention studies on young healthy adults showed that ingestion of EDs with absorbed caffeine doses of around 100 mg and below did not result in significant changes in BP (Al-Fares et al., 2015; Alford et al., 2001; Doerner et al., 2015). However, acute[1] ED intakes with absorbed caffeine doses of up to 200 mg typically led to a significant increase in SBP by 3–9 mmHg (Elitok et al., 2015; Franks et al., 2012; Grasser et al., 2014, 2015; Majeed et al., 2017; Marczinski et al., 2014; Miles-Chan et al., 2015; Ragsdale et al., 2010; Steinke et al., 2009) and by 2–5 mmHg in DBP (Elitok et al., 2015; Grasser et al., 2014; Hajsadeghi et al., 2016; Majeed et al., 2017; Marczinski et al., 2014; Miles-Chan et al., 2015; Steinke et al., 2009) compared to baseline. Higher acute ED consumption with absorbed caffeine doses between 200 and 320 mg have resulted in similar increments in SBP (Basrai et al., 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) compared to ingested caffeine doses via EDs between 100 and 200 mg. One uncontrolled open-label study showed no significant changes in SBP at ED consumption with caffeine amounts above 200 mg (240 mg) (Higgins et al., 2017). Stronger BP changes were observed in an open-label study performed in the USA, in which 960 ml of a “Monster” ED were administered (Kozik et al., 2016). Here, the SBP increased by nearly 20 mmHg after consumption (from 132 ± 7.83 to 151 ± 11.21 mmHg, $p = 0.001$). However, a control group was not included and the administered caffeine amount was not indicated. In this context, it has to be considered, that in the USA no legal maximum levels have been set for caffeine and other ingredients in EDs. No data are available for higher intakes (more than 1 L ED), for children and adolescents and for chronic consumption.

In general, BP increases 30 min after ED consumption, reaches a maximum after 60–90 min and decreases to baseline after about two to four hours (Basrai et al., 2019; Elitok et al., 2015; Fletcher et al., 2017; Grasser et al., 2014; Hajsadeghi et al., 2016; Kurtz et al., 2013; Miles-Chan et al., 2015; Ragsdale et al., 2010; Shah et al., 2016c), which is consistent with the pharmacokinetics of caffeine (EFSA, 2015).

6.2.2. Effects of ED consumption on HR

An elevated HR at rest is associated with a higher risk of cardiovascular disease and mortality (Cooney et al., 2010). So far, there are no reference values for HR; hence no clear statement can be made regarding the threshold value above which an increased health risk is possible (Stoschitzky, 2011). However, in the USA a revised clinical

[1] The term “acute” is defined as a time period of up to three hours.

guideline based on an analysis of current cardiology practice and epidemiological survey data defines a resting pulse rate of > 90 beats per minute (bpm) as tachycardia and of < 50 bpm as bradycardia (Ostchega et al., 2011).

The identified studies in which ED amounts with no more than 200 mg caffeine were ingested showed an increase in HR (+2 to + 8 bpm, + 16 bpm in connection with sport activity) (Alford et al., 2001; Baum and Weiss, 2001; Elitok et al., 2015; Franks et al., 2012; Grasser et al., 2014, 2015; Steinke et al., 2009), no change (Al-Fares et al., 2015; Doerner et al., 2015; Menci et al., 2013), or a drop in HR (- 3 to - 5 bpm) (Hajsadeghi et al., 2016; Ragsdale et al., 2010). For ED consumption with ingested caffeine doses of more than 200 mg up to 320 mg, two studies showed an increase in HR (although in one study not significantly (Fletcher et al., 2017)) by approximately + 3 to + 4 bpm (Basrai et al., 2019; Fletcher et al., 2017), while in other studies HR was hardly influenced (Higgins et al., 2017; Kurtz et al., 2013; Phan and Shah, 2014; Rashti et al., 2009; Shah et al., 2016b, 2016c; Svatikova et al., 2015). A meta-analysis also showed no significant HR changes after ED consumption (ingested caffeine does between 80 and 240 mg or unknown) (Shah et al., 2016a).

Overall, the outcome data regarding the impact of acute ED consumption on HR is contradictory, so that no firm conclusions can be drawn regarding the effects of acute ED consumption of up to 1 L (corresponding to up to 320 mg caffeine) on HR. Moreover, no data are available for higher intakes (more than 1 L ED), for children and adolescents and for chronic consumption.

6.2.3. Effects of ED consumption on the QTc interval

The QT interval is a measured value in the analysis of the electrocardiogram and represents the duration of ventricular electrical systole, i.e. the time required for completion of both ventricular depolarisation and repolarization (Kautzner, 2002). A significant prolongation of the QT interval indicates a delayed cardiac ventricular repolarization, which may be the cause of a life-threatening ventricular tachycardia, e. g. at worst the Torsade-de-pointes, which can develop into ventricular fibrillation and therefore to sudden cardiac death (FDA, 2005). Prolongations of the QT interval can be congenital (genetic) or acquired and can have many causes such as ion channel diseases, myocarditis, drugs etc. (Lazzerini et al., 2015).

Since the duration of ventricular repolarization shortens with increasing HR, a frequency correction of the QT interval has to be made (QTc) for which a correction formula is used (FDA, 2005; Haverkamp et al., 2002). According to the *German Society of Pediatric Cardiology*, the following threshold values represent a prolonged QTc interval: > 460 ms for children (1–15 years), > 450 ms for male adolescents and men (> 15 years) and > 470 ms for female adolescents and women (> 15 years) (DGPK, 2011).

In the studies which examined the QTc interval and which used ED amounts with no more than 200 mg of caffeine for intervention, this parameter was not significantly affected (Brothers et al., 2016; Elitok et al., 2015; Hajsadeghi et al., 2016; Ragsdale et al., 2010; Steinke et al., 2009). Only in one study with normal-weight and obese subjects QTc prolongation was observed in obese participants at these doses, but overweight subjects exhibit already higher QTc intervals at baseline than normal weight persons (Alsunni et al., 2015).

In the studies in which about one liter ED with 320 mg caffeine was ingested, two showed a significant prolongation of QTc interval, compared to baseline (+3 to + 8 ms) (Basrai et al., 2019; Shah et al., 2016c). In the study by Fletcher et al. a significant difference in the QTc interval was observed after 2 h of ED consumption compared to the caffeine group, but this was due to a reduction of the QTc interval within the caffeine arm after two hours. This difference was not apparent when QTc values before and after ED consumption were compared within the ED arm alone (Fletcher et al., 2017). A serious prolongation of the QTc interval was shown by an open-label study in the USA (Kozik et al., 2016), in which 14 healthy participants consumed 960 ml of a “Monster” ED. In this study, the QTc interval increased on average by 80 ms after ED consumption from 423 ± 22.74 ms to 503 ± 24.56 ms ($p < 0.001$) which represents per definition a “prolonged QTc interval” and which therefore might be a risk for potential adverse heart rhythm disturbances. Unfortunately, the administered caffeine doses were not indicated in this study and are difficult to estimate, as the USA have not set any legal maximum levels for caffeine and other ingredients in EDs.

Moreover, in an intervention study with patients affected by pre-existing familial long QT syndrome, moderate ED consumption with ingested caffeine and taurine amounts of 160 mg and 2000 mg respectively, resulted in a serious QTc prolongation of more than 50 ms up to a value of maximal 557 ms in some participants, though the increase of the QTc interval was not significant for the whole ED group (Gray et al., 2017).

Overall, moderate acute ED consumption with a caffeine intake of up to 200 mg does not seem to affect the QTc interval in young healthy adults (except in a study with overweight persons, but not to a point of concern (Alsunni et al., 2015)). In connection with an ED consumption of 1 L, three out of four studies showed a significant increase of the QTc interval. In one of these studies serious prolongations were induced in young healthy adults by EDs.

No data are available for higher acute intakes (more than 1 L ED), for children and adolescents or for chronic consumption.

6.2.4. Effects of ED consumption on myocardial contractility (e.g. inotropic effects)

Heart function is affected by myocardial contractility. An increase in contractility leads to an increased cardiac output (L/min) (Vincent, 2008). Certain changes in cardiac output can be considered as a temporary adaptation response to the varying oxygen demand of the myocardium and skeletal muscle depending on varying exogenous and endogenous stimuli (e.g. exercise) (Duncker and Bache, 2008). Parameters for recording the contractility of the myocardium include among others the fractional shortening (FS), the peak systolic strain rate and the left ventricular end-systolic diameter (LVESD).

In several identified intervention studies an increased myocardial contractility was observed after ED consumption (Baum and Weiss, 2001; Doerner et al., 2015; Grasser et al., 2014, 2015; Menci et al., 2013; Miles-Chan et al., 2015).

Three of these studies which included a caffeine control group indicated that these effects are pertinent to EDs since in the caffeine control group no effects were observed in these parameters.

In a double-blind cross-over study, 13 endurance-trained athletes received before training either a 500 ml (a) placebo drink (“Red Bull” without taurine, glucuronolactone and caffeine, but with glucose and sucrose) or (b) caffeine control drink (“Red Bull” without taurine, glucuronolactone, but with caffeine (160 mg), glucose and sucrose) or (c) *verum* drink (original “Red Bull” beverage with taurine (2000 mg), glucuronolactone (1200 mg), caffeine (160 mg), glucose and sucrose. Echocardiographic examinations after exercise showed only in the *verum* group a significant increase in fractional shortening and stroke volume of the heart together with a significant decrease in left ventricular end-systolic diameter (LVESD). Since these ventricular effects were not evident in the placebo and caffeine groups, the authors assumed that the combination of taurine and caffeine in the original Red Bull drink increased the left ventricular contractility of the heart (Baum and Weiss, 2001).

In the study by Doerner et al., 32 healthy volunteers drank a body surface-adapted amount of a commercially available ED (168 ml/m^2) with a typical content of caffeine (0.03%) and taurine (0.4%) (in average corresponding to 105 mg caffeine and 1304 mg taurine). Ten of the participants were randomly chosen to serve as a caffeine only control group, who on another day (> 1 week apart) received a commercially available drink with a comparable amount of caffeine (34 mg/100 ml), but without taurine. One hour after ED consumption

cardiac magnetic resonance spectroscopy demonstrated a small but significant increase of the peak systolic strain rate, which is a parameter for regional contractility (Sinning, 2009). This effect was not observed in the caffeine control group. The authors assumed that the ED ingredient taurine was the most probable mediator because of its known positive inotropic effects (Doerner et al., 2015).

In another blinded controlled randomized cross-over study, 18 healthy young men (25.4 ± 1.3 years old) ingested on four separate days, 355 ml of either (1) "Red Bull" (114 mg caffeine, 1420 mg taurine, 85 mg glucuronolactone, 39 g sugar) (2) sugar-free "Red Bull", (3) water + 120 mg caffeine or (4) water (Miles-Chan et al., 2015). Whereas no differences between sugary and sugar-free "Red Bull" and the caffeine-control were observed with respect to BP, different effects were shown on cardiac parameters. Only the consumption of the sugary "Red Bull", but not of the caffeine-control or sugar-free "Red Bull", significantly enhanced HR, stroke volume, cardiac output, the contractility index and the double product (reflecting increased myocardial load) (for all parameters $p < 0.01$). The authors postulated that the impact of sugary "Red Bull" on myocardial function could be an effect of the combination of caffeine and sugar, mediated by insulin to which inotropic effects have been attributed (Miles-Chan et al., 2015).

Overall, there are indications that the consumption of EDs can increase myocardial contractility, an effect that was not induced by the caffeine control drinks in these studies. No data are available for higher intakes (more than 500 ml ED), for children and adolescents or for chronic consumption.

6.2.5. Adverse effects of ED consumption

The following data on adverse effects associated with ED consumption refer only to the identified human intervention studies (acute effects in healthy young adults).

In two studies in which young healthy adults received a single dose of EDs with 80 mg caffeine, it was stated that no adverse effects occurred (Franks et al., 2012; Hajsadeghi et al., 2016).

In the study by Steinke et al. (N = 15) an ED amount with 200 mg caffeine and 2000 mg taurine was administered for seven days (Steinke et al., 2009). Only mild effects such as jitteriness (n = 4), gastrointestinal symptoms or abdominal cramps (n = 3), increased urination (n = 1), disturbed sleep (n = 1) and more forceful heartbeats (n = 1) were indicated. A control group was not included.

In another study, healthy young volunteers (N = 20) who consumed an energy shot amount with 215 mg caffeine (Kurtz et al., 2013) reported the following undesirable effects: jitteriness (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) also reported headache (n = 1), jitteriness (n = 1), palpitations (n = 1), sleepiness (n = 3) and abdominal pain (n = 1).

The same dose of caffeine via energy shots was consumed by 10 participants in another study (Phan and Shah, 2014). Two subjects felt palpitations and another one experienced dizziness with the caffeinated energy shot. One participant who consumed a decaffeinated energy shot reported headache.

In the study by Basrai and co-workers, the acute use of 750 or 1000 ml control product, ED "Red Bull" (320 mg/L caffeine, 4000/L mg taurine, 308/L mg glucuronolactone, 92/L mg inositol), control product plus caffeine or control product plus taurine provoked moderate to severe symptoms in all four interventions in some participants (Basrai et al., 2019). However, after the administration of 1000 ml the highest proportion of participants (7 out of 19) were affected after the use of the ED, whereas after the administration of 750 ml the highest proportion of participants were affected after the use of the control product plus caffeine (6 out of 19). Moreover, *severe* symptoms, which were developed by five out of 38 individuals, occurred only after the administration of ED or the control product plus caffeine (Basrai et al., 2019).

In another study, 15 participants (N = 18) reported the following effects after acute consumption of 946 ml ED (320 mg caffeine, amount of taurine and glucuronolactone unknown): anxiety (n = 3), difficulty falling asleep (n = 4), dizziness (n = 3), dyspepsia/upset stomach (n = 4), epistaxis (n = 1), headache (n = 2), jitteriness (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 undesirable effects (Fletcher et al., 2017).

In the other identified intervention studies adverse or undesirable effects were not discussed and it remains unclear if they were assessed.

Overall, after moderate acute ED consumption with ingested caffeine amounts of up to 200 mg by young healthy adults, adverse effects have hardly been reported. The ingestion of higher amounts of such beverages (up to 1 L) induced modest to severe adverse effects in some participants. However, some persons also indicated adverse effects after drinking higher amounts of the caffeine control without typical other ingredients of EDs. In some studies some individuals reported undesirable effects even after the ingestion of a drink without caffeine. No data are available for higher intakes (more than 1 L ED), for children and adolescents or for chronic consumption.

6.2.6. Case studies on EDs

In recent years, a large number of case reports in association with the consumption of EDs have been published (Supplementary Table 2). The main symptoms observed were cardiovascular (chest pain, tachycardia, infarction, cardiac arrhythmia and cardiac arrest etc.), psychobehavioural (anxiety, psychosis, hallucinations) and neurological (e.g. epilepsy). In healthy adults, adverse effects were observed in a temporal context particularly in cases of very high/excessive ED consumption. However, causal relationships from these case reports could not be assessed.

Moreover, the Food and Drug Administration (FDA) collected a large number of voluntary reports (physicians, family members, consumers) about adverse effects associated with ED consumption in a database, but pointed out that these event reports for specific products did 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).

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) also recorded adverse health effects after the consumption of EDs as part of its nutrivigilance system (https://www.anses.fr/en/system/files/NUT2012sa0212EN.pdf) (ANSES, 2013). ANSES derived causality relationships based on various criteria (e.g. two rapporteurs, chronological scores including information concerning the time of onset, the course of the adverse effect, re-occurrence if the product was reintroduced, and exclusion of other possible causes). The derived causal relationships ranged from "very likely", "likely", "possible", "unlikely" to "ruled out". For example, in 95 cases cardiovascular manifestations were reported. According to ANSES, the causality analysis yielded the following result: very likely for 5 cases; probable for 9 cases; possible for 25 cases; unlikely for 55 cases; ruled out for 1 case.

Although causality relationships have not been established in most cases, the large number of case reports on adverse effects after consumption of high amounts of EDs gives cause for concern that abusive over-consumption of such beverages is associated with adverse health effects.

6.2.7. Risks associated with combined consumption of energy drinks and alcohol

Mixing alcohol with EDs has become increasingly popular among adolescents and young adults. Based on individual studies Verster and co-workers reported that in Europe, between 3.4% and 46.1% in this age group consume EDs in association with alcoholic beverages (Verster et al., 2018). In the survey commissioned by EFSA 29%–71% of the ED-consuming children and adolescents in 16 EU Member States (in

average 53%) reported that they had drunk EDs together with alcohol at least once at a single session (in terms of total interviewed children in average 36%) (Zucconi et al., 2013).

Since both the acute consumption of alcohol (Brunner et al., 2017) and caffeine (EFSA, 2015; Nawrot et al., 2003; Wikoff et al., 2017) may cause cardiac arrhythmias, the question is raised whether the simultaneous consumption of high amounts of alcohol and EDs could increase the risk of acute cardiovascular problems. If additional cardiovascular stimulating activities, such as intensive dancing, are undertaken, the potential risks of adverse effects such as arrhythmias might be further augmented.

There is also an ongoing discussion as to whether the consumption of EDs might mask the intoxication effects of alcohol, which could be explained by counteracting neurochemical processes related to adenosine. While alcohol increases the sedative activity of adenosine by blocking the reuptake of adenosine, caffeine inhibits adenosine effects by blocking the adenosine receptor (Marczinski et al., 2014). A masking effect may result in consumers' underestimating their level of intoxication, frequently described as “wide awake drunkenness” (Arria and O'Brien, 2011), and it could have a number of consequences. Consumption of alcohol with energy drinks may result in a false sense of confidence that may promote risk-taking behaviour. Increased risks of accidents (e. g. driving while under the influence of alcohol, sexual risk behaviour) and poorer risk perception have been observed compared to alcohol intake alone (Marczinski and Fillmore, 2014; Roemer and Stockwell, 2017). In contrast, meta-analysis conducted in the context of a literature review indicated that mixing alcohol with EDs did not increase overall alcohol consumption and associated risk-taking behaviour (Verster et al., 2018). Moreover, it is debatable if the reduction in the perceived intensity of intoxication is unique to alcohol mixed with EDs or if it might be seen with any alcoholic mix containing sugar (Forward et al., 2017). In addition, heterogeneous results on the subjective and objective effects of alcohol mixed with EDs have been reported (Bonar et al., 2015). Therefore, no robust conclusions on alcohol intoxication in connection with ED and risk-taking behaviour regarding causality can be drawn.

As shown in Supplementary Table 1, several case reports of adverse events (e.g. spontaneous coronary artery dissection, atrial fibrillation) have been reported in the scientific literature following co-abuse of alcohol and EDs. Although a cause and effect relationship cannot be established from such case reports, they raise concerns over the combination of mixing EDs with alcohol.

Apart from the cardiovascular effects following ED consumption together with alcohol, renal adverse effects have also been reported. A 17-year old boy suffered acute renal failure after consuming 3 L of EDs in combination with 1 L of vodka (Schoffl et al., 2011). Further evidence regarding renal adverse effects is provided by a recent animal study (Costa-Valle et al., 2018) which showed that EDs (10 ml/kg) and alcohol (2 g/kg) (20% v/w) induced a potential transitory nephrotoxicity as observed by the increase in urinary N-acetyl-β-D-glucosaminidase activity, which was not shown for ED or alcohol alone.

Compared to one ED, consumption of three or more EDs was significantly associated with the majority of both stimulant and alcohol intoxication self-reported unwanted effects (Droste et al., 2017). No dose-response studies have been identified to determine the quantities and ratio of EDs and alcohol regarded as being safe with respect to cardiovascular, renal or other parameters. More research is needed to elucidate the mechanisms of adverse effects of the combination of EDs with alcohol.

6.2.8. Exposure to EDs

Studies that assessed both chronic and acute exposure to EDs were considered.

6.2.8.1. Exposure data for children and adolescents with focus on Germany

6.2.8.1.1. Survey in 16 EU Member States (Zucconi et al., 2013). In a survey commissioned by EFSA, which was conducted in 16 Member States of the European Union (EU) in 2012 (Zucconi et al., 2013), 68% of 31.070 interviewed children and adolescents (10–18 years old) indicated that they had been drinking EDs at least once over the last year (in Germany 60% of 1068). These subjects were defined as ED consumers. From these ED consumers, 12% indicated that they drank EDs in a “single session” in quantities of 1 L or more (in Germany 17%). A “single session” was defined as a period of time of a couple of hours (e. g. a night out, a study or sport session). Of the total survey sample, about 8% reported consuming 1 L or more of EDs in a “single session” (in Germany about 10%).

Furthermore, 8% of the total survey sample (5% of survey participants in Germany) and 12% of the ED consumers (9% of ED consumers in Germany) declared that they consumed EDs on 4–5 days per week or more frequently.

These results indicate that individuals with excessive ED consumption on certain occasions represent the actual risk group with regard to *acute* caffeine intake from EDs. This acute risk can be approximately quantified by the data in the Zucconi study. However, this study is not suitable for assessing the chronic risk of caffeine intake from EDs, since no information was provided on the quantities of EDs consumed on a long-term basis. Therefore, it is not known which proportion of chronic ED consumers exceeds the caffeine intake that is considered to be safe according to EFSA.

6.2.8.1.2. EFSA's Comprehensive European Food Consumption Database. EFSA's Comprehensive European Food Consumption Database (hereinafter referred to as Comprehensive Database) (EFSA, 2015) contains consumption data from numerous national surveys in the EU, collected via single or repeated 24- or 48-h dietary recalls or dietary records covering three to seven days per subject. It was calculated, that ED contribution to the total caffeine intake of adolescents in the EU was between 0% and 10%. However, it should be taken into account that the data collection phase for several databases took place more than 10 years ago, i. e. at a time when EDs were less present on the market (Statista, 2017). Moreover, due to the methodology, irregularly consumed foods are probably not adequately recorded and the acute caffeine intake from possible high ED consumption on certain days/occasions might be underestimated.

6.2.8.1.3. Data from the DONALD- and NVS II-Study. Lachenmeier and colleagues used both the DOrtmund Nutritional and Anthropometric Longitudinally Designed (DONALD) study and the German National Nutrition Survey (NVS) II to estimate the caffeine intake from beverages (Lachenmeier et al., 2013).

Based on the non-representative DONALD study (study period 2007–2011) with 316 children and adolescents aged 9–19 years, 941 nutrition protocols (3-day weighed dietary records) were available. According to these data, the contribution of EDs to daily caffeine intake appeared to be minor (on average 0.7 g/day). However, 3-day (and even 7-day) weighed dietary records can underestimate the consumption of irregularly consumed foods and so a possible acute high ED consumption on certain days is not necessarily recorded (Marakis G, 2018). In addition, the demographic characteristics of the sample (i.e. higher educational attainment and higher socio-economic status (Kroke et al., 2004)), might have influenced ED consumption.

Moreover, Lachenmeier and colleagues used the NVS II (14–80 years) to determine caffeine intake from beverages (coffee, tea and soft drinks) for certain age groups (15,371 individual diet history interviews of the last four weeks, study period 2005 to 2006). In the absence of an ED classification code, it was estimated that ED consumption represented 5% of total soft drink consumption. For the age group of 14–18 years, a caffeine intake of 0.9 mg/kg bw/day for male participants and 0.6 mg/kg bw/day for female participants was determined. Caffeine intake by EDs was calculated to be negligible. However, as already mentioned, the absence of a classification code for EDs hinders accurate calculation of the caffeine intake from EDs and the data are more than ten years old.

6.2.8.2. Exposure data for adults with focus on Germany

6.2.8.2.1. Survey in 16 EU Member States (Zucconi et al., 2013). In the aforementioned survey commissioned by EFSA (Zucconi et al., 2013), 30% of the 14,557 adults surveyed (aged 18 to 65) reported that they had been drinking EDs at least once over the last year (in Germany 30% of 1553) (Zucconi et al., 2013). As mentioned above, these subjects were defined as ED consumers. Among the ED consumers, 11% indicated that they drank EDs on certain occasions (in a "single session") in quantities of 1 L or more (19% in Germany). Based on the total number of adults surveyed, about 3% admitted to drink such amounts in a "single session" (about 5% in Germany).

Furthermore, 12% of adult ED consumers reported consumption of EDs on 4–5 days a week or more frequently (11% in Germany). Based on the total number of adults surveyed, around 4% stated that they regularly consume EDs in this way (3% in Germany). However, in regard to regular ED consumption the quantity of the ingested EDs was not indicated in the study, so that chronic caffeine intake from EDs cannot be quantified.

6.2.8.2.2. Event-related survey of high consumers of EDs (BfR, 2013). A survey initiated by the German Federal Institute for Risk Assessment (BfR) on the event-related consumption of EDs in 2013 also provided indications that some people drink EDs on certain occasions in high quantities (BfR, 2013). In the survey, attendees at LAN (local area network gaming) parties, sports events, music festivals and clubs, who had consumed more than 500 ml of EDs or more than 60 ml of energy shots over the past 24 h at the time of the questioning, were interviewed in more detail. A total of 508 interviews were conducted (489 after data cleaning). The majority of participants were between 15 and 30 years old. Few respondents were 31 years or older except for sporting events where the average age of respondents was 33 years. Those interviewed in more detail stated that on average they consumed about 1 L of pure ED or 1.5 L mixed with alcoholic beverages at certain occasions. Especially at LAN parties high amounts of EDs were consumed (i.e. about 1.5 L of EDs only or about 2.5 L of EDs mixed with alcohol).

6.2.8.3. Further studies on ED consumption by children and adolescents in Europe. In a questionnaire survey conducted in Poland from 2012 to 2013, 2629 pupils were interviewed (12–20 years, 55% from junior schools and 45% from senior high school, N = 2629) (Nowak and Jasionowski, 2015). EDs were consumed by 67% of the sample (75% among boys only). About 2% of the total participants indicated ED consumption on a daily basis; corresponding to 3.1% of ED consumers, and 8% several times a week; corresponding to 12% of ED consumers. The authors indicated that those drinking EDs on a daily basis consumed 205 mg of caffeine per day only from EDs.

In a smaller Polish study (N = 329) with younger children (11–13 years) conducted at Warsaw schools in 2009–2010, 24% of the students said that they consumed EDs and 4% indicated that they did so several times a week (median: 500 ml/week) (Wierzejska et al., 2016).

Another survey study conducted in Veneto (Italy) from 2011 to 2012 included 916 children with a mean age of 12.2 years (± 1.1) (Gallimberti et al., 2013). Among the older children (8th grade), 16.5% of the boys said that they drank EDs at least once a week, compared to about 8.6% of the girls. No quantities were listed.

Kristjansson et al. used data from the "2013 Youth in Iceland" study (N = 11,267), which collected health-related data from children (10–12 years) from all primary schools in Iceland (Kristjansson et al., 2014). Of the boys, 7.1% said they drank one ED or more each day; for the girls it was 2.8%.

In Lithuania, in 2012, 1747 schoolchildren from 10 secondary schools in Kaunas (8th grade) participated in a survey on the consumption of certain foods considered to be "unhealthy" (Vilija and Romualdas, 2014). Of the children surveyed, 21% said they consumed EDs daily. Quantities were not listed.

A Dutch study surveyed 509 students (11–16 years, median 13 years) in terms of their caffeine (e.g. coffee) and ED consumption (Van Batenburg-Eddes et al., 2014). Of the respondents, 6% drank one or more EDs per day.

In Greece, the Hellenic Food Authority carried out a survey (Sept 2011–Feb 2012) regarding drink consumption using a specific semi-quantitative questionnaire with an emphasis placed on EDs (including ED knowledge and consumption patterns) among 4562 teenagers aged 16–18 years old (55.4% males) (EFET, 2012). The study showed that EDs were consumed by 43.9% of the teenagers aged 16–18 years old at least once per month. About 7 out of 10 of ED users (or 30.4% of all participants) reported consumption of EDs at least once per week. Among those who were ED users, 17.0% reported that the first time they consumed EDs was during primary school (6–12 years old), 47.9% during secondary school (13–15 years old), and 23.7% during high school (16–18 years old). Among the ED users, 8.1% reported that the maximum number of EDs that they had consumed in one day was more than 5 cans.

A study from the United Kingdom used data from the National Diet and Nutrition Survey 2008–10 (N = 2126) to examine the caffeine intake from different caffeine containing beverages (Fitt et al., 2013). Consumption data were collected via a 4-day weighed dietary record. For adolescents aged 11 to 18 the caffeine intake by EDs and soft drinks (boys: n = 155; girls: n = 145) was in the same range as the caffeine intake from tea (boys: n = 91; girls: n = 90) and coffee (boys: n = 27; girls: n = 27). Average daily caffeine intake from EDs and soft drinks was 40.8 ± 24.0 (boys) and 36.0 ± 21.6 (girls) mg/day for 11 to 18-year-old consumers. A 95th percentile stratified by age is not indicated. However, a 4-day nutritional protocol may not necessarily capture a high acute ED consumption on certain days.

An Austrian study surveyed 700 subjects aged 14 to 39 with a semiquantitative food frequency questionnaire (FFQ) in order to assess caffeine intake (Rudolph et al., 2014). Caffeine intake of all consumers was on average 357 ± 400 mg/day and at the 95th percentile 957 mg/day. Major contributors to caffeine intake were coffee (60.8%), EDs (11.9%) and cola beverages (9.5%). For adolescents 14–17 years of age, the mean daily caffeine intake from EDs was 46.6 ± 95.7 mg/day. A possible acute high ED consumption on certain days was not indicated. It is, however, not known whether this was queried in the context of the study.

In an Italian study (Santangelo et al., 2018), from the 1213 adolescents aged 12–19 years who participated, 2.6% (only boys: 4.5%) reported daily consumption of EDs. Among daily ED consumers, caffeine intake from EDs was estimated to be 105.8 ± 52.5 mg/day. A possible acute high ED consumption on certain days was not indicated. It is, however not known whether this was queried.

Verster and Koenig published a review on caffeine intake and its sources in 2018 (Verster and Koenig, 2018). In this review, only studies that were nationally representative and that included caffeine intakes from all sources were considered. Caffeine intake was estimated for the USA, Canada, Europe, Australia, New Zealand and Asia. The studies evaluated by the authors for Europe have already been listed above (EFSA, 2015; Fitt et al., 2013; Lachenmeier et al., 2013; Rudolph et al., 2014; Zucconi et al., 2013). The authors concluded that EDs contributed little to total caffeine intake across all age groups.

Overall, with regard to acute consumption of EDs, the available data so far indicate that ED consumption on specific days (occasions/events) can be very high (1 L and more, corresponding in Germany to an intake of up to 320 mg caffeine and more), exceeding the caffeine doses that EFSA considers to be safe (3 mg/kg body weight consumed as a single dose or within a short period of time). Therefore, persons with such consumption behaviour represent the actual risk group with regard to acute ED consumption. Data from old national dietary surveys may lead to underestimation of irregularly consumed foods such as EDs and are therefore not suitable to quantify high acute ED use. National surveys following the EU Menu methodology as recommended by EFSA, that combine dietary recalls/dietary records and a Food Propensity Questionnaire (EFSA, 2009a), are expected to provide a more accurate

picture of ED consumption (acute and chronic) in countries across Europe in the future.

7. Discussion – cardiovascular risk characterisation in relation to ED consumption

Based on intervention studies, we characterized the effects of EDs in their entire composition on blood pressure, heart rate, QTc interval, myocardial contractility and other adverse symptoms (e.g. palpitations). Since some effects of EDs, such as increased blood pressure or adverse effects, may also be caused by caffeine in general and because hazard identification of the individual ingredients reveals that caffeine seems to be the major bioactive substance of EDs, we assessed the observed effects of EDs in their entirety not only in relation to the absorbed amount of EDs but also in particular in relation to the caffeine doses ingested via EDs.

Moreover, since information on the ingested amounts of the individual ingredients of EDs was mainly given for caffeine, we used the caffeine doses that were regarded as being of no health concern according to EFSA (EFSA, 2015) to define moderate ED consumption.

7.1. Moderate acute consumption of EDs

Taking into account a large number of intervention studies with EDs and cardiovascular parameters which have not yet been considered by EFSA (e.g. QTc interval, inotropic effects), we conclude that acute[2] moderate[3] ED consumption (corresponding to a caffeine intake of up to 200 mg) is unlikely to pose a cardiovascular health risk for healthy adults. This conclusion is still in accordance with the caffeine doses of no concern for this group as derived by EFSA in 2015 (EFSA, 2015).

The observed changes on BP, QTc interval, HR or myocardial contractility in combination with moderate ED consumption by young healthy adults do not seem to give rise to cardiovascular safety concerns, if they occur occasionally and under normal consuming conditions. Moreover, in association with moderate ED consumption by young healthy adults, unwanted effects such as palpitations, nausea etc. were very rarely reported.

However, there are no published studies investigating a dose-response relationship between acute exposure to EDs and possible adverse effects on the cardiovascular system in children and adolescents (BfR, 2017). This lack of data makes it difficult to come to a robust conclusion on safe levels of ED intake for children and adolescents. Nevertheless, there are so far no indications that the intake of caffeine from EDs, which according to EFSA (EFSA, 2015) is deemed not to pose a risk for healthy children and adolescents (3 mg/kg bw as an acute single dose or as habitual intake throughout the day), is not safe, even under conditions of use as an ingredient in EDs in the EU.

7.2. High acute consumption of EDs

The identified intervention studies analyzing cardiovascular endpoints in combination with ED consumption and involving only young healthy adults, examined effects of an ingestion of maximally 1 L of EDs. No intervention studies are available for a more excessive ED consumption of more than 1 L. However, intervention studies with such amounts are not feasible for ethical reasons.

No conclusions can be drawn regarding the impact of high acute ED consumption on HR or myocardial contractility, since the data were contradictory (HR) or were only analysed in combination with acute moderate ED consumption (myocardial contractility). Nevertheless, there are indications that EDs have a greater impact on myocardial contractility than other caffeinated beverages without other typical ED ingredients (Baum and Weiss, 2001; Doerner et al., 2015; Miles-Chan et al., 2015). With respect to the question which ingredients or which combination of ingredients could be responsible for these potential effects, the data are contradictory. Both taurine and sugar, possibly in combination with caffeine, are being discussed as potential inducers or contributors. However, there is uncertainty about the health effects of high, especially chronically high consumption of EDs in regard to myocardial contractility.

High ED consumption corresponding to caffeine doses of more than 200 mg and up to 320 mg significantly increased BP, although the changes were only moderate in young healthy adults (up to + 9 mmHg). The enhancement is probably due to caffeine, but there are indications that taurine may possibly attenuate these increases (Sun et al., 2016). In the observed range, these induced acute changes in BP in healthy adults are regarded as physiological and not harmful to health if they occur occasionally and under normal environmental conditions. However, in one study in which young healthy adults drank 1 L of EDs (caffeine amount not indicated) SBP increased by nearly 20 mmHg. Perhaps this could be critical for more sensitive persons (e.g. children or individuals with preexisting high BP).

No robust conclusions can be drawn for higher acute intakes (more than 1 L ED), for children and adolescents and for chronic consumption, since there are no data available.

ED consumption of 1 L resulted in significant prolongations of the QTc interval in three out of the four studies analyzing this endpoint in adults (Basrai et al., 2019; Kozik et al., 2016; Shah et al., 2016c), an effect which was not observed with moderate ED drinking. One study, which was conducted in the USA, observed enhanced QTc intervals in healthy young adults, which can be defined as serious (Kozik et al., 2016) and could therefore represent a potential health risk. However, as the ingested caffeine amount was not indicated in this study and no statutory limits for ED ingredients exit in the USA, it is not possible to estimate the exact amount of caffeine ingested.

In conclusion, based on the available studies, it can be assumed that excessive acute ED consumption could lead to QTc prolongations of possible health concern even in some healthy young adults. Since significant increases in the QTc interval have already been observed in healthy adults in association with the consumption of 1 L ED, it can be assumed that more sensitive individuals such as children and adolescents could possibly react with stronger changes in the QTc interval. Moreover, patients with preexisting long QT syndrome might be at higher risk for critical QTc prolongation, probably even at moderate ED consumption (Gray et al., 2017).

Moreover, in the identified studies with acutely administered high ED amounts or concentrated shots corresponding to caffeine intakes of more than 200 mg, moderate to severe adverse effects such as palpitations, severe nausea, shortness of breath, severe tremor, anxiety and jitteriness were reported by some participants (Basrai et al., 2019; Fletcher et al., 2017; Kurtz et al., 2013; Phan and Shah, 2014). The adverse effects seem to become more frequent and stronger with increasing ingested caffeine amounts. Similar effects were also observed in the caffeine control, when used, suggesting that caffeine might be responsible for most of these adverse effects. Some individuals reported undesirable effects even after the ingestion of a drink without caffeine. It is not clear whether this is due to other ingredients in this beverage or to possible excitement about participating in the study.

Since drinking high amounts of EDs was associated with adverse effects in some young healthy adults in the identified intervention studies, it can be assumed that this would also present a risk to more sensitive groups such as children and adolescents.

Results of surveys on ED consumption indicate that people with excessive ED consumption on certain occasions represent the actual risk

[2] The term “acute” is defined as a time period of up to three hours.

[3] The term “moderate” is defined as the consumed quantity of EDs that does not lead to an exceedance of the caffeine amount that is considered to be safe according to EFSA. Based on the German national statutory limits for caffeine (320 mg/L) this represents a maximum of up to 625 ml acutely consumed EDs for healthy adults.

group with regard to *acute* caffeine intake from EDs. The acute caffeine intake considered to be safe according to EFSA for a 13-year-old boy weighing approximately 50 kg (RKI, 2013) is 150 mg. With the consumption of two commercially available ED cans á 250 ml with 80 mg caffeine per can, respectively, an amount of 160 mg of caffeine would be ingested, leading to an exceedance of the safe value. With a consumption of 1 L (e.g. four cans á 250 ml), the caffeine intake would amount to 320 mg, which would be more than twice the caffeine intake that is considered to be safe for a boy of this body weight. It is worth mentioning, that VKM also uses EFSA's caffeine dose values of no concern as toxicological reference points in its risk assessment of EDs in relation to children and adolescents (VKM, 2019).

Since caffeine is purported to be responsible for most of the adverse effects, ingestion of other caffeine containing foods, if consumed in similar quantities and in short periods of time, could result in adverse effects too. However, the consumption behaviour of children and adolescents with respect to caffeine-containing beverages such as coffee seems to be different from that regarding EDs (MRI, 2008; Zucconi et al., 2013). Even though some adolescents drink coffee, so far there seem to be no indications that they (or a relevant number of them) consume such beverages in excessive amounts within a short period of time. However, ED consumption in excessive quantities within a couple of hours at specific events often in combination with alcohol is very popular among some adolescents and young adults in a number of European countries (BfR, 2013; Zucconi et al., 2013) (see section on exposure). Thereby a substantial part of the children and adolescents exceeds the caffeine intake that EFSA considers safe, which thus poses a risk of possible acute adverse effects. The same applies to adults with such consumption behaviour, but the proportion of adults drinking excessive amounts of EDs is lower than among children and adolescents (Zucconi et al., 2013).

This identified risk for children and adolescents may be additionally influenced by the individual sensitivity. It can be assumed, that many children may have been less exposed to caffeine in their past (and thus are less likely to be accustomed to caffeine consumption) and could therefore react in a particularly sensitive manner to caffeine intake. In addition, caffeine intake from other caffeine sources together with EDs within narrow timeframes on certain occasions might augment some of the potential adverse effects of EDs. Also, accompanying factors such as alcohol consumption as already mentioned or strenuous physical activity might adversely influence health outcomes. Since some studies (although with small sample sizes) showed that BP was significantly higher during exercise with caffeine than with placebo, EFSA suggested an additive effect of caffeine and resistance training on BP during exercise (EFSA, 2015). In this context it is noteworthy that in the survey commissioned by EFSA 27% of adolescent ED consumers who drank EDs during sport activities (corresponding to about 10% of adolescent ED consumers), reported to drink three or more cans during a single sport session (Zucconi et al., 2013).

In addition, it was shown that awareness of the possible health risks associated with excessive consumption of EDs, especially in connection with intensive sports or the consumption of alcohol, was low or insufficient in adolescents and young adults (BfR, 2013). Therefore, there is reason to assume that children and adolescents in general are not always sufficiently aware of the risk of excessive consumption of these beverages.

7.3. Chronic consumption of EDs

There are no published studies investigating a dose-response relationship between chronic exposure to EDs and possible adverse effects in adults and children and adolescents. Therefore, the effects of long-term moderate and high intakes are unclear.

However, experts from the field of pediatric cardiology, toxicology, pharmacology, epidemiology and nutritional medicine agreed that it could not be ruled out that a chronically very high intake of EDs by children and adolescents could promote the development of cardiovascular disease (BfR, 2017).

With regard to regular ED consumption, data across Europe have shown that around 2%–8% of the total number of surveyed children and adolescents consume EDs every day or 4–5 days a week (Kristjansson et al., 2014; Nowak and Jasionowski, 2015; Santangelo et al., 2018; Van Batenburg-Eddes et al., 2014; Zucconi et al., 2013). However, there is less information about the amounts of EDs regularly consumed alone or in combination with other caffeine sources. Thus, based on the currently available data, the proportion of children and adolescents that may consume more than the safe intake of caffeine according to EFSA cannot be quantified.

8. Conclusion

On the basis of the current literature, our present assessment supports the conclusion that acute moderate consumption of EDs corresponding to a caffeine intake of up to 200 mg is unlikely to pose a cardiovascular health risk to healthy adults, which is in accordance with EFSA's opinion of 2015.

Although there is no scientific evidence with respect to children and adolescents that the acute caffeine intake levels considered as safe by EFSA could not hold true for caffeine intakes through ED consumption, robust conclusions cannot be drawn, due to gaps in knowledge in this regard.

It has already been mentioned that, according to Regulation (EU) No 1169/2011, in the EU beverages containing more than 150 mg/L of caffeine have to be labelled with the indication “High caffeine content. Not recommended for children or pregnant or breast feeding women.” (Regulation (EU) No 1169/2011, 2014).

Health risks may result from an acute excessive consumption of EDs. In view of the identified adverse effects (e. g. prolongation of the QTc interval, palpitations, severe nausea, shortness of breath, severe tremor, anxiety etc.) caused by excessively high ED consumption (e.g. about 1 L) in some young healthy adults, it is noteworthy that a substantial proportion of ED-consuming children and adolescents (in average 12% in 16 EU Member States) stated to consume excessively high amounts of EDs (1 L and more) on certain occasions. This problem may further be compounded by the co-ingestion of alcohol and in combination with intense physical activity. About half of the ED-consuming children and adolescents (53%) interviewed in 16 EU Member States reported that they had drunk EDs together with alcohol at least once on a certain occasion (Zucconi et al., 2013). This finding deserves attention, since both the acute consumption of alcohol and caffeine can cause cardiac arrhythmias. However, more research is needed to elucidate dose-response relationships of simultaneous consumption of ED and alcohol to determine the extent or ratio of consumption that might pose a health concern. Moreover, since some studies showed an additive effect of caffeine and physical activity on blood pressure, it is of concern, that about 10% of ED consuming children and adolescents (in 16 EU Member States) declared to consume three cans of EDs and more during sport activities (Zucconi et al., 2013), although more studies are necessary to derive substantiated dose-response relationships of ED consumption in combination with sport activity.

A survey has shown that the awareness of the interviewed adolescents and young adults regarding the potential health risks of excessive ED consumption, especially in association with the consumption of high amounts of alcohol, is in general low or inadequate (BfR, 2013). This situation might be further exacerbated by marketing practices and advertisements regarding EDs, appealing particularly to younger people such as adolescents.

Risk awareness among children and adolescents regarding excessive consumption of EDs could be increased by target-group-specific measures in health education in order to prevent health risks and support self-responsibility for a health-promoting lifestyle.

In particular, educational programs could be developed to make

children, adolescents, teachers and parents aware of the potential risks associated with excessive ED consumption.

Although some governmental institutions have already provided educational material in form of flyers and other informational material (BZfE (Germany), 2018; EFET (Greece), 2018; SGL (Cyprus), 2011), possible excessive ED consumption by a substantial proportion of children and adolescents seems to still be a problem. In such a situation, intensifying and expanding awareness campaigns, especially in schools where actual risk groups can be reached, could contribute to attainment of a more sustainable effect. It is noted, that in some countries further measures have also been considered: e.g. some food retail chains have voluntarily restricted the sale of these drinks to children. In certain countries (Lithuania, Latvia), the sale of EDs to minors has even been banned (Republic of Latvia, 2016; Republic of Lithuania, 2014).

In this context, it is noted that future regular monitoring of acute and chronic habitual ED composition across Europe, also taking into account particularly sensitive segments of the population (e. g. children and adolescents), would facilitate the identification of trends in consumption patterns and provide a basis for more refined risk assessments. In addition, such monitoring programs would support the evaluation of the effectiveness of any measures aiming at minimizing risks resulting from excessive consumption of EDs.

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Conflicts of interest

All authors report no conflict of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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