

Stimulants Added to Alcohol Beverages

Research Review and Discussion

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EXECUTIVE SUMMARY

According to the European Food Safety Association (EFSA) Panel on Dietetic Products, Nutrition and Allergies (2015), single doses of caffeine up to 200 mg “do not give rise to safety concerns for the general healthy adult population.” At doses above 400 mg, adverse effects begin to emerge, with reports of symptoms such as anxiety, nausea, jitteriness and nervousness. Levels over 500 mg are described as excessive. In the research literature, daily caffeine intake of 100-200 mg appears to be regarded as moderate, whilst levels of intake above 500 mg are regarded as high and increasingly less healthy. In the United States, the Food & Drug Administration (FDA) has cited up to 400 mg of caffeine per day as being not generally associated with dangerous, negative effects (FDA, 2013), consistent with the conclusions of the EFSA Panel on Dietetic Products, Nutrition and Allergies (2015).

Reviewing regulations on caffeine (without alcohol) applying in various countries, the maximum permitted caffeine content for cola type beverages and other soft drinks falls between 145 mg/l and 200 mg/l, equating to 36-50 mg of caffeine in a 250 ml beverage serving or 72-100 mg in a 500 ml serving. These levels are consistent with low caffeine doses. In contrast, the maximum permitted caffeine content for energy drinks is generally higher, at between 320 mg/l and 350 mg/l, although some countries specify that beverages containing more than 145 or 150 mg/l should be labelled “high caffeine content”.

Considering research into physiological effects of alcohol and caffeine, co-ingestion of high dosages may prolong the effects of caffeine, but subjective and objective alcohol intoxication appear not to be affected relative to ingestion of alcohol alone. Some experimental studies of psychomotor and cognitive performance have reported antagonism of the effects of alcohol by caffeine, but most research to date shows no significant reduction of alcohol-induced impairment and it has been suggested that the effects of caffeine may be restricted to countering impairment of psychomotor task performance. The EFSA Panel on Dietetic Products, Nutrition and Allergies (2015), concluded that alcohol consumption at doses up to about 0.65 g/kg body weight would not affect the safety of single doses of caffeine up to 200 mg. In a 70 kg individual, this would equate to an alcohol intake of 45.5 g (i.e. several drinks), and it should be noted that individual servings of alcohol beverages that contain caffeine typically contain much less than 200 mg; for example, an alcohol beverage containing 100 mg/l caffeine would contain 25 mg of caffeine in a 250 ml serving.

Further research is needed on the relationship between alcohol mixed with energy drinks (AmED) or caffeinated alcohol beverages (CAB) and risk-taking behaviour, as concerns remain, but a causal link has not been established and there are weaknesses in the data currently available. The prevalence and effects of AmED use, the possible masking of the effects of alcohol by caffeine, and the specific effects of premixed caffeinated alcohol beverages all merit further investigation.

1. Background

In October 2012, leading global producers of beer, wine and spirits made a collective commitment to build on their long-standing and ongoing efforts to reduce harmful drinking through the Beer, Wine and Spirits Producers' Commitments (Global Actions, 2012), which outline 10 targeted actions, in five areas, to be implemented over the next five years ("Beer, wine and spirits producers", 2010). As part of a series of actions aimed at providing consumer information and responsible product innovation, the global producers *"commit not to produce any beverage alcohol products that contain excessive amounts of added stimulants, such as caffeine, guarana and taurine, and ... not market any beverage alcohol product or promote any beverage alcohol combination as delivering energising or stimulating effects"*.

This report examines scientific data and current opinion from peer-reviewed research literature, and from a number of technical and regulatory sources available in the public domain, with a view to defining "excessive amounts" of added stimulants – primarily caffeine - and establishing a consensus on appropriate levels. Terminology and definitions are clarified, and the metabolic and pharmacological profile of caffeine is outlined, with consideration of its physiological effects and toxicity in humans. Research on alcohol and caffeine in combination is reviewed, including the growing body of research on the mixing of alcohol and energy drinks. Details of regulatory advice and expert scientific opinion are included to highlight the current consensus on the health effects and safety of caffeine, both in isolation and in combination with alcohol.

In the context of premixed alcohol beverages produced by signatories to the Commitments, caffeine is the only stimulant of note. It occurs as a natural component of cola, used in some premixed spirits beverages, and of coffee, used in coffee liqueurs. The report also considers research on guaraná (which contains caffeine as an active component), taurine and ginseng, in light of their inclusion in some energy drinks.

2. Energy drinks and caffeinated alcohol beverages

2.1. Terminology

There are some variations in the terminology used in the technical and research literature. The following terms and acronyms are used in this report: -

Acronym	Group Name	Description	Notes
ED	Energy Drinks	Premixed non-alcohol beverages containing caffeine and other stimulants.	Commercially produced beverages, subject to the regulatory authority of the jurisdictions in which they are marketed.
CAB	Caffeinated Alcohol Beverages	Premixed, ready-to-drink (RTD) alcohol beverages, containing caffeine, sometimes with other stimulants as well.	
AmED	Alcohol mixed with Energy Drinks	Hand mixed beverages, prepared <i>ad hoc</i> .	Beverages with a final composition determined by the consumer or by on-premise servers and not by the producers of the alcohol beverage or ED.

2.2. Energy drinks (ED)

Energy drinks are non-alcohol beverages, marketed as increasing energy levels and wakefulness or boosting attention span (Torpy & Livingston, 2012). Since Red Bull was first introduced in Austria in 1987, the global energy drink market has grown exponentially (Reissig et al., 2009; Burrows et al, 2013) and it continues to expand. It has been estimated that the combined markets for energy and sport drinks will reach GBP1.8 billion by 2016, a 95% increase on 2008 estimates (Intel, 2011) and the volume of energy drinks consumed worldwide is expected to exceed 6.4 billion litres by the same year (Canadean, 2012).

Caffeine is the main functional ingredient of energy drinks and additional caffeine may be derived from natural ingredients, such guaraná, kola nut and yerba maté (Seifert, et al., 2011). They may also contain a wide variety of other natural substances, many derived from plants and herbs, with claimed stimulant properties (O'Brien et al., 2008; Kaminer, 2010; McLellan & Lieberman, 2012). Many energy drinks have similar ingredient profiles (Heckman, et al., 2010) and some group certain ingredients together as part of an “energy blend”, rather than listing them individually (Higgins et al., 2010), so the exact concentrations used may not be apparent.

Energy drinks often contain the following ingredients: -

- Caffeine.
- Guaraná (which is an independent source of caffeine).
- Taurine.
- Ginseng.
- B vitamins.
- Sugars or sweeteners.
- Glucuronolactone (an organic metabolite with claimed detoxifying properties).

A number of other ingredients may also be added, including, for example: -

- Ginkgo biloba (a tree extract containing flavonoids).
- Milk thistle (a plant extract containing the flavonoid silymarin).
- Yerba maté (a plant extract containing small amounts of caffeine).
- Kola nut (the core ingredient of cola and a source of caffeine)
- Green tea (tea that has undergone minimal oxidation - high in flavonoids and lower in caffeine than regular tea).
- Amino acids and biogenic amines other than taurine (e.g., carnitine, creatine, synephrine [bitter orange extract]).

In 2012, McLellan and Lieberman considered whether energy drinks contain active components other than caffeine and concluded that there is little evidence that any ingredient other than caffeine (or caffeine from guarana) is associated with enhanced cognitive or physical performance.

The caffeine content of energy drinks ranges from 30 - 505 mg per can or bottle, in serving sizes of 250 - 500 ml, but typically falling between 80 and 141 mg caffeine per serving (Reissig et al., 2009; Higgins et al., 2010; Howland et al., 2011; Szpak & Allen, 2012; Nomisma-Areté consortium, 2013). For comparison, the caffeine content of a cup of brewed coffee may fall between 100 mg and in excess of 500 mg, depending on strength and serving size, with instant coffee and brewed tea containing approximately

75mg and 50mg, respectively (McCusker, et al., 2003; Szpak & Allen, 2012). In soft drinks, caffeine levels are typically 100 mg/l - equivalent to 25 mg in a 250 ml serving - but can be as high as 200 mg/l in some products (Drewnowski, 2001).

Information on energy drink consumption practices varies considerably. In the USA, there has been a particular focus on college-aged students (Peacock et al., 2012), with more than 50% reporting regular consumption of energy drinks in some surveys (Malinauskas et al., 2007; O'Brien et al. 2008). However, energy drink consumption is not limited to young adults. A recent, large-scale European study looked at a wider population and found 68% of adolescents reporting ED consumption in comparison to 30% of adults, but no difference between the two age categories in high, regular (chronic) ED consumption (12% in adults and adolescents) or high, occasional (acute) ED consumption (11% for adults, 12% for adolescents) (Nomisma-Areté consortium, 2013).

Considering mean daily intake of energy drinks, the Scientific Committee on Food of the European Commission (DG SANCO), has classified consumption into “mean chronic” (125 ml/day), “high chronic” (350 ml/day) and “acute” (750 ml/day) (EC Scientific Committee on Food, 2003). For a typical ED product containing 320 mg/l of caffeine, these classifications would equate to 40 mg, 112 mg and 240 mg of caffeine per day.

2.3. Caffeinated alcohol beverages (CAB) vs alcohol mixed with energy drinks (AmED)

Caffeinated alcohol beverages (CAB) are premixed, ready-to-drink (RTD) products that contain alcohol and other stimulants similar to those used in energy drinks (Brache et al., 2012). Some malt-based products or “caffeinated beers” may contain added caffeine and fruit flavourings, but not necessarily other ingredients typically found in energy drinks.

There has been relatively little research on CAB consumption specifically, as opposed to alcohol mixed with energy drinks (AmED). One recent study of undergraduate students (MacKillop et al., 2012) reported 68% prevalence of ad hoc AmED consumption in the last month in comparison to 29% of CAB consumption, suggesting that ad hoc AmED consumption plays a larger role in increased risk than premixed CAB. Although there is a significant body of research on student drinking behaviour, the prevalence of AmED also extends to the adult population. In one European study, for example, the prevalence of mixing alcohol with energy drinks was similar for adults (56%) and adolescents (53%) (Nomisma-Areté consortium, 2013).

For the purposes of this report, research on the health and behavioural effects of AmED – explored in the following sections - is pertinent to the effects of premixed CAB, since both involve the concurrent consumption of alcohol and caffeine. However, as noted in section 2.1, the alcohol content and

stimulant content of CAB may be determined by regulatory requirements, whilst the same is not the case for AmED. The practice of mixing alcohol beverages with ED is widespread, but the final content of beverages consumed is unregulated and outside the control of the respective producers.

Please refer to section 4 for a review of research on AmED (and alcohol and caffeine in combination) and section 5 for an outline and discussion of global regulations and expert opinion relating to caffeine and CAB.

3. Caffeine

Caffeine (1,3,7-trimethylxanthine) is a widely consumed stimulant, which occurs naturally in many plant species (Acquas, et al., 2012). Most caffeine consumed comes from dietary sources and mainly from coffee and tea (Barone & Roberts, 1996; IFIC, 1998), but it is also added to some other beverages, foods and pharmaceutical products (Barone & Roberts, 1984).

3.1. Pharmacokinetics

In adults, caffeine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations are reached within 45–90 mins (Bonati et al., 1982; Blanchard & Sawers, 1983; Arnaud, 1993; Nawrot et al., 2003; Babu et al., 2008). Caffeine doses of 5 to 8 mg/kg (350 - 560 mg for a 70 kg individual) achieve peak plasma concentrations of between 8 and 10 mg/l (Bonati et al., 1982).

Caffeine is metabolised in the liver by demethylation to three primary metabolites: paraxanthine (1,7-dimethylxanthine), theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine) (James, 1997). Paraxanthine is the major metabolite, accounting for 84% of the demethylations (Lelo et al., 1986), so its effects contribute to the physiological actions of caffeine (Benowitz et al., 1995). Further metabolism produces monomethylxanthines, dimethyl and monomethyl uric acids, trimethyl- and dimethylallantoin and uracil derivatives (Arnaud, 1998). Approximately 5% of caffeine is excreted unchanged in the urine (Bonati & Garattini, 1984).

The elimination half-life of caffeine varies from 2.7 to 9.9 hours, reflecting substantial variability between adult individuals (Blanchard & Sawers, 1983), and averages approximately 5 hours (Blanchard & Sawers, 1983; Pfeifer & Notari, 1988). Plasma caffeine levels will, thus, increase over a period of time if the frequency of intake exceeds the rate of elimination. In typical caffeine consumers, peak levels occur in the early evening (Lorist & Tops, 2003).

Caffeine elimination follows apparent first-order kinetics over a range of doses (Bonati et al., 1982). Research suggests that an acute caffeine dose of approximately 500 mg increases its elimination half-life, indicating that metabolism becomes saturated at this level (Kaplan et al., 1997), although chronic consumption of at least 500 mg per day appears to have no effect on caffeine pharmacokinetics (George et al, 1986).

There is evidence that short-term administration of alcohol inhibits the metabolism of caffeine and may prolong its effects. According to Mitchell and colleagues (1983), a dose of 0.8 g/kg of alcohol (56g alcohol for 70kg individual) reduced the rate of caffeine clearance by 37% and increased its elimination half-life by 50%, whilst another study (George et al, 1986) found similar results: 50g of alcohol reduced the

rate of caffeine clearance by 36% and increased the elimination half-life by 72%. George and colleagues (1986) also reported that “regular intake” of caffeine and alcohol prolonged the half-life of caffeine by 47% and reduced clearance by 28%. More recently, Azcona and colleagues (1995) reported that 0.8 g/kg alcohol increased the area under the curve (AUC) for a dose of 400 mg of caffeine, also indicating a prolonged exposure to caffeine in the presence of alcohol.

The difficulty in determining the overall time course and impact of caffeine is due partly to individual variability associated with factors such as genetics (Yang et al., 2010) age, sex, disease and concurrent ingestion of other substances (Blanchard & Sawers, 1983). The metabolites of caffeine – theophylline, theobromine and paraxanthine - are also psychoactive and will have some bearing on the pharmacokinetics of caffeine (Grilly, 2006). Elimination of caffeine is reported to be more rapid in men over 65 than those under 25 (Blanchard & Sawers, 1983) and slightly faster in women relative to men (Callahan, et al., 1983), except during the luteal phase of the menstrual cycle, when it may slow down (Lane et al., 1992). Since caffeine is metabolised primarily in the liver, its clearance can also be compromised by chronic disease or dysfunction of the liver (James, 1997).

3.2. Physiological and behavioural effects

Caffeine is a mild vasodilator, which increases metabolic rate (James, 1997). It is highly dose responsive and acts mainly by blocking A₁ and A_{2A} adenosine receptors in the brain (Fredholm et al., 1999; Acquas, 2012). This increases activity in the central nervous system, leading to a number of physiological outcomes, including increases in blood pressure, renin and catecholamine release, lipolysis, respiration and intestinal peristalsis (Smit & Rogers, 2000).

At levels typically consumed in the diet, caffeine is considered a safe compound. It is not classified as a drug of dependence in the DSM-V (American Psychiatric Association, 2013), although the DSM-V does include diagnoses of caffeine intoxication and caffeine withdrawal. Caffeine withdrawal, is typically marked by a throbbing headache, and can occur after abstinence from a dose of caffeine as low as 100 mg or one strong cup of coffee per day (Griffiths, et al., 1990). The ICD-10 (World Health Organization, 1992) does recognize a diagnosis of caffeine dependence. The International Agency for Research on Cancer has found inadequate evidence for carcinogenicity of caffeine in humans (IARC, 1991).

In addition to its stimulatory and ergogenic effects, caffeine imparts a bitter taste that can modify the flavours of other ingredients in foods and beverages and contribute to their overall sensory appeal (Drewnowski, 2001; Tinley et al., 2003; Riddell et al., 2012). The flavour threshold of caffeine is reported to be approximately 94 mg/l in water (Drewnowski, 2001).

Low and moderate levels of caffeine are reported to have largely positive effects on behaviour and there is little significant evidence of negative health effects, whilst some have reported withdrawal affects to be modest where they are experienced (Fredholm et al., 1999; Smith, 2002). In one study of the discrimination of caffeine in coffee, subjects could easily detect a content of 178 mg and, whilst some could detect lower amounts, mood changes were only observed with amounts of 100 mg or more (Griffiths et al, 1990). Doses around 100 mg were preferred by moderate coffee drinkers and were found to induce no adverse physiological effects (Hughes et al., 1992).

There are few dose-response studies on the psychostimulant effects of caffeine (Smit & Rogers, 2000), but as little as 32 mg has been reported to have a positive effect on cognitive function (Lieberman et al., 1987; Smith et al., 1999; Durlach, 1999). This is believed to be due largely to indirect action on arousal, mood, and concentration (Nehlig, 2010). Moderate doses, of around 75 mg, improve cognitive performance, including attention, reaction time, visual searching, psychomotor speed, and memory (Lieberman et al., 2002; Ryan et al., 2002; Scholey & Kennedy, 2004; Hewlett & Smith, 2006), whilst a dose of 256 mg has been shown to improve auditory vigilance and visual reaction time with no concurrent adverse physiological effects (Lieberman et al., 1987). Caffeine abstainers tend to perform less well on measures of performance skills than caffeine drinkers when challenged with caffeine (Jacobsen & Thurman-Lacey, 1992).

When referring to caffeine as potentially “energising” (i.e. increasing energy expenditure in the body), it should be noted that such effects are difficult to substantiate scientifically. In 2011, the European Food Safety Association (EFSA) Panel on Dietetic Products, Nutrition and Allergies published a Scientific Opinion that found no evidence for an energising effect of caffeine, whilst accepting that caffeine increases alertness and attention (EFSA, 2011). The EFSA Panel concluded that: “a cause and effect relationship” was established between the consumption of caffeine and increased alertness and attention. It added that, if a product were to make a claim for increasing alertness and attention in an adult, it would need to contain at least 75 mg of caffeine in a serving.

With regard to ergogenic effects, physical performance is reported to be enhanced by caffeine doses of 3 to 6 mg/kg body weight (210 - 420 mg for a 70 kg individual) before exercise (Graham & Spriet, 1995; Graham, 2001), whilst one study found that a dose of 9 mg/kg conferred no additional benefit over a 6mg/kg dose (Bruce et al., 2000). However, ergogenic effects are subject to wide individual variation, due to factors such age, sex, fatigue level and caffeine usage history (James, 1997).

People reporting a high daily caffeine intake are more likely to respond to caffeine. For example, Attwood and colleagues (2007) observed improved reaction times and a reduction in self-rated sleepiness in high consumers in comparison to moderate consumers, after a caffeine dose of > 200mg. High consumers were also more likely to perceive positive effects of caffeine.

Some researchers have suggested that improvements associated with caffeine consumption are due primarily to a reversal of the effects of withdrawal in caffeine drinkers who have been caffeine-deprived (James, 1994; Rogers et al., 2003; James & Keane, 2007), but others have found no evidence to support this (Christopher et al., 2005; Hewlett & Smith, 2007).

With regard to daily intake of caffeine, there is also considerably variability in the data (see Appendix 2B). In a 2003 review, Nawrot and colleagues stated that habitual daily caffeine intake of more than 500 mg represents “a significant health risk and may therefore be regarded as ‘abuse’”. They also concluded that a “moderate daily caffeine intake of \leq 400 mg (for a 70 kg person) was not associated with any adverse effects”. In contrast, in a report for the Australia New Zealand Food Authority, Smith and colleagues (2000) proposed that a daily intake of just 210 mg caffeine (for a 70 kg adult) was associated with adverse effects, based on observations of increased anxiety.

Some population subgroups are seen as being at greater risk from caffeine consumption. For example, it has been proposed that women of reproductive age should limit their caffeine consumption to \leq 300 mg per day and that children should consume \leq 2.5 mg/kg body weight per day (Nawrot et al., 2003). There is also evidence for genetic variability in the wider human population, with a specific genotype of the adenosine A_{2A} receptor being associated with lower intakes of caffeine (Cornelis et al, 2007).

3.3. Toxicity

Excessive consumption of caffeine can lead to problems, especially in sensitive individuals (Smith, 2002). In adults, ingestion of 4-12 mg/kg per day of caffeine (280–840 mg for a 70 kg individual), has been associated with anxiety and jitteriness (Seifert et al., 2011) and higher doses have been associated with dysphoria (e.g. Garrett & Griffiths, 1997) and seizures (e.g. Pendleton, et al., 2013). However, intake of caffeine is generally reported to be self-limiting, as there is minimal development of tolerance to reinforcing and aversive effects (Fredholm et al., 1999). Establishing an upper limit for caffeine intake is confounded by variability in definitions of dosage levels, adverse effects and reporting context (see Appendix 1A), but it has been suggested that amounts in excess of 500mg are unlikely to be beneficial (Hasenfratz & Bättig, 1994).

At extremely high levels of intake, toxic effects of caffeine include vomiting, abdominal pain, CNS symptoms and cardiac tachyarrhythmias (Holmgren et al., 2004). A dose of 10 g is estimated to be lethal for adults, but deaths have been reported after ingestion of 5 g and one patient reportedly survived taking 24 g of caffeine (Garriott et al., 1985; Stavric 1988). Ventricular fibrillation is usually the final cause of death (Holmgren et al., 2004). There have been relatively few reports of fatalities from caffeine ingestion

in the literature (Nawrot et al., 2003; Thelander et al., 2010; Sepkowitz, 2012). Caffeine overdoses are usually associated with medications in tablet form (typically containing 100 mg caffeine) (Thelander et al., 2010), not beverages. However, caffeinated alcohol beverages have been implicated in some recent cases of alcohol poisoning (Howland, et al., 2011). In context, achieving an acute caffeine dose of 10 g would require consumption of more than 33 servings of a beverage containing 300 mg of caffeine, or 125 servings of one containing 80 mg, in a single session.

4. Alcohol mixed with caffeine or with energy drinks (AmED)

4.1. Prevalence of AmED

The practice of combining alcohol with energy drinks (AmED) is widespread and reported to be growing (Malinauskas et al., 2007; Oteri et al., 2007; Arria et al., 2010; Attila & Cakir, 2010; Berger et al., 2011; Rossheim & Thombs, 2011), particularly in college student or young adult male populations (Levy & Tapsell, 2007; O'Brien et al., 2008; Reissig et al., 2009).

In one US survey, 24% of students who had consumed alcohol in the past 30 days reported consuming AmED within the same time period (O'Brien et al., 2008) and 48% of one sample of Italian students reported lifetime AmED use (Oteri et al., 2007). Approximately one third of respondents to another US survey reporting that they had consumed at least one energy drink in their lifetime, but only 6% reported AmED consumption over the same time period (Berger et al., 2011). In contrast, a survey conducted for the European Food Safety Authority found that around 60% of respondents reported consuming energy drinks with alcohol, mostly mixing them at the time of consumption (Nomisma-Areté consortium, 2013).

More recently, in a survey of Brazilian students, Eckschmidt et al (2013) found that 70% reported drinking alcohol in the past 12 months, with 25.6% reporting AmED consumption. The number of AmED consumers drinking on a weekly basis was twice the number in the alcohol only group (56% vs 23.3%), the odds that AmED users had engaged in binge drinking were almost five times greater than for the alcohol only group and the odds of engaging in hazardous drinking were twice those of the alcohol only group (a WHO-ASSIST score of 11 or more was considered an indicator of hazardous drinking). The authors acknowledged that AmED users may be sensationseekers with decreased inhibition and low levels of control and cautioned that selection bias may have influenced the outcome of their study.

In the US Monitoring the Future (MTF) Survey, 19.7% of combined 8th, 10th and 12 grade students surveyed in 2011 acknowledged consuming AmED, but this level has declined steadily between 2011 and 2015, when 13.0% reported consuming AmED (Miech, et al., 2016). In contrast, the MTF Survey has shown a fluctuating pattern of AmED use in college students and young adults between 2011 and 2015 (Miech et al., 2016; Johnston et al., 2016). In 2015, the annual prevalence for consumption of alcohol beverages containing caffeine was 42.3% for those with the peak modal age of 23-24, compared with 21.4% for those aged 29 to 30. Analysis of MTF Survey data from 2012 and 2013 (Martz et al., 2015) suggests that academic and social factors may be associated with greater AmED use in 12th grade (high school senior) students. An association was found between AmED and other substance use, including binge drinking, marijuana use and other illicit drugs and, by controlling for binge drinking, the authors indicated that AmED use may increase risk for alcohol-related unsafe driving.

4.2. Association of AmED with higher alcohol intoxication and risk taking

Prior to the emergence of energy drinks, caffeine and alcohol were commonly combined through consumption of alcohol with caffeinated mixers (Thombs et al., 2010) or through proximal consumption of alcohol and caffeine, such as drinking coffee after a meal with alcohol. However, in recent years, a number of studies have suggested that the specific practice of combining caffeinated energy drinks with alcohol may be associated with higher levels of intoxication, which can lead to increases in risk behaviour and alcohol-related harms (Arria et al., 2011; Berger et al., 2011; Howland et al., 2011; McKetin, et al., 2015). Marczinski et al (2014) proposed a neurological basis for increased consumption of alcohol associated with AmED. They believe that AmED increases the reward from alcohol by raising dopamine levels, and that this is facilitated by the presence of caffeine. A later paper by the same group (2016) found that consumption of an energy drink with alcohol increased the desire to drink alcohol more than drinking alcohol alone. Although the focus of this report is research in human subjects, it should also be noted that there are a number of animal model studies showing an increase in the intake of alcohol when mixed with moderate doses of caffeine.

As noted by Thombs and colleagues (2011), there are drawbacks and gaps in current research on the effects of AmED on intoxication and risk. For example, a majority of the studies on subjective experience are based on retrospective survey data, which can suffer from measurement problems, such as sampling issues or inaccuracies in self-reported recall (Clapp et al., 2007; Thombs et al., 2009). Also, most retrospective survey studies do not examine simultaneous consumption of alcohol and caffeine; in some cases, reported instances of alcohol and caffeine consumption are days or weeks apart. Peacock and Bruno (2015) distinguish various types of AmED consumers; the majority of risky behaviour consists of drinking more than planned and spending more money. Risky behaviours increased regardless of whether consuming alcohol only or AmED. These behaviours correlated with their personal impulsivity scores, rather than with the combined use of alcohol and ED. Also, most studies to date have employed a cross-sectional design, rather than a longitudinal one, which would limit inferences about the nature of the relationship over time (Arria et al, 2014). Also, other potential confounding factors, such as expectancy, have not been addressed.

Whilst evidence suggests a correlation between high caffeine or energy drink consumption and high alcohol consumption, these limitations in study methodology preclude a decision on whether or not the relationship is causal. It could be argued that it is lifestyle-related, in that heavier drinkers are more inclined to mix alcohol with energy drinks or to consume caffeinated alcohol beverages than lighter drinkers. As Verster and Alford concluded in a 2011 editorial, "reviewing the scientific literature, one can only conclude that there is no direct scientific evidence of a causal relationship between mixing energy drinks with alcohol and adverse behavior, such as increased alcohol consumption." More recently,

McKetin et al. (2015) noted that there was a growing body of evidence that mixing alcohol with energy drinks may facilitate related harmful behaviours, but that a causal link still needs to be confirmed.

Some researchers have noted that the risks and impairments associated with excessive alcohol consumption are present whether alcohol is consumed on its own or mixed with caffeine or caffeinated energy drinks (Peacock et al., 2012, 2013), whereas others have observed an additional risk with AmED, after adjusting for risk-taking propensity (Brache & Stockwell, 2011). One explanation that has been proposed is that individuals who combine energy drinks with alcohol underestimate their true level of impairment, making them more likely to engage in high-risk behaviours (Arria & O'Brien, 2011). There is some evidence that caffeine can mask the subjective experience of intoxication when alcohol has also been consumed (Fudin & Nicastro, 1988; Ferreira et al., 2006; Marczinski et al., 2006), but other researchers have concluded that the combination of caffeine and alcohol has no effect on the judgement of subjective intoxication or shows no differential effect when compared with alcohol alone (Benson, et al., 2014; Benson & Scholey, 2014; Peacock, et al., 2014; Verster, et al., 2015).

There have been very few field studies in natural drinking environments, in which acute alcohol intoxication might be assessed objectively following AmED consumption. There has also been no research on potential dose-response effects of energy drinks in relation to alcohol intoxication, which would also help to further clarify the nature of the association.

4.3. Antagonistic effects of caffeine on measures of alcohol impairment

A focal point for experimental research in this area is to establish whether or not subjective experiences are paralleled by objective measurement of impairment or negative behavioural outcomes (Hindmarch et al., 1992).

Experimental studies have confirmed that that blood alcohol levels are not higher in association with AmED; actual or perceived levels of blood alcohol are reported to be unaltered by consumption of caffeine up to approximately 400 mg, with an associated blood alcohol concentration of 0.12 g/l (Rush et al., 1993; Liguori and Robinson, 2001; Howland et al., 2011).

A number of studies on possible antagonistic effects of caffeine on alcohol-induced impairment have looked at effects on psychomotor and cognitive performance. Most experimental studies have also assessed subjective measures of intoxication to address potential parallels between objective measures of performance and subjective feelings of intoxication. Some studies have reported antagonism of the effects of alcohol by caffeine or caffeinated energy drinks relative to alcohol on its own (Franks et al., 1975; Kerr et al., 1991; Hasenfratz et al., 1993; Azcona et al., 1995), whilst others have found a worsening of the effects (Osborne & Rogers, 1983). The majority of research shows no significant reduction of

alcohol-induced impairment in performance, or mixed results (Forney & Hughes, 1965; Nuotto et al., 1982; Ferreira et al., 2004; Ferreira et al., 2006; Howland et al., 2011; Marczinski et al., 2011; Marczinski et al., 2012; Alford et al., 2012).

One possibility is that stimulation from caffeinated energy drinks antagonises some, but not all, alcohol-induced impairments (Liguori & Robinson, 2001; Marczinski & Fillmore, 2006) and that this may be restricted to effects of caffeine on impairment of psychomotor task performance (Kerr et al., 1991; Hasenfratz et al., 1993; Azcona et al., 1995). For example, the sedative effects of alcohol may be countered by increased alertness from caffeine, but overstimulation could still elicit some negative physiological effects (Peacock et al., 2012).

Antagonistic effects of caffeine may also be related to the amount of alcohol consumed, as low levels of caffeine appear to decrease some psychomotor and cognitive impairments associated with alcohol, whilst there is no effect at higher blood alcohol levels (Liguori & Robinson, 2001). In an early study by Moskowitz and Burns (1981) caffeine had been reported to antagonise driving impairments at breath alcohol concentrations between 0.05 and 0.06%, but not at 0.11%, whereas Liguori and Robinson observed limited antagonism at the 0.08% limit.

Frequency of caffeine consumption may also have an effect. Brice and Smith (2002) noted that many experimental studies are not representative of real life situations, as they often give subjects a single large dose of caffeine, rather than several small doses. They compared four 65g doses of caffeine (in coffee) over several hours with a single 200mg dose and found that both regimes led to increases in alertness and anxiety, whilst improving performance on psychomotor and cognitive tasks. Examining Brice and Smith's point further, the most-cited experimental studies of AmED gave subjects individual doses of between 26 and 105g of alcohol, with a mean of just under 50g (based on doses for a 70 kg person). In comparison, caffeine doses given ranged from 42 to 500 mg, with some doses being consistent with a single serving of mixer or energy drink and others being part of a range of doses used to identify potential dose-related effects. Whilst the lower caffeine doses used may reflect the content of some energy drinks, the alcohol levels used appear too high to be representative of single servings of alcohol drinks. Only one study (Howland et al., 2011) looked at the effects of caffeine in context, using a dose of 69 mg of caffeine in servings of beer or non-alcohol beer. Those authors reported no effect of caffeine on driving performance, attention, or reaction time in comparison to alcohol alone.

It is important to note that some studies use a within-subjects design (e.g. Osborne & Rogers, 1983; Liguori & Robinson, 2001; Attwood et al., 2012; Peacock et al., 2013), testing the effects of different conditions on the same individuals at different times, whilst other studies use a between-subjects design (e.g. Fillmore et al., 2002; Marczinski et al., 2012; Alford et al., 2012), testing different conditions concurrently on different groups. In the latter case, even if the groups are matched, differences in

individual responses to caffeine may have an impact on the outcome, especially as some studies test fewer than 20 participants.

Drawing clear conclusions from current experimental data is difficult, because performance tasks, doses of caffeine (or ED) and alcohol, and methodologies are not directly comparable. There is also a lack of research on consumption of alcohol and caffeine in typical daily patterns. Further, as already noted by James (1997), since most people are not caffeine abstainers, it is likely they would have consumed caffeine, for example as coffee or tea, or from other sources, prior to consuming AmED. Measuring plasma caffeine and alcohol levels during experimental sessions would perhaps provide a more accurate assessment.

4.4. The role of expectancies

Fillmore and colleagues demonstrated that task performance can be affected in an experimental setting if the subject is told whether or not to expect caffeine (Fillmore & Vogel-Sprott, 1992; Fillmore, et al., 1994) or, more specifically, if they are told what to expect, regardless of the actual caffeine intake (Fillmore & Vogel-Sprott, 1992). They suggested that this expectancy effect could also play a part in antagonism by caffeine of the subjective assessment of intoxication and subsequent behavioural effects of alcohol (Fillmore et al., 2002; Fillmore & Vogel-Sprott, 1995). More recently, it has been noted that caffeine may have differential effects on attention in people who expect caffeine to stimulate them (Oei & Hartley, 2005) and Fillmore and Vogel-Sprott (1995) showed, in one study, that alcohol-induced impairment could be reduced by the administration of caffeine, whether or not caffeine was expected.

Since the work of Fillmore and colleagues, expectancy theory has expanded to look at AmED and establish more clearly that AmED consumers are not a homogenous group (Peacock et al, 2015); there are differences in consumption patterns and differences in expectancy (Heinz et al., 2013) as there are with caffeine. In addition, research has attempted differentiate between problems arising from AmED practice and those due to alcohol consumption alone.

Some researchers have examined expectancy in different classes of drinker. For example, Lau-Barraco and colleagues (2014) looked at High Alcohol/High AmED drinkers, High Alcohol/Moderate AmED drinkers, High Alcohol/Low AmED drinkers and Low Alcohol/Low AmED drinkers (65.87%). They found that the High Alcohol/High AmED group endorsed significantly more caffeine dependence symptoms than the other three groups and was more likely to report positive caffeine expectancies, such as feeling more energized and alert, although differences with the other groups were not statistically significant. Mallet et al (2014) used a similar typology and found that whilst light drinkers were not identified as AmED consumers, moderate / heavy drinkers who were also heavy AmED consumers had higher expectancies about AmED and reported that the majority of their overall alcohol consumption

consisted of AmED. In addition, they experienced more negative physical consequences than those who were low AmED consumers.

In both of the above studies, high AmED consumers were in a minority, leading Mallet et al to suggest that there is a subgroup of high-risk individuals who experience a substantial number of problems.

4.5. Influence of sensation-seeking or impulsive personality

Differences in personality appear to have an impact on drinking choices and, specifically, on the outcomes of AmED. For example, one early study reported that people with low impulsivity were hindered by the administration of caffeine in the morning, whereas high-impulsives benefited from it, with the opposite effect occurring in the evening (Revelle et al., 1980). Researchers have also examined the hypothesis that individuals with sensation-seeking or impulsive traits may be drawn to energy drinks, heavy alcohol consumption and risky behaviours (Miller, 2008; O'Brien et al., 2008; Howland et al., 2011), rather than AmED consumption being the cause. Heavy drinkers reportedly score more highly on measures of sensation (and novelty) seeking (Mundt & Ross, 1993; Cyders, et al., 2007) and impulsivity and sensation seeking traits are associated with energy drink use (Arria, et al., 2010). Further, AmED users tend to be younger males who show a high propensity for impulsivity and risk taking (Miller et al., 2008; O'Brien et al., 2008; Berger et al., 2011; Brache & Stockwell, 2011). Another study appeared to confirm that AmED consumers have a higher tendency for risk-taking and substance involvement, but this was not fully explained by the confounding effects of those behaviours (Arria et al., 2011). Brache and Stockwell (2011) controlled for risk-taking propensity and reported that frequent AmED drinkers were still twice as likely as less frequent AmED drinkers to experience negative outcomes, such as drinking and driving or injury.

Looking at more recent research, Heinz et al (2013) found that caffeine decreased levels of perceived intoxication and prevented decline in desire to continue drinking during a session. Alcohol decreased experimental response accuracy except in those who both expected and received caffeine, which the researchers suggest indicates an interaction between the pharmacological effects of caffeine and expectancy. Amblung et al (2013) found significant associations between greater frequency of AmED consumption and higher demand for alcohol and measures of impulsivity and sensation seeking. Although Heinz et al (2013) also found that caffeinated alcohol use correlated positively with impulsivity and frequency of risk behaviours, they concluded that caffeine, or the expectation of caffeine, does not render a direct, uniform effect on impulsive and risky behaviour under alcohol, thus supporting Verster and Alford's (2011) assertion that there is no causal relationship between AmED and adverse behaviour, such as increased alcohol consumption.

In a survey of 30-day alcohol drinkers, O'Brien et al (2013) found that students that reported drinking AmED or premixed caffeinated alcohol beverages (CAB) were more likely than those drinking alcohol only to report having been taken advantage of sexually, driven under the influence of alcohol or ridden with a driver under the influence of alcohol. Their conclusion was that sensation seeking only partially accounts for the relationship between AmED and negative alcohol-related consequences, supporting the findings of Brache and Stockwell (2011).

Overall, there remains a suggestion that AmED consumption itself has some impact on negative outcomes, rather than just in association with impulsive or sensation seeking behaviour.

4.6. Metabolic effects of AmED

Under normal conditions, the volume of body water rarely fluctuates by more than 1% per day, so dehydration resulting in a loss of body mass of as little as 2% could result in impaired cognitive and physical function, headaches and fatigue (Benelam & Wyness, 2010). Concerns have been raised about the dehydrating effects of energy drinks and their use in combination with alcohol, the principal issue being the caffeine content of some of these products. Since caffeine and alcohol are both diuretics, it has been suggested that a “double dehydration” or hypohydration effect could occur if they are consumed together or in close proximity (Stookey, 1999).

Some researchers have questioned the diuretic effect of caffeine at low to moderate levels of consumption, without alcohol. Armstrong (2002) noted that, whilst caffeine stimulates a mild diuresis, there is no evidence of a debilitating effect from fluid-electrolyte imbalance and little evidence that caffeine doses of up to 680 mg have a significant effect on urine output when compared to water. Maughan and Griffin (2003) observed that 250-300 mg of caffeine led to short-term stimulation of urine output in caffeine-deprived individuals, but that tolerance in regular caffeine consumers significantly reduces the effect and at lower caffeine doses there is no diuretic effect. In a recent meta-analysis of the literature on caffeine and diuresis, Zhang et al (2015) concluded: “Caffeine ingestion did not lead to excessive fluid loss in healthy adults and the diuretic effect does not exist with exercise.” They suggested that caffeine is “a safe ergogenic aid that can be used ... without concerns for any negative impact on fluid balance.”

Typically, the fluid in a caffeinated beverage would be expected to compensate for the short-term diuretic effect from caffeine, so, when consumed in combination with alcohol, the total volume of water would be a key factor in avoiding additional dehydration. Alcohol beverages vary in their water content, which in turn impacts on their effect on overall water balance (James & Ralph 2001) and the extent of diuresis due to alcohol would also depend on the amount consumed (Eggleston, 1942). The threshold for

increasing urine output is around 4% alcohol by volume (Shirreffs & Maughan, 1997), which is consistent with most commercially available alcohol beverages.

Although excessive alcohol consumption can lead to dehydration, there is evidence that when the body is already dehydrated, the diuretic action becomes blunted in an attempt to restore fluid balance (Hobson & Maughan, 2010). Further of note is the fact that alcohol beverages may be used successfully for rehydration following exercise. For example, Jimenez-Pavon et al (2015) found that, after exercise in the heat with subsequent water losses, the acute intake of up to 660 ml of beer had no deleterious effects on markers of hydration.

Energy drinks sweetened with sugars are reported to slow down gastric emptying; reducing peak blood alcohol levels when compared to artificially sweetened mixers (Trout & Bernstein, 1986; Elias et al., 1968; Wu et al, 2006). It has been suggested that the effect of caffeine on alcohol intoxication may, thus, be enhanced when artificially sweetened mixers are combined with alcohol. In one field study, Rossheim and Thombs (2011) found that the number of diet cola drinks used as mixers had a significant association with patron intoxication, whereas the number of drinks mixed with regular cola and energy drinks had no significant associations with intoxication.

5. Global regulations and expert opinion

Two aspects to regulation of caffeine intake are considered here. Firstly, regulations relating to caffeine as an ingredient of non-alcohol beverages and foods, which are informed by expert opinion on its safety in humans. Secondly, regulations concerning caffeine in alcohol beverages and related expert scientific opinion on the potential consequences of caffeine-alcohol interactions.

5.1. Caffeine safety

In countries that have introduced regulations, the maximum permitted caffeine content for cola type beverages and other soft drinks falls between 145 mg/l and 200 mg/l, which equates to approximately 36 - 50 mg of caffeine in a 250 ml beverage serving or 72 - 100 mg in a 500 ml serving. The maximum permitted caffeine content for energy drinks is higher, at between 320 mg/l and 350 mg/l, although in some countries (EU, South Africa, New Zealand) it is specified that beverages containing more than 145/150 mg/l should be labelled “high caffeine content”, whilst in Argentina, this is a labelling requirement for beverages containing more than 20 mg/100ml or 200 mg/l. One country (Canada) permits concentrations up to 400 mg/l, but specifies a cap of 180 mg per serving. These figures equate to 80 - 88 mg of caffeine in a 250 ml beverage serving or 160 - 175 mg in a 500 ml serving.

In the USA, the Food and Drug Administration (FDA) approved caffeine as “Generally Recognised As Safe” (GRAS) for non-alcohol, cola-type beverages, in concentrations no higher than 200 parts per million, or approximately 200 mg/L (FDA, 2009). Under GRAS guidelines, a manufacturer is obliged to provide proof that an additive is safe for its intended use based on published scientific literature, and that there is a consensus of scientific opinion regarding the safety of the use of the substance. (FDA, 2012a; FDA, 2012b).

In 2013, at the request of the US Commissioner of the Food and Drug Administration, the Institute of Medicine (IOM) held a workshop on the safety of caffeine in food and dietary supplements. (IOM, 2014). The objectives of the workshop captured the critical issues associated with caffeine consumption in general and energy drinks in particular:

1. *Evaluate the epidemiological, toxicological, clinical, and other relevant literature to describe important health hazards associated with caffeine consumption*
2. *Delineate vulnerable populations who may be at risk from caffeine exposure*
3. *Describe caffeine exposure and risk of cardiovascular and other health effects on vulnerable populations, including additive effects with other ingredients and effects related to preexisting conditions*
4. *Explore safe caffeine exposure levels for general and vulnerable populations*

5. *Identify data gaps on caffeine stimulant effects including but not limited to cardiovascular, central nervous system, or other health outcomes*

In 2013, in a letter to FDA Commissioner Margaret A Hamburg, a group of scientists concluded: *“there is no general consensus among qualified experts that the addition of caffeine in the amounts used in energy drinks is safe under its conditions of intended use as required by the GRAS standard”* (Arria et al., 2013).

Product liability is another consideration for producers of energy drinks that may also have some pertinence to CAB. For example, referring to US laws and regulations, Peterson contends that “by revamping product labels to adequately disclose caffeine levels, risks, warning signs, and consumption restrictions, energy drink producers will proactively combat key arguments raised in products liability litigation and stimulate better adaptation to changing market regulatory conditions (Peterson, 2013).

In the European Union, EU Food Information Regulation (EU) No. 1169/2011 was implemented on 13 December 2014. This mandatory regulation requires specific labelling for beverages high in caffeine and foods where caffeine has been added for a physiological effect, and is intended to help consumers identify foods that, unlike coffee or tea, may not be expected to have a high caffeine content.

The Regulation (Annex III, Section 4) applies to beverages which: -

- *“are intended for consumption without modification and contain caffeine, from whatever source, in a proportion in excess of 150 mg/l, or,”*
- *are in concentrated or dried form and after reconstitution contain caffeine, from whatever source, in a proportion in excess of 150 mg/l”*

Such beverages must be labelled:

- ***“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 a reference in brackets and in accordance with Article 13(1) of this Regulation to the caffeine content expressed in mg per 100 ml.”

The Regulation does not apply in the following circumstances: -

- ***If the name of the product includes ‘coffee’ or ‘tea’.*** The Regulation does not apply to beverages based on coffee, tea or coffee or tea extract where the name of the food includes the term ‘coffee’ or ‘tea’ (e.g. iced tea).
- ***If caffeine is added for flavouring.*** The Regulation would not apply if caffeine was added to drinks (or foods) as a flavouring. Such products must then comply with EU flavouring Regulation (EU) No 1334/2008, which limits the use of caffeine for flavouring

purposes to particular foods and drinks and sets associated maximum levels. According to Regulation (EU) No 1169/2011 where caffeine is used as a flavouring, the term 'caffeine' must appear after the word 'flavouring(s)' in the list of ingredients.

Following a request from the European Commission in 2013, the European Food Safety Association (EFSA) Panel on Dietetic Products, Nutrition and Allergies published a scientific opinion on the safety of caffeine, providing advice on *“caffeine intakes, from all dietary sources that do not give rise to concerns about adverse health effects for the general healthy population and subgroups thereof”* (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2015).

The panel concluded: -

“Caffeine intakes from all sources up to 400 mg per day (about 5.7 mg/kg body weight per day for a 70 kg adult) consumed throughout the day do not give rise to safety concerns for healthy adults in the general population, except pregnant women” (pregnant woman should have no more than 200 mg of caffeine per day).

“Single doses of caffeine up to 200 mg (about 3 mg/kg body weight for a 70 kg adult) from all sources do not give rise to safety concerns for the general healthy adult population.”

In June 2014, Australia and New Zealand promulgated a policy guideline on Regulatory Management of Caffeine in the Food Supply (Australia and New Zealand Food Regulation Ministerial Council, 2014). Among other things the guideline contained specific policy principles for caffeine:

“The regulatory management of caffeine in the food supply should: (a) be based on risk analysis ensuring consideration of general population and taking into account vulnerable population groups including children, adolescents, pregnant and lactating women and caffeine sensitive consumers; (b) consider exposure to caffeine from all dietary sources; and (c) be informed by emerging evidence and the regulation of caffeine in overseas jurisdictions.”

For further details, see Appendix 3, “Global regulations for caffeine content of soft drinks and energy drinks”.

5.2. Safety of caffeine and alcohol in combination

Many countries have addressed perceived issues with energy drinks (see Appendix 3), with different regulatory and legislative approaches being applied to CAB and AmED. It is important, at this point, to reiterate the difference between CAB and AmED, with the former being directly produced by commercial vendors and the latter practice being initiated by consumers.

In the US, a group of scientists raised concerns in 2009 about caffeinated alcohol beverages with the co-chairs of the National Association of Attorneys General Youth Access to Alcohol Committee (Arria et al., 2009), who passed on the letter to the FDA, adding their own concerns (Blumenthal, et al., 2009). The scientists stated:

“Based on our findings and our comprehensive review of the scientific literature on this topic, we conclude that there is no evidence to support the claim that caffeine is “generally recognized as safe” (“GRAS”) for use in alcoholic beverages.”

In November 2009, the United States Food and Drug Administration (FDA) sent a request to manufacturers of caffeinated alcohol beverages (CAB) to provide information on the safety of adding caffeine to their products (FDA weblink, 2009). In November of 2010, the FDA followed up that request with a warning letter to four companies stating that the caffeine added to their malt alcohol beverages was an “unsafe food additive” and said that further action, including seizure of their products, was possible under US federal law (FDA weblink, 2010; FDA, 2010).

The FDA’s action was followed by warning letters from the US Federal Trade Commission (FTC) (FTC weblink, 2010) and the US Alcohol and Tobacco Tax and Trade Bureau (TTB) (TTB weblink). The US FTC cited incidents “suggesting that alcohol containing added caffeine presents unusual risks to health and safety,” and, as a result, that marketing of such beverages may constitute an unfair or deceptive practice that violates the FTC Act. Finally, the TTB stated that, if the FDA deemed caffeinated beverage products adulterated under the US Federal Food, Drug and Cosmetic Act, it would consider such products mislabeled under the Federal Alcohol Administration Act, making it a violation for industry members to sell or ship the products in interstate or foreign commerce. This, in effect, ended the marketing of CAB in the US.

In the UK, in 2012, in response to a request from the UK Food Standards Agency (FSA), the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) released a statement on the interaction of caffeine and alcohol and their combined effects on health and behaviour (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, 2012). The COT statement followed an extensive review of pertinent research and legislation, and concluded that:

“Overall ... the current balance of evidence does not support a harmful toxicological or behavioural interaction of caffeine and alcohol. However, because of limitations in the available data, there is substantial uncertainty, and if important new evidence emerges in the future, then this conclusion should be reviewed.”

In 2015, the European Food Safety Authority's (EFSA's) Panel on Dietetic Products, Nutrition and Allergies published a scientific opinion on the safety of caffeine that addressed "...possible interactions between caffeine and other constituents of so-called "energy drinks", alcohol, p-synephrine and physical exercise." (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2015).

On this question, the EFSA Panel concluded:

"Alcohol consumption at doses up to about 0.65 g/kg body weight, leading to a blood alcohol concentration of about 0.08 %, would not affect the safety of single doses of caffeine up to 200 mg from any dietary source, including "energy drinks". Up to these levels of intake, caffeine is unlikely to mask the subjective perception of alcohol intoxication."

The EFSA Panel noted that studies linking high levels of consumption of caffeine and energy drinks with high alcohol intakes, consumption of other psychotropic drugs and increased risk-taking behaviours were "either cross-sectional or retrospective and did not allow a causal role to be attributed to either caffeine or "energy drinks". It was also found that alcohol consumption is unlikely to exacerbate the effects of caffeine on the cardiovascular system or central nervous system. The Panel acknowledged that there were concerns about the effects of caffeine and alcohol on the central nervous system and the possibility that caffeine could mask the subjective perception of alcohol intoxication, leading to increased "risk-taking" behaviour". However, it concluded that human intervention studies yielded conflicting results.

Health Canada has promulgated guidance that permits the sale of energy drinks as foods and does not authorise the sale of alcohol versions of the products or their use as ingredients in other foods, including alcohol beverages. The Canadian Food and Drug Regulations do not permit the addition of caffeine to any alcohol beverage. However, some alcohol beverages are permitted to have flavouring ingredients that naturally contain caffeine, e.g., guarana or coffee (cf. the EU legislation on flavourings outlined under section 5.1). They are also permitted to have as ingredients cola or other soft drinks that are themselves permitted to contain caffeine as a food additive.

It is important to recognize differing regulations and the influence that academic research opinion can have in that context. One research team from The Netherlands, Australia and the UK has consistently reported that the problem may not be the combination of alcohol and caffeine, but the drinkers themselves. Their findings cast some doubt on the conclusion that there is a harmful toxicological or behavioural interaction between caffeine and alcohol (Verster, et al., 2016; Verster, et al., 2015; Benson, et al., 2014; Alford, et al., 2014; Johnson, et al., 2016).

6. Additives other than caffeine

Some researchers have suggested that caffeine cannot be solely responsible for improvements in performance associated with energy drinks (Scholey & Kennedy, 2004; Marczynski et al., 2011), whilst others have concluded that the negative psychological and physiological side effects reported almost certainly relate to the caffeine content (Peacock et al., 2012). Researchers also appear to concur that taurine, guaraná and ginseng show no negative health effects at the concentrations typically added to energy drinks (Hurlock & Lee, 2012). It should be noted that the amounts typically used in energy drinks are invariably below those that might be expected to have therapeutic or adverse effects.

6.1. Guaraná

Guaraná (*Paullinia cupana*) is a rainforest vine that grows in the Brazilian Amazon. It has a long history of use in Brazil as the active component of tonic sodas, but in the last 20 years it has emerged globally as a key ingredient in nutraceutical and energy drinks (Smith & Atroch, 2010). Guaraná seed extracts contain caffeine (known as 'guaranine' in this context) at concentrations between 2% and 15% of dry weight (Finnegan, 2003; Weckerle, et al., 2003; Lima, et al., 2005; Babu et al., 2008), as well as saponins and tannins (Espinola, et al., 1997), which have antioxidant properties (Mattei, et al., 1998) and flavonoids, which can reduce blood platelet aggregation (Subbiah & Yunker, 2008).

Guaraná has been suggested to improve cognitive performance, mental fatigue, and mood at physiologically relevant dosages (Haskell, et al., 2007; Kennedy, et al., 2008; Scholey & Haskell, 2008) and in animal studies, it has been shown to exert no toxic effects when consumed in acute high dosages as well as in chronic lower dosages (Mattei, et al., 1998). Given that caffeine is the primary active component of guaraná, much of the research relating to caffeine is pertinent. However, there are some points of difference. For example, caffeine from guaraná is reported to be released more slowly than pure caffeine, providing a more subtle and prolonged stimulatory effect (Scholey & Haskell, 2008). It is also believed to have a potentially longer half-life, because of interactions with other compounds in the plant, according to some reports (Babu et al., 2008).

Caffeine derived from guaraná should be considered part of the total caffeine content of premixed beverages with added caffeine.

6.2. Taurine

Taurine (2-aminoethane sulfonic acid) is an amino acid found in high concentrations in heart and muscle tissue and the brain, where it acts as an agonist or a partial agonist at glycine receptors (Huxtable, 1992; Olive, 2002). It also occurs in the human diet and is commonly added to energy drinks at concentrations of around 4 g/l (Higgins et al., 2010; Nomisma-Areté consortium, 2013). The mean daily intake of taurine from all sources has been estimated at between 40 and 400 mg (ANZFA, 2001).

Taurine is reported to have physiologically beneficial effects in humans (Kendler, 1989; Ikeda, 1997) and, a literature review conducted by Finnegan in 2003, found no evidence that consumption was a risk to human health. In contrast, McLellan and Lieberman (2012) highlighted flaws in studies often cited to support the addition of taurine to energy drinks (Geis, et al., 1994; Barthel, et al., 2001; Bell & McLellan, 2002) and concluded that there is little evidence to support taurine addition for cognitive or physical benefit.

The benefits of taurine supplementation in exercise have been attributed to its antioxidant effects (McLellan & Lieberman, 2012). However, Galloway and colleagues (2008) found that three 1.66 g doses of taurine over seven days significantly increased plasma taurine levels, but did not alter resting skeletal muscle taurine content and had no effect on metabolic responses to 120 min of exercise. A dose of 1.66 g would be equivalent to 415 ml of an energy drink containing a typical taurine level of 4 g/l (Higgins et al., 2010; Nomisma-Areté consortium, 2013).

Beverages containing taurine have been reported to enhance the positive effects of ethanol, possibly by countering its depressant effects (Ferreira et al., 2004), although the extent of this effect and the precise role of taurine remain speculative (Ginsburg & Lamb, 2008). It has also been reported a major metabolite of taurine, taurocholic acid, can decrease ethanol preference (Ward et al., 2000).

In 2003, the European Food Safety Authority (EFSA) issued a scientific opinion on the use of taurine in energy drinks (EC Scientific Committee on Food, 2003). EFSA's Panel on Food Additives and Nutrient Sources added to Food (ANS) concluded that, "a sufficient margin of safety exists for mean and high-level regular consumers of energy drinks, drinking on average 125ml and 350ml per person per day respectively; hence, exposure to taurine at these levels is not a safety concern." The Panel also considered that cumulative interactions between taurine and caffeine were unlikely. The Committee noted a No Observable Adverse Effect Level (NOAEL) of at least 1000 mg/kg of taurine per kg body weight per day for pathological changes. For a 60 kg person, this would be 43-fold higher than the estimated 95th percentile for exposure to taurine from energy drinks. In animal studies, evidence was found for some behavioural effects at a level of 300 mg/kg body weight of taurine per day and, whilst that is also much

higher than the levels achieved in humans from exposure to energy drinks, it precluded the setting of an upper safe level for daily taurine intake (EC Scientific Committee on Food, 2003).

Based on current research and regulatory decisions, addition of taurine to beverages at a concentration of up to 4g/l would appear to be safe.

6.3. Ginseng

Ginseng is a widely used herbal medicine, derived from any of several species of the genus *Panax* (Geng et al., 2010). It contains more than 40 active compounds, including ginsenosides, steroid-like compounds that are also responsible for its bitter taste. Ginseng extract is added to some energy drinks at concentrations of between 100 and 420 mg/l (approximately 25 to 120 mg per serving) and, in terms of flavour profile, the natural bitterness of ginseng is additive to that provided by caffeine, which tends to limit the levels added to such beverages (Tamamoto et al., 2010).

There has been some study of the efficacy of ginseng in increasing energy (Court, 2000), but there is little validating research (Vogler et al. 1999; Kitts & Hu, 2000). There appears to be little evidence to support a positive effect of ginseng on physical performance, although methodological flaws have been highlighted in the existing clinical research (Bahrke et al., 2009; Lee & Son, 2011). The claimed health benefits of ginseng are mainly attributed to its antioxidant, anti-inflammatory and cytoprotective properties (Jung et al., 2002; Rausch et al., 2006; Yun, 2001). It may also have beneficial effects on cognitive performance, although some report a lack of convincing evidence for enhancement of cognitive function in healthy participants (Geng et al., 2010).

In relation to its combination of with alcohol, ginseng may protect against alcohol-induced gastric damage (Yeo et al., 2008). It has also been shown to accelerate alcohol clearance in blood by increasing metabolism (Lee et al, 2003) and to reduce plasma alcohol levels (Lee, et al. 1987).

In a recent, systematic literature review on the efficacy and safety of ginseng, strong evidence was found for a positive effect on glucose metabolism, psychomotor function, and pulmonary disease, and the authors concluded that, in general, ginseng has a good safety profile with low incidence of adverse effects, based on daily doses of ginseng extract of between 200 and 1125 mg per day (Lee & Son, 2011).

7. Summary

7.1. Defining caffeine intake levels

Referring to the research extracts in Appendix 2A, acute caffeine doses of under 100 mg are generally regarded as low, exerting positive effects on cognitive function and mood, but with no adverse effects. The upper end of that range is also the lowest level at which most people can detect the bitter taste of caffeine and begin to discriminate its presence. Doses of between 100 mg and 200 mg are in the low-to-moderate range, still enhancing cognitive performance, but producing positive subjective effects. According to the EFSA Panel on Dietetic Products, Nutrition and Allergies (2015), single doses of caffeine up to 200 mg “do not give rise to safety concerns for the general healthy adult population.” Moderate doses of between 200mg and 400 mg are required to elicit positive physical benefits in relation to exercise, but there are some reports of anxiety experienced in this range. At higher doses, above 400 mg, adverse effects begin to emerge, with reports of symptoms such as anxiety, nausea, jitteriness and nervousness. Levels over 500 mg are described as excessive.

Fig. 1 Summary of typical experimental caffeine doses.

LOW	LOW-TO-MODERATE	MODERATE	HIGHER	EXCESSIVE	
0 mg	100 mg	200 mg	300 mg	400 mg	500+ mg

Appendix 2B reveals a more confusing picture for daily caffeine intake, since the figures reflect the wide variation in consumption in different populations, as well as individual differences. Broadly speaking, a daily caffeine intake of 100 - 200 mg appears to be regarded as moderate, whilst levels of intake above 500 mg are regarded as high and increasingly less healthy. In the United States, the Food & Drug Administration (FDA) has cited up to 400 mg of caffeine per day as being not generally associated with dangerous, negative effects (FDA, 2013) and that is consistent with a Scientific Opinion published by the EFSA Panel on Dietetic Products, Nutrition and Allergies (2015).

Looking at regulations applying in various countries, the maximum permitted caffeine content for cola type beverages and other soft drinks falls between 145 mg/l and 200 mg/l, which equates to 36 - 50 mg of caffeine in a 250 ml beverage serving or 72 - 100 mg in a 500 ml serving. These levels are consistent with low doses relative to the levels summarised in Figure 1, above, and may reflect the fact that children would be among the consumers of beverages in these categories.

The maximum permitted caffeine content for energy drinks is generally higher, at between 320 mg/l and 350 mg/l, although some countries (EU, South Africa, New Zealand) specify that beverages

containing more than 145 or 150 mg/l should be labelled “high caffeine content” and one country (Canada) permits concentrations up to 400 mg/l, but specifies a cap of 180 mg per serving. These figures would allow approximately 80 - 88 mg of caffeine in a 250 ml beverage serving or 160 - 175 mg in a 500 ml serving, which places them in the low-to-moderate range relative to the levels summarised in Figure 1.

7.2. Alcohol and caffeine interactions

A number of bodies have provided expert opinion on the safety of caffeine when mixed with alcohol. In 2009, the US Food and Drug Administration (FDA) approved caffeine as “Generally Recognised As Safe” (GRAS) for non-alcohol, cola-type beverages, in concentrations no higher than 200 parts per million (~ 200 mg/l) (FDA, 2009), but subsequently clarified that caffeine was unsafe for use as an additive to alcohol beverages (FDA, 2010). In 2012, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT, 2012) noted uncertainties in the available research, but concluded: “...the current balance of evidence does not support a harmful toxicological or behavioural interaction of caffeine and alcohol”. More recently, the European Food Safety Association (EFSA) Panel on Dietetic Products, Nutrition and Allergies (2015), concluded that alcohol consumption at doses up to about 0.65 g/kg body weight would not affect the safety of single doses of caffeine up to 200 mg, concluding that “up to these levels of intake, caffeine is unlikely to mask the subjective perception of alcohol intoxication.”

Considering research into physiological effects of alcohol and caffeine, co-ingestion of high dosages may prolong the effects of caffeine, but subjective and objective alcohol intoxication appear not to be affected relative to ingestion of alcohol alone. Some experimental studies of psychomotor and cognitive performance have reported antagonism of the effects of alcohol by caffeine, but the majority of research to date shows no significant reduction of alcohol-induced impairment and it has been suggested that the effects of caffeine may be restricted to countering impairment of psychomotor task performance. With regard to behavioural research, it has been noted that energy drink consumers usually consume more alcohol and may therefore experience more alcohol-related harm; so risk-taking associated with AmED use may result from increased alcohol intake rather than interaction of caffeine and alcohol.

Further research is needed on the relationship between AmED and risk-taking behaviour, as concerns remain, but a causal link has not been established. The prevalence and effects of AmED use, the possible masking effect of alcohol by caffeine, and the effects of premixed caffeinated alcohol beverages all merit further investigation. There are weaknesses in the currently available data, which should be addressed. For example, longitudinal studies are required in addition to cross-sectional data - the majority of studies on subjective experience to date have been based on retrospective survey data and self-reports. Researchers have attempted to address potential confounding factors, but there is often incomplete correction for personality traits and other factors, such as expectancy. Future research could

focus on sensation-seeking or impulsive personality traits, which may lead to individuals being drawn to energy drinks, heavy alcohol consumption or risky behaviours. Further research is also indicated across demographic groups, since the majority of survey-based research on AmED to date has focused on college-aged students in the USA.

It has not been possible in this report to define excessive levels of caffeine, or other stimulants, in alcohol beverages in the context of the original Commitment, but it is possible to identify suitable reference points for non-harmful intake of caffeine in combination with alcohol. The FDA GRAS ruling for cola-type beverages suggests that caffeine content of 200 mg/l is not harmful, although the FDA clarified that this should not be applied to alcohol beverages. As noted, EFSA suggests that the safety of 200 mg of caffeine would not be affected by alcohol intake at levels up to 0.65 g/kg. In a 70 kg individual, this would equate to an alcohol intake of 45.5 g (i.e. several drinks), and it should be noted that individual servings of alcohol beverages – where they contain caffeine - typically contain much less than 200 mg of caffeine; for example, an alcohol beverage containing 100 mg/l caffeine would contain 25 mg of caffeine in a 250 ml serving.

References

- Acquas, E., De Luca, M. A., Fenu, S., Longoni, R., & Spina, L. (2012). Caffeine and the brain: an overview. In: Preedy V. (Ed.) *Caffeine: Chemistry, Analysis, Function and Effects*, Royal Society of Chemistry, London, pp247-267.
- Alford, C., Hamilton Morris, J., & Verster, J. C. (2012). The effects of energy drink in combination with alcohol on performance and subjective awareness. *Psychopharmacology*, 222(3), 519-532.
- Alford, C., Scholey, A., & Verster, J. C. (2015). Energy drinks mixed with alcohol: are there any risks? *Nutrition Reviews*, 73(11), 796-798.
- Amblung, M., Few, L. R., Howland, J., Rohsenow, D. J., Metriks, J., & Mackillop, J. (2013). Impulsivity and alcohol demand in relation to combined alcohol and caffeine use. *Exp Clin Psychopharmacol*, 21(6), 467-474.
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.
- Anderson, C. & Horne, J. A. (2006). A high sugar content, low caffeine drink does not alleviate sleepiness by may worsen it. *Human Psychopharmacology: Clinical and Experimental*, 21, 299-303.
- Argentina Ministry of Health, 2012, http://www.conal.gov.ar/actas/Acta_94_Anexo06.pdf, accessed, October 29, 2016.
- Armstrong, L. E. (2002). Caffeine, body fluid-electrolyte balance, and exercise performance. *International Journal of Sport Nutrition and Exercise Metabolism*, 12(2), 189-206.
- Arnaud, M. J. (1998). Pharmacokinetics and metabolism of caffeine. In: Snel, J. and Lorist, M. M. (Eds.) *Nicotine, caffeine and social drinking. Behaviour and brain function*, OPA, Amsterdam, 153-165.
- Arria, A. M., Bugbee, B. A., Caldeira, K. M., & Vincent, K. B. (2014). Evidence and knowledge gaps for the association between energy drink use and high-risk behaviors among adolescents and young adults. *Nutrition Reviews*, 72(S1), 87-97.
- Arria, A. M., O'Brien, M. C., Griffiths, R. R., et al., (2013). Re: The Use of Caffeine in Energy Drinks, Letter to The Honorable Margaret A. Hamburg, M.D., Commissioner, FDA, March 19, 2013, 14pp.
- Arria, A. M. & O'Brien, M. C. (2011). The 'high' risk of energy drinks. *Journal of the American Medical Association*, 305(6), 600-601.
- Arria, A. M., Caldeira, K. M., Kasperski, S. J., O'Grady, K. E., Vincent, K. B., Griffiths, R.R., & Wish, E. D. (2010). Increased alcohol consumption, nonmedical prescription drug use, and illicit drug use are associated with energy drink consumption among college students. *Journal of Addiction Medicine*, 4(2), 74-80.
- Arria, A. M., Caldeira, K. M., Kasperski, S. J., Vincent, K. B., Griffiths, R. R., & O'Grady, K. E. (2011). Energy drink consumption and increased risk for alcohol dependence. *Alcoholism: Clinical and Experimental Research*, 35(2), 365-375.
- Arria, A. M., O'Brien, M. C., Goldberger, B. A., Griffiths, R. R., & Miller, K. E. (2009). Re: The Use of Caffeine in Alcoholic Beverages. Letter to Co-chairs of the National Association of Attorneys General Youth Access to Alcohol Committee, 5pp.
- Attila, S. & Cakir, B. (2011). Energy-drink consumption in college students and associated factors. *Nutrition*, 27(3), 316-322.
- Attwood, A. S., Higgs, S., & Terry, P. (2007). Differential responsiveness to caffeine and perceived effects of caffeine in moderate and high regular caffeine consumers. *Psychopharmacology*, 190, 469-477.
- Attwood, A. S., Rogers, P. J., Ataya, A. F., Adams, S., & Munafo, M. R. (2012). Effects of caffeine on alcohol-related changes in behavioural control and perceived intoxication in light caffeine consumers. *Psychopharmacology*, 221(4), 551-560.
- Australia New Zealand Food Authority (2001). *Inquiry Report: Formulated Caffeinated Beverages*. 02/02, 8 August, 23pp.
- Australia and New Zealand Food Regulation Ministerial Council (2014). *Ministerial Policy Guideline, Regulatory management of caffeine in the food supply*, June 27 2014, <http://www.foodstandards.gov.au/code/fofr/Documents/Caffeine%20July%202014.pdf>, accessed 10/31/2016.
- Azcona, O., Barbanaj, M. J., Torrent, J., & Jané, F. (1995). Evaluation of the central effects of alcohol and caffeine interaction. *British Journal of Clinical Pharmacology*, 40, 393-400.
- Babu, K. M., Church, R. J., & Lewander, W. (2008). Energy drinks: The new eye-opener for adolescents. *Clinical Pediatric Emergency Medicine*, 9, 35-42.
- Bahrke, M. S., Morgan, W. P., & Stegner, A. (2009). Is Ginseng an ergogenic aid? *International Journal of Sport Nutrition and Exercise Metabolism*, 19, 298-322.
- Barone, J. J. & Roberts, H. (1984). Human consumption of caffeine. In: Dews P. B. (ed) *Caffeine: perspectives from recent research*. Springer, Berlin, pp59-73.
- Barone, J. J. & Roberts, H. R. (1996). Caffeine consumption. *Food and Chemical Toxicology*, 34(1), 119-129.
- Barthel, T., Mechau, D., Wehr, T., Schnitker, R., Liesen, H., & Weiß, M. (2001). Readiness potential in different states of physical activation and after ingestion of taurine and/or caffeine containing drinks. *Amino Acids*, 20, 63-73.
- Beer, wine and spirits producers (2010). *Reducing harmful use of alcohol: Beer, wine and spirits producers' commitments*. 2010, 9pp.
- Bell, D. G. & Mcllellan, T. M. (2002). Exercise endurance 1, 3, and 6 h after caffeine ingestion in caffeine users and nonusers. *Journal of Applied Physiology*, 93, 1227-1234
- Bempong, D. K., Houghton, P. J. (1992). Dissolution and absorption of caffeine from guarana. *Journal of Pharmacy and Pharmacology*, 44, 769-771.
- Benelam, B. & Wyness, L. (2010). Hydration and health: a review. *Nutrition Bulletin*, 35, 3-25.
- Benowitz, N. L., Jacob, P., Mayan, H., & Denaro, C. (1995). Sympathomimetic effects of paraxanthine and caffeine in humans. *Clinical Pharmacology and Therapeutics*, 58, 684-691.
- Benson, S. & Scholey, A. (2014). Effects of alcohol and energy drink on mood and subjective intoxication: a double-blind, placebo-controlled crossover study. *Human Psychopharmacology: Clinical and Experimental*, 29, 360-369.
- Benson, S., Verster, J. C., Alford, C., & Scholey, A. (2014). Effects of mixing alcohol with caffeinated beverages on subjective intoxication: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, 47, 16-21.
- Berger, L. K., Fendrich, M., Chen, H. Y., Arria, A. M., & Cisler, R. A. (2011). Sociodemographic correlates of energy drink consumption with and without alcohol:

- results of a community survey. *Addictive Behaviors*, 36(5), 516-519.
- Blanchard, J. & Sawers, S. J. (1983). The absolute bioavailability of caffeine in man. *European Journal of Clinical Pharmacology*, 24(1), 93-98.
- Blumenthal, R., Shurtleff, M., & Limtiaco, A. G. (2009). Re: Alcoholic energy drinks. Letter to Dr M. A. Hamburg, Commissioner, FDA, 4pp.
- Bonati, M. & Garattini, S. (1984). Interspecies comparison of caffeine disposition. In: Dewes P. B. (ed) *Caffeine: perspectives from recent research*. Springer, pp48-56.
- Bonati, M., Latini, R., Galletti, F., Young, J. F., Tognoni, G., & Garattini, S. (1982). Caffeine disposition after oral doses. *Clinical Pharmacology and Therapeutics*, 32, 98-106
- Bonita, J. S., Mandarano, M., Shuta, D., & Vinson, J. (2007). Coffee and cardiovascular disease: in vitro, cellular, animal, and human studies. *Pharmacology Research*, 2007, 55, 187-198.
- Brache, K. & Stockwell, T. (2011). Drinking patterns and risk behaviors associated with combined alcohol and energy drink consumption in college drinkers. *Addictive Behaviors*, 36(12), 1133-1140.
- Brache, K., Thomas, G., & Stockwell, T. (2012). Caffeinated alcoholic beverages in Canada: Prevalence of use, risks and recommended policy responses. Ottawa, ON: Canadian Centre on Substance Abuse, 32pp.
- Brice, C. F. & Smith, A. P. (2002). Effects of caffeine on mood and performance: a study of realistic consumption. *Psychopharmacology*, 164, 188-192.
- Bruce, C. R., Anderson, M. E., Fraser, S. F., Stepto, N. K., Klein, R., Hopkins, W. G., & Hawley, J. A. (2000). Enhancement of 200-m rowing performance after caffeine ingestion. *Medicine and Science in Sports and Exercise*, 32, 1958- 1963.
- Bucci, L. R. (2000). Selected herbals and human exercise performance. *American Journal of Clinical Nutrition*. 72(Suppl), S624-S636.
- Burrows, T., Pursey, K., Neve, M., & Stanwell, P. (2013). What are the health implications associated with the consumption of energy drinks? A systematic review. *Nutrition Reviews*, 71(3), 135-148.
- Callahan, M. M., Robertson, R. F., Branfman, A. R., McComish, M. F., & Yesair, D. W. (1983). Comparison of caffeine metabolism in three non-smoking populations after oral administration of radiolabelled caffeine. *Drug Metabolism and Disposition*, 11, 211-217.
- Canadean (2012). *Global Energy Drinks Report 2012*, Canadean, December 2012, 736pp.
- Christopher, G., Sutherland, D., & Smith, A. (2005). Effects of caffeine in nonwithdrawn volunteers. *Human Psychopharmacology Clinical and Experimental*, 20, 47-53.
- Clapp, J.D., Holmes, M.R., Reed, M.B., Shillington, A.M., & Freisthler, B. (2007). Measuring college students' alcohol consumption in natural drinking environments. Field methodologies for bars and parties.. *Evaluation Review*, 31, 469-489.
- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (2012). *COT Statement on the interaction of caffeine and alcohol and their combined effects on health and behaviour*, 2012/04, December 2012, 22pp.
- Cornelis, M. C., El-Sohemy, A., & Campos, H. (2007). Genetic polymorphism of the adenosine A2A receptor is associated with habitual caffeine consumption. *American Journal of Clinical Nutrition*, 6(1), 240-244.
- Court, W. E. (2000). The pharmacology and therapeutics of ginseng. In: Court, W. E. (Ed.), *Ginseng: the Genus Panax*. CRC Press, 117-197.
- Curry, K. & Stasio, M. J. (2009). The effects of energy drinks alone and with alcohol on neuropsychological functioning. *Human Psychopharmacology: Clinical and Experimental*, 24(6), 473-481.
- Cyders, M. A., Smith, G. T., Spillane, N. S., Fischer, S., Annus, A. M., & Peterson, C. (2007). Integration of impulsivity and positive mood to predict risky behavior: development and validation of a measure of positive urgency. *Psychological Assessment*, 19(1), 107-118.
- Dietary Guidelines Advisory Committee (DGAC), Scientific Report of the 2015 Dietary Guidelines Advisory Committee, USDA/DHHS, February 2015 [Part D. Chapter 5: Food Sustainability and Safety, p23].
- Dorfman, L. J. & Jarvik, M. E. (1970). Comparative stimulant and diuretic actions of caffeine and theobromine in man. *Clinical Pharmacology and Therapeutics*, 11(6), 869-872.
- Drewnowski, A. (2001). The science and complexity of bitter taste. *Nutrition Reviews*, 59(6), 163-169.
- Duchan, C. (2013). Popular energy drinks and alcohol. In: Watson, R. R., Preedy, V. R., & Zibadi, S. (Eds.) *Alcohol, Nutrition & Health Consequences*, Springer: New York, pp255-263.
- Durlach, P. J. (1999). The effects of a low dose of caffeine on cognitive performance. *Psychopharmacology*, 1999, 140, 116-119.
- Eggleton, M. G. (1942). The diuretic action of alcohol in man. *Journal of Physiology*, 101, 172- 191.
- Eckschmidt, F., De Andrade, A. G., Dos Santos, B., De Oliveira, L. G. (2013). The effects of alcohol mixed with energy drinks (AmED) on traffic behaviors among Brazilian college students: a national survey. *Traffic Injury Prevention*, 14, 671-679.
- Elias, E., Gibson, G.J., Greenwood, L.F., Hunt, J.N., & Tripp, J.H. (1968). The slowing of gastric emptying by monosaccharides and disaccharides in test meals. *Journal of Physiology*, 194, 317-326.
- Espinola, E. B., Dias, R. F., Mattei, R. et al. (1997). Pharmacological activity of guarana (*Paullinia cupana* mart.) in laboratory animals. *Journal of Ethnopharmacology*, 1997, 55, 223-229.
- EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). (2011). Scientific Opinion on the substantiation of health claims related to caffeine and increased fat oxidation leading to a reduction in body fat mass (ID 735, 1484), increased energy expenditure leading to a reduction in body weight (ID 1487), increased alertness (ID 736, 1101, 1187, 1485, 1491, 2063, 2103) and increased attention (ID 736, 1485, 1491, 2375) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA Journal* 9(4), 2054: 1-29.
- EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). (2015). Scientific Opinion on the safety of caffeine. *EFSA Journal* 13(5), 4102: 1-120.
- European Commission, DG SANCO (2003). Opinion of the Scientific Committee on Food on additional information on "energy" drinks. *Scientific Committee on Food, ECF/CS/PLEN/ENDRINKS/16 Final*, European Commission, Brussels, 5 March 2003, 25pp
- European Commission, Regulation (EU) No 1334/2008, *Official Journal of the European Union*.
- European Commission, Regulation (EU) No 1169/2011, *Official Journal of the European Union*.
- FDA (2009). *Caffeine*. 21 CFR §§ 182.1180, Ch. I (4-1-09 Edition).

- FDA (2010). FDA Warning Letters issued to four makers of caffeinated alcoholic beverages, FDA News Release, November 17, 2010.
- FDA (2012a). Eligibility for classification as generally recognized as safe (GRAS).. 21 CFR §§ 170.30.
- FDA (2012b). Subchapter B - Food For Human Consumption (Continued); Part 170 - Food Additives, Subpart A - General Provisions; § 170.3 Definitions.. 21 CFR §§ 170.3.
- FDA (2013). FDA to investigate added caffeine. FDA Consumer Health Information, May 2013, 2pp.
- Ferreira, S. E., Hartmann Quadros, I. M., Trindade, A. A., Takahashi, S., Koyama, R. G., & Souza-Formigoni, M. L.O. (2004). Can energy drinks reduce the depressor effect of ethanol? An experimental study in mice. *Physiology & Behavior*, 82, 841-847.
- Ferreira, S. E., de Mello, M. T., Pompeia, S., de Souza Formigoni, M. L. (2006). Effects of energy drink ingestion on alcohol intoxication. *Alcoholism: Clinical and Experimental Research*, 30(4), 598-605.
- Ferreira, S. E., Túlio de Mello, M., Rossi, M. V., & Souza-Formigoni, M. L. O. (2004). Does an energy drink modify the effects of alcohol in a maximal effort test?. *Alcoholism: Clinical and Experimental Research*, 28 (9), 1408-1412.
- Fillmore, M. & Vogel-Sprott, M. (1992). Expected effect of caffeine on motor performance predicts the type of response to placebo. *Psychopharmacology*, 106, 209-214.
- Fillmore, M. T., Mulvihill, L. E., & Vogel-Sprott, M. (1994). The expected drug and its expected effect interact to determine placebo responses to alcohol and caffeine. *Psychopharmacology*, 115, 383-388.
- Fillmore, M. T. & Vogel-Sprott, M. (1995). Behavioral effects of combining alcohol and caffeine: contribution of drug-related expectancies. *Experimental and Clinical Psychopharmacology*, 3(1), 33-38.
- Fillmore, M. T., Roach, E. L., & Rice, J. T. (2002). Does caffeine counteract alcohol-induced impairment? The ironic effects of expectancy. *Journal of Studies on Alcohol*, 63, 745-754.
- Finnegan, D. (2003). The health effects of stimulant drinks. *Nutrition Bulletin*, 28, 147-155.
- Forney, R. B. & Hughes, F. W. (1965). Effect of caffeine and alcohol on performance under stress of audiofeedback. *Quarterly Journal of Studies on Alcohol*, 26, 206-212.
- Franks, H. M., Hagedorn, H., Hensley, V. R., Hensley, W. J., & Starmer, G. A. (1975). The effect of caffeine on human performance, alone and in combination with ethanol. *Psychopharmacology*, 45, 177-181.
- Frary, C. D., Johnson, R. K., & Wang, M. Q. (2005). Food sources and intakes of caffeine in the diets of persons in the United States. *Journal of the American Dietetic Association*, 105(1), 110-113.
- Fredholm, B. B., Bättig, K., Holmén, J., Nehlig, A., & Zvartau, E. E. (1999). Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews*, 51(1), 83-133.
- Fudin, R. & Nicasastro, R. (1988). Can caffeine antagonize alcohol-induced performance decrements in humans?. *Perceptual and Motor Skills*, 1988, 67, 375-391.
- Galloway, S. D. R., Talanian, J. L., Shoveller, A. K., Heigenhauser, G. J. F., & Spriet, L. L. (2008). Seven days of oral taurine supplementation does not increase muscle taurine content or alter substrate metabolism during prolonged exercise in humans. *Journal of Applied Physiology*, 105, 643-651.
- Garrett, B. E., & Griffiths, R. R. (1997). The role of dopamine in the behavioral effects of caffeine in animals and humans. *Pharmacology, Biochemistry and Behavior*, 57, 533-541.
- Garriott, J. C., Simmons, L. M., Poklis, A., & Mackell, M. A. (1985). Five cases of fatal overdose from caffeine-containing "look-alike" drugs. *Journal of Analytical Toxicology*, 9(3), 141-143.
- Geis, K-R., Jester, I., Falke, W., et al (1994). The effect of a taurine-containing drink on performance in 10 endurance-athletes. *Amino Acids*, 7, 45-56.
- Geng, J., Dong, J., Ni, H., Lee, M. S., Wu, T., Jiang, K., Wang, G., Zhou, A. L., & Malouf, R. (2010). Ginseng for cognition. *Cochrane Database Systematic Reviews*, 12, CD007769. doi: 10.1002/14651858.CD007769.pub2.
- George, J., Murphy, T., Roberts, R., et al (1986). Influence of alcohol and caffeine consumption on caffeine elimination. *Clinical and Experimental Pharmacology and Physiology*, 13, 731-736.
- Ginsburg, B. C. & Lamb, R. J. (2008). Taurine and ethanol interactions: behavioral effects in mice. *European Journal of Pharmacology*, 578(2-3), 228-237.
- Graham, T. E. (2001). Caffeine and exercise metabolism, endurance and performance. *Sports Medicine*, 31(11), 785-807.
- Graham, T. E. & Spriet, L. L. (1995). Metabolic, catecholamine, and exercise performance responses to various doses of caffeine. *Journal of Applied Physiology*, 1995, 78, 867-874.
- Griffiths, R. R., Evans, S. M., Heishman, S. J., Preston, K. L., Sannerud, C. A., Wolf, B., & Woodson, P. P. (1990). Low-dose caffeine discrimination in humans. *Journal of Pharmacology and Experimental Therapeutics*, 252, 970-978.
- Grilly, D. M. (2006). Psychostimulants. In: *Drugs and Human Behavior*, Pearson Education Inc., Boston, 5th edition, 184-188.
- Hasenfratz, M., Bunge, A., Dal Pra, G., & Battig, K. (1993). Antagonistic effects of caffeine and alcohol on mental performance parameters. *Pharmacology Biochemistry and Behavior*, 46, 463-465.
- Hasenfratz, M. & Bättig, K. (1994). Acute dose-effect relationships of caffeine and mental performance, EEG, cardiovascular and subjective parameters, *Psychopharmacology*, 114, 281-287.
- Haskell, C. F., Kennedy, D. O., Wesnes, K. A., Milne, A. L., & Scholey, A. B. (2007). A double-blind, placebo-controlled, multi-dose evaluation of the acute behavioural effects of guaraná in humans. *Journal of Psychopharmacology*, 21(1), 65-70.
- Heckman, M. A., Sherry, K., & Gonzalez de Mejia, E. (2010). Energy drinks: an assessment of their market size, consumer demographics, ingredient profile, functionality, and regulations in the United States. *Comprehensive Reviews In Food Science And Food Safety*, 9, 303-317.
- Heinz, A. J., Kassel, J. D., & Smith, E. V. (2009). Caffeine expectancy: instrument development in the Rasch Measurement Framework. *Psychology of Addictive Behavior*, 23(3), 500-511.
- Hewlett, P. & Smith, A. (2006). Acute effects of caffeine in volunteers with different patterns of regular consumption. *Human Psychopharmacology Clinical and Experimental*, 21, 167-180.
- Hewlett, P. & Smith, A. (2007). Effects of repeated doses of caffeine on performance and alertness: new data and secondary analyses. *Human Psychopharmacology: Clinical and Experimental*, 22, 339-350.
- Higgins, J. P., Tuttle, T. D., & Higgins, C. L. (2010). Energy beverages: Content and safety. *Mayo Clinic Proceedings*, 85(11), 1033-1041

- Hindmarch, I., Alford, C., Barwell, F., & Kerr, J. (1992). Measuring the side effects of psychotropics: the behavioural toxicity of antidepressants. *Journal of Psychopharmacology*, 6, 198-203.
- Hobson, R. M. & Maughan, R. J. (2010). Hydration status and the diuretic action of a small dose of alcohol. *Alcohol and Alcoholism*, 45(4), 366-373.
- Holmgren, P., Nordén-Petersson, L., & Ahlner, J. (2004). Caffeine fatalities - four case reports. *Forensic Science International*, 139, 71-73.
- Howland, J., Rohsenow, D. J., Arnedt, J. T., Bliss, C. A., Hunt, S. K., Calise, T. V., Heeren, T., Winter, M., Littlefield, C., & Gottlieb, D. J. (2011). The acute effects of caffeinated versus non-caffeinated alcoholic beverage on driving performance and attention/reaction time. *Addiction*, 106(2), 335-341.
- Howland, J., Rohsenow, D. J., Calise, T. V., MacKillop, J., & Metrik, J. (2011). Caffeinated alcoholic beverages: an emerging public health problem. *American Journal of Preventive Medicine*, 40(2), 268-271.
- Hughes, J. R., Hunt, W. K., Higgins, S.T., Bickel, W.K., Fenwick, J. W., & Pepper, S. L. (1992). Effect of dose on the ability of caffeine to serve as a reinforcer in humans. *Behavioural Pharmacology*, 3, 221-218.
- Huntley, E. D. & Juliano, L. M. (2012). Caffeine expectancy questionnaire (caffEQ): construction, psychometric properties, and associations with caffeine use, caffeine dependence, and other related variables. *Psychological Assessment*, 24(3), 592-607.
- Hurlock, L. & Lee, M. G. (2012). Potential health problems with the use of energy drinks. *West Indian Medical Journal*, 61(1), 1-2.
- Huxtable, R. J. (1992). Physiological actions of taurine. *Physiological Reviews*, 72(1), 101-163
- IARC (1991). Caffeine. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 51: Coffee, Tea, Mate, Methylxanthines and Methylglyoxal, p291 (last updated 17 November 1997).
- Ikeda, H. (1977). Effects of taurine on alcohol withdrawal. *Lancet*, 310(8036), 509.
- International Food Information Council Foundation (1998). *Caffeine & Health: Clarifying The Controversies*. IFIC Review, IFIC, Washington, D.C., 16pp.
- IOM (Institute of Medicine) (2014). *Caffeine in food and dietary supplements: Examining safety: Workshop summary*. Washington, DC: The National Academies Press.
- Jacobson, B. H. & Thurman-Lacey, S. R. (1992). Effect of caffeine on motor performance by caffeine-naïve and familiar subjects. *Perceptual and Motor Skills*, 74, 151-157.
- James, J. E. (1994). Does caffeine enhance or merely restore degraded psychomotor performance? *Neuropsychobiology*, 30, 124-125.
- James, J. E. (1997). *Understanding Caffeine. A Biobehavioral Analysis*. Sage Publications, California, 227pp.
- James, J. E. & Keane, M. A. (2007). Caffeine, sleep and wakefulness: implications of new understanding about withdrawal reversal. *Human Psychopharmacology Clinical and Experimental*, 22, 549-558.
- James, W. P. T. & Ralph, A. (2001). Alcohol: its metabolism and effects. In: *Human Nutrition and Dietetics*, (J. S. Garrow, W. P. T. James, A. Ralph eds), Chapter 8, pp. 121-36. Churchill Livingstone: London, UK.
- Jimenez-Pavon, D., Cervantes-Borunda, M. S., Diaz, L. E., Marcos, A., & Castillo, M. J. (2015). Effect of a moderate intake of beer on markers of hydration after exercise in the heat: a crossover study. *Journal of the International Society of Sports Nutrition*, 12, 26.
- Johnson, S.J., Alford, C., Stewart, K., Verster, J.C. (2016). A UK student survey investigating the effects of consuming alcohol mixed with energy drinks on overall alcohol consumption and alcohol-related negative consequences. *Preventive Medicine Reports*, 4, 496-501.
- Johnston, L. D., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E. & Miech, R. A. (2016). Monitoring the Future national survey results on drug use, 1975-2015: Volume 2, College students and adults ages 19-55. Ann Arbor: Institute for Social Research, The University of Michigan. Table 4-3.
- Juliano, L. M., Anderson, B. A., & Griffiths, R. R. (2011). Caffeine. In J. H. Lowinson, P. Ruiz, R. B. Millman, & J. G. Langrod (Eds.), *Substance abuse: A comprehensive textbook* (5th ed., pp. 335-353). Baltimore, MD: Lippincott, Williams, & Wilkins.
- Jung, M. Y., Jeon, B. S., & Bock, J. Y. (2002). Free, esterified, and insoluble-bound phenolic acids in white and red Korean ginsengs (Panax ginseng CA Meyer). *Food Chemistry*, 79(1), 105-111.
- Kaminer, Y. (2010). Problematic use of energy drinks by adolescents. *Child and Adolescent Psychiatric Clinics of North America*, 19(3), 643-650.
- Kaplan, G. B., Greenblatt, D. J., Ehrenberg, B. L., Goddard, J. E., Cotreau, M. M., Harmatz, J. S., Shader, R. I., et al (1997). Dose-dependent pharmacokinetics and psychomotor effects of caffeine in humans. *Journal of Clinical Pharmacology*, 37(8), 693-703.
- Kendler, B. S. (1989). Taurine: an overview of its role in preventive medicine. *Preventive Medicine*, 18(1), 79-100.
- Kerr, J. S., Sherwood, N., & Hindmarch, I. (1991). Separate and combined effects of the social drugs on psychomotor performance. *Psychopharmacology*, 104, 113-119.
- Kitts, D. & Hu, C. (2000). Efficacy and safety of ginseng. *Public Health Nutrition*, 3(4A):473-485.
- Koh, P-O. (2009). Ginkgo biloba extract (egb 761) prevents increase of bad-bcl-xl interaction following cerebral ischemia. *American Journal of Chinese Medicine*, 37(5), 867-876.
- Lane, J. D., Steege, J. F., Rupp, S. L., & Kuhn, C. M. (1992). Menstrual cycle effects on caffeine elimination in the human female. *European Journal of Clinical Pharmacology*, 43, 543-546.
- Lau-Barraco, C., Milletich, R. J., & Linden, A. N. (2014). Caffeinated alcohol consumption profiles and associations with use severity and outcome expectancies. *Addictive Behaviors*, 39(1), 308-315.
- Lee, F. C., Ko, J. H., Park, J. K., & Lee, J. S. (1987). Effects of Panax ginseng on blood alcohol clearance in man. *Clinical and Experimental Pharmacology and Physiology*, 14, 543-546.
- Lee, Y. J., Pantuck, C. B., Pantuck, E. J. (1993). Effect of ginseng on plasma levels of ethanol in the rat. *Planta Medica*, 59, 17-19.
- Lee, N-H. & Son, C-G. (2011). Systematic review of randomized controlled trials evaluating the efficacy and safety of ginseng, *Journal of Acupuncture and Meridian Studies*, 4(2), 85-97.
- Lelo, A., Miners, J. O., Robson, R. A., & Birkett, D. J. (1986). Quantitative assessment of caffeine partial clearances in man. *British Journal of Clinical Pharmacology*, 22, 183-186.
- Levy, G., Tapsell, L. (2007). Shifts in purchasing patterns of non-alcoholic, water-based beverages in Australia, 1997-2006. *Nutrition and Dietetics*, 64, 268-279.
- Lieberman, H. R., Wurtman, R. J., Emde, G. G., Roberts, C., Coviella, I. L. (1987). The effects of low doses of

- caffeine on human performance and mood. *Psychopharmacology*, 92(3), 308-312.
- Lieberman, H. R., Tharion, W. J., Shukitt-Hale, B., Speckman, K. L., & Tulley, R. (2002). Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training. *Psychopharmacology*, 164, 250-261.
- Liguori, A. & Robinson, J. H. (2001). Caffeine antagonism of alcohol-induced driving impairment. *Drug and Alcohol Dependence*, 63, 123-129.
- Lima, W. P., Carnevali Jr, L. C., Eder, R., Fernando, L., Costa Rosa, B. P., Bacchi, E. M., & Seelaender, M. C. L. (2005). Lipid metabolism in trained rats: Effect of guarana (*Paullinia cupana* Mart.) supplementation. *Clinical Nutrition*, 24, 1019-1028
- Loke, W.H. (1988). Effects of caffeine on mood and memory. *Physiology and Behavior*, 44, 367-372.
- Lorist, M. M. & Tops, M. (2003). Caffeine, fatigue, and cognition. *Brain and Cognition*, 53, 82-94.
- Mackillop, J., Howland, J., Rohsenow, D. J., Few, L. R., Amlung, M. T., Metrik, J., & Vehige Calise, T. (2012). Initial development of a measure of expectancies for combinations of alcohol and caffeine: the caffeine-alcohol combined effects questionnaire (CACEQ). *Experimental and Clinical Psychopharmacology*, 20(6), 466-472.
- Malinauskas, B. M., Aeby, V. G., Overton, R. F., Carpenter Aeby, T., Barber Heidal, K. (2007). A survey of energy drink consumption patterns among college students. *Nutrition Journal*, 6, Art No 35, 7pp
- Mallet, K. A., Marzell, M., Scaglione, N., Hultgren, B., & Turrisi, R. (2014). Are all alcohol and energy drink users the same? Examining individual variation in relation to alcohol mixed with energy drink use, risky drinking and consequence. *Psychol Addict Behav*, 28(1), 97-104.
- Marczinski, C. A. & Fillmore, M. T. (2006). Clubgoers and their trendy cocktails: implications of mixing caffeine into alcohol on information processing and subjective reports of intoxication. *Experimental and Clinical Psychopharmacology*, 14(4), 450-458
- Marczinski, C. A., Fillmore, M. T., Bardgett, M. E., & Howard, M. A. (2011). Effects of energy drinks mixed with alcohol on behavioral control: risks for college students consuming trendy cocktails. *Alcoholism: Clinical and Experimental Research*, 35(7), 1282-1292
- Marczinski, C. A., Fillmore, M. T., Henges, A. L., Ramsey, M. A., & Young, C. R. (2012). Effects of energy drinks mixed with alcohol on information processing, motor coordination and subjective reports of intoxication. *Experimental and Clinical Psychopharmacology*, 20(2), 129-138.
- Marczinski, C. A. (2014). Combined alcohol and energy drink use: hedonistic motives, adenosine, and alcohol dependence. *Alcoholism: Clinical and Experimental Research*, 38(7), 1822-1825.
- Marczinski, C. A., Fillmore, M. T., Stamates, A. I., & Maloney, S. F. (2016). Desire to drink alcohol is enhanced with high caffeine energy drink mixers. *Alcoholism: Clinical and Experimental Research*, 40(9), 1982-1990.
- Martz, M. E., Patrick, M. E., & Schulenberg, J. E. (2015). Alcohol mixed with energy drink use among US 12th-grade students: prevalence, correlates, and associations with unsafe driving. *J. Adoles Health*, 56(5), 557-563.
- Mattei, R., Dias, R. F., Espinola, E. B., et al (1998). Guarana (*Paullinia cupana*): Toxic behavioral effects in laboratory animals and antioxidant activity in vitro. *Journal of Ethnopharmacology*, 60, 111-116.
- Maughan, R. J. & Griffin, J. (2003). Caffeine ingestion and fluid balance: a review. *Journal of Human Nutrition and Dietetics*, 16, 411-420.
- McCusker, R. R., Goldberger, B. A., & Cone, E. J. (2003). Technical Note: Caffeine content of specialty coffees. *Journal of Analytical Toxicology*, 27, 520-522.
- McKetin R., Coen, A., & Kaye, S. (2015). A comprehensive review of the effects of mixing caffeinated energy drinks with alcohol. *Drug & Alcohol Dependence* [early online publication].
- McLellan, T. M. & Lieberman, H. R. (2012). Do energy drinks contain active components other than caffeine? *Nutrition Reviews*, 70(12), 730-744.
- Miech, R. A., Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2016). Monitoring the Future national survey results on drug use, 1975–2015: Volume I, Secondary school students. Ann Arbor: Institute for Social Research, The University of Michigan. Tables F-2, 2-2, 4-4a, 4-6.
- Miller, K. E. (2008). Energy drinks, race, and problem behaviors among college students. *Journal of Adolescent Health*, 43, 490-497.
- Miller, K. E. (2008). Wired: energy drinks, jock identity, masculine norms, and risk taking. *Journal of American College Health*, 56(5), 481-489.
- Mintel (2011). Generation Zzz: younger consumers kept awake by energy drinks, Mintel Press Release, October 2011, 2pp.
- Mitchell, M. C., Hoyumpa, A. M., Schenker, S., Johnson, R. F., Nichols, S., & Patwardhan, R. V. (1983). Inhibition of caffeine elimination by short-term ethanol administration. *Journal of Laboratory and Clinical Medicine*, 101(6), 826-834.
- Moskowitz, H., Burns, M. (1981). The effects of alcohol and caffeine, alone and in combination, on skills performance. In: Goldberg, L. (Ed.), *Alcohol, Drugs and Traffic Safety*, Vol. 3. Almqvist & Wiksell, Stockholm, Sweden, pp969–983.
- Mundt, J. C. & Ross, L. E. (1993). Methodological issues for evaluation of alcohol and other drug effects: examples from flight-simulator performance. *Behavior Research Methods: Instruments & Computers*, 25, 360-365.
- Nawrot, P., Jordan, S., Eastwood, J., Rotstein, J., Hugenholtz, A., & Feeley, M. (2003). Effects of caffeine on human health. *Food Additives and Contaminants*, 20(1), 1-30.
- Nehlig, A. (2010). Is caffeine a cognitive enhancer? *Journal of Alzheimer's Disease*, 20, S85-S94.
- Nomisma-Areté consortium: Zucconi, S. Volpato, C. Adinolfi, F. Gandini, E. Gentile, E. Loi, A., & Fioriti, L. (2013). Gathering consumption data on specific consumer groups of energy drinks. *European Food Safety Authority, Supporting Publications 2013:EN-394*, 190pp
- Nuotto, E., Mattila, M. J., Seppala, T., Konno, K. (1982). Coffee and caffeine and alcohol effects on psychomotor function. *Clinical Pharmacology and Therapeutics*, 31, 68-76.
- Oborne, D. J. & Rogers, Y. (1983). Interactions of alcohol and caffeine on human reaction time. *Aviation, Space and Environmental Medicine*, 54, 528-534.
- O'Brien, M. C., McCoy, T. P., Rhodes, S. D., Wagoner, A., & Wolfson, M. (2008). Caffeinated cocktails: energy drink consumption, high-risk drinking, and alcohol-related consequences among college students. *Academic Emergency Medicine*, 15(5), 453-460
- O'Brien, M. C., McCoy, T. P., Egan, K. L., Goldin, S., Rodes, S. D., & Wolfson, M. (2013). Caffeinated alcohol, sensation seeking, and injury risk. *Journal of Caffeine Research*, 3(2), 59-66.

- Oei, A., & Hartley, L. R. (2005). The effects of caffeine and expectancy on attention and memory. *Human Psychopharmacology Clin Exp.*, 20, 193-202.
- Olive, M. F. (2002). Interactions between taurine and ethanol in the central nervous system. *Amino Acids*, 23(4), 345-357.
- Oteri, A., Salvo, F., Patrizio Caputi, A. P., & Calapai, G. (2007). Intake of energy drinks in association with alcoholic beverages in a cohort of students of the School of Medicine of the University of Messina. *Alcoholism: Clinical and Experimental Research*, 31(10), 1677-1680
- Paganini-Hill, A., Kawas, C. H., & Corrada, M. M. (2007). Non-alcoholic beverage and caffeine consumption and mortality: the LeisureWorld Cohort Study. *Preventive Medicine*, 2007, 44, 305-310.
- Peacock, A., Bruno, R., Martin, F. H., & Carr, A. (2013). The impact of alcohol and energy drink consumption on intoxication and risk-taking behavior. *Alcoholism: Clinical and Experimental Research*, published early online, 12 March 2013, 9pp
- Peacock, A., Bruno, R., Martin, F. H., & Carr, A. (2014). Self-reported physiological and psychological side-effects of an acute alcohol and energy drink dose. *Appetite*, 76, 60-65.
- Peacock, A., Bruno, R., & Martin, F. H. (2012). The subjective physiological, psychological, and behavioral risk-taking consequences of alcohol and energy drink co-ingestion. *Alcoholism: Clinical and Experimental Research*, 36(11):2008-15.
- Peacock, A. & Bruno, R. (2015). Young adults who mix alcohol with energy drinks: Typology of risk-taking behaviour. *Addictive Behaviors* [early online publication].
- Peacock, A., Droste, N., Pennay, A., Lubman, D. I., Miller, P., Newcombe, D., & Bruno, R. (2015). Self-reported risk-taking behavior during matched-frequency sessions of alcohol versus combined alcohol and energy drinks consumption: Does co-ingestion increase risk-taking? *Alcoholism: Clinical & Experimental Research*, [early online publication], 1-8.
- Pendleton, M., Brown, S., Thomas, C. M., & Odie, B. (2013). Potential toxicity of caffeine when used as a dietary supplement for weight loss. *Journal of Diet Suppl.*, 10(1), 1-5.
- Peterson, E. A. (2013). Caffeine catastrophe: energy drinks, products liability and market strategy," *Internal Journal of Marketing Studies*, 5(2), 50-58.
- Pfeifer, R. W. & Notari, R. E. (1988). Predicting plasma caffeine concentrations resulting from consumption of food or beverages: A simple method and its origin. *Drug Intelligence and Clinical Pharmacy*, 22, 953-959.
- Rausch, W. D., Liu, S., Gille, G., & Radad, K. (2006). Neuroprotective effects of ginsenosides. *Acta Neurobiologiae Experimentalis (Wars)*, 66, 369-375.
- Reissig, C. J., Strain, E. C., & Griffiths, R. R. (2009). Caffeinated energy drinks - a growing problem. *Drug and Alcohol Dependence*, 99(1-3), 1-10
- Revelle, W., Humphreys, M. S., Simon, L., & Gilliland, K. (1980). The interactive effect of personality, time of day, and caffeine: a test of the arousal model. *Journal of Experimental Psychology: General*, 109(1), 1-31.
- Riddell, L. J., Sayompark, D., Oliver, P., & Keast, R. S. J. (2012). Caffeine as an ingredient in sugar sweetened beverages. In: Preeedy V. (Ed.) *Caffeine: Chemistry, Analysis, Function and Effects*, Royal Society of Chemistry, London, pp22-38.
- Rogers, P. J., Martin, J., Smith, C., Heatherley, S. V., & Smit, H. J. (2003). Absence of reinforcing, mood and psychomotor performance effects of caffeine in habitual non-consumers of caffeine. *Psychopharmacology*, 167, 54-62.
- Rosenfeld L. S., Mihalov, J. J., Carlson, S. J., & Mattia, A. (2014). Regulatory status of caffeine in the United States, *Nutrition Reviews*, 72 (S1), 22-33.
- Rossheim, M. E. & Thombs, D. L. (2011). Artificial sweeteners, caffeine, and alcohol intoxication in bar patrons. *Alcoholism: Clinical and Experimental Research*, 35(10), 1891-1896
- Rush, C. R., Higgins, S. T., Hughes, J. R., Bickel, W. K., & Wiegner, M. S. (1993). Acute behavioral and cardiac effects of alcohol and caffeine, alone and in combination, in humans. *Behavioural Pharmacology*, 4, 562-572
- Ryan, L., Hatfield, C., & Hofstetter, M. (2002). Caffeine reduces time-of-day effects on memory performance in older adults. *Psychological Science*, 13, 68-71.
- Scholey, A. B. & Kennedy, D. O. (2004). Cognitive and physiological effects of an "energy drink": an evaluation of the whole drink and of glucose, caffeine and herbal flavouring fractions. *Psychopharmacology*, 176, 320-330.
- Scholey, A. & Haskell, C. (2008). Neurocognitive effects of guarana plant extract. *Drugs Future*, 33, 869-874.
- Seifert, S. M., Schaechter, J. L., Hershoin, E. R., & Lipshultz, S. E. (2011). Health effects of energy drinks on children, adolescents, and young adults. *Pediatrics*, 127, 511-528.
- Sepkowitz, K. A. (2012). Energy drinks and caffeine-related adverse effects. *JAMA*, Published online December 19, E1-E2.
- Shirreffs, S. M. & Maughan, R. J. (1997). Restoration of fluid balance after exercise-induced dehydration: effects of alcohol consumption. *Journal of Applied Physiology*, 83, 1152-1158.
- Smit, H. J. & Rogers, P. J. (2000). Effects of low doses of caffeine on cognitive performance, mood and thirst in low and higher caffeine consumers. *Psychopharmacology*, 152, 167-173.
- Smith, A. P., Sturgess, W., & Gallagher, J. (1999). Effects of a low dose of caffeine given in different drinks on mood and performance. *Human Psychopharmacology*, 1999, 14, 473-482.
- Smith, P. F., Smith, A., Miners, J., McNeil, J., & Proudfoot, A. (2000). *Report of the Expert Working Group on the Safety Aspects of Dietary Caffeine*. Canberra: Australia New Zealand Food Authority.
- Smith, A. (2002). Effects of caffeine on human behavior. *Food and Chemical Toxicology*, 40, 1243-1255.
- Smith, N. & Atroch, A. L. (2010). Guarana's journey from regional tonic to aphrodisiac and global energy drink. *eCAM*, 7(3), 279-282.
- Stavric, B. (1988). Methylxanthines: toxicity to humans. 2. Caffeine. *Food and Chemical Toxicology*, 26, 645-662.
- Stookey, J. D. (1999). The diuretic effects of alcohol and caffeine and total water intake misclassification. *European Journal of Epidemiology*, 15(2), 181-188.
- Subbiah, M. T. R. & Yunker, R. (2008). Studies on the nature of anti-platelet aggregatory factors in the seeds of the Amazonian herb guarana (*Paullinia cupana*). *International Journal of Vitamin Nutrition Research*, 78, 96-101.
- Szpak, A. & Allen, D. (2012). A case of acute suicidality following excessive caffeine intake. *Journal of Psychopharmacology*, 26(11), 1502-1510.
- Tamamoto, L. C., Schmidt, S. J., & Lee, S-Y. (2010). Sensory profile of a model energy drink with varying levels of functional ingredients - caffeine, ginseng, and taurine. *Journal of Food Science*, 75(6), S272-S278.

- Temple, J. L., Dewey, A. M., & Briatico, L. N. (2010). Effects of acute caffeine administration on adolescents. *Experimental and Clinical Psychopharmacology*, 18(6), 510-520.
- Thelander, G., Jönsson, A. K., Personne, M., Forsberg, G. S., Magnusson Lundqvist, K., & Ahlner, J. (2010). Caffeine fatalities - Do sales restrictions prevent intentional intoxications?. *Clinical Toxicology*, 48, 354-358.
- Thombs, D. L., O'Mara, R. J., Tsukamoto, M., Rossheim, M. E., Weiler, R. M., Merves, M. L., & Goldberger, B. A. (2010). Event-level analyses of energy drink consumption and alcohol intoxication in bar patrons. *Addictive Behaviors*, 35(4), 325-330
- Thombs, D., Rossheim, M., Barnett, T. E., Weiler, R. M., Moorhouse, M. D., & Coleman, B. N. (2011). Is there a misplaced focus on AmED? Associations between caffeine mixers and bar patron intoxication. *Drug and Alcohol Dependence*, 116(1-3), 31-36
- Thombs, D.L., O'Mara, R., Dodd, V.J., Merves, M.L., Weiler, R.M., Goldberger, B.A., Pokorny, S.B., Moore, C., Reingle, J., & Gullet, S.E. (2009). Event-specific analyses of poly-drug abuse and concomitant risk behavior in a college bar district in Florida. *Journal of the American College Health*, 57, 575-585.
- Tinley, E. M., Yeomans, M. R., & Durlach, P. J. (2003). Caffeine reinforces flavour preference in caffeine-dependent, but not long-term withdrawn, caffeine consumers. *Psychopharmacology*, 166, 416-423.
- Torpy, J. M. & Livingston, E. H. (2012). Energy drinks. *JAMA*, Published online December 19, E1.
- Trout, D. L. & Bernstein, P. A. (1986). Intake and gastric emptying of mono- versus disaccharides by rats. *Journal of Nutrition*, 116, 1682-1693.
- Verster, J. C. & Alford, C. (2011). Unjustified concerns about energy drinks (editorial). *Current Drug Abuse Reviews*, 4, 1-3.
- Verster, J. C., Benjaminsen, M. E., van Lanen, J. H. M., van Stavel, N. M. D., & Olivier, B. (2015). Effects of mixing alcohol with energy drink on objective and subjective intoxication: results from a Dutch on-premise study. *Psychopharmacology*, 232, 835-842.
- Verster, J. C., Benson S., Johnson, S. J., Scholey, A., & Alford, C. (2016). Mixing alcohol with energy drink (AMED) and total alcohol consumption: a systematic review and meta-analysis. *Hum. Psychopharmacol Clin Exp*, 31, 2-10.
- Vogler, B. K., Pittler, M.H., & Ernst, E. (1999). The efficacy of ginseng. A systematic review of randomized clinical trials. *European Journal of Clinical Pharmacology*, 55(8), 567-575.
- Warburton, D. M., Bersellini, E., & Sweeney, E. (2001). An evaluation of a caffeinated taurine drink on mood, memory and information processing in healthy volunteers without caffeine abstinence. *Psychopharmacology*, 158, 322-328.
- Ward, R. J., Martinez, J., Ball, D., Marshall, E. J., & De Witte, P. (2000). Investigation of the therapeutic efficacy of a taurine analogue during the initial stages of ethanol detoxification: preliminary studies in chronic alcohol abusers. *Advances in Experimental Medicine and Biology*, 483, 375-381
- Weckerle, C. S., Stutz, M. A., & Baumann, T. W. (2003). Purine alkaloids in Paullinia. *Phytochemistry*, 64, 735-742
- World Health Organization, The ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines (1992). World Health Organization, Geneva, pp 358 & 360.
- Wu, K-L., Chaikomin, R., Doran, S., Jones, K. L., Horowitz, M., & Rayner, C. K. (2006). Artificially sweetened versus regular mixers increase gastric emptying and alcohol absorption. *American Journal of Medicine*, 116, 802-804.
- Yang, A., Palmer, A. A., & de Wit, H. (2010). Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology*, 211, 245-257.
- Yeo, M., Kim, D-K., Cho, S. W., & Hong, H. D. (2008). Ginseng, the root of panax ginseng c.a. Meyer, protects ethanol-induced gastric damages in rat through the induction of cytoprotective heat-shock protein 27. *Digestive Diseases and Sciences*, 53, 606-613.
- Yun, T. K. (2001). Panax ginseng - non-organ-specific cancer preventive? *Lancet Oncology*, 2, 49-55.
- Zhang, Y., Coca, A., Casa, D. J., Antonio, J., Green, J. M., & Bishop, P. A. (2015). Caffeine and diuresis during rest and exercise: A meta-analysis". *J Sci Med Sport*, 18(5), 569-574.

Appendix 1: Process and methodology

A comprehensive survey was carried out of peer-reviewed research, covering the metabolic and pharmacological profile of caffeine in humans and the potential physiological and behavioural effects of alcohol mixed with caffeine or with energy drinks (AmED). The majority of the research used dated from 1988 onwards, with selected papers and books from earlier dates, and an emphasis was placed on key reviews and meta-analyses.

The primary source for peer-reviewed research was the research database of the Centre for Information on Beverage Alcohol (CBA), which collates alcohol-specific research from major academic databases, including Medline and PsychInfo, dating back to 1988, but with some earlier records. Comprehensive reviews and meta-analyses were prioritised in the initial review process, but key studies were reviewed independently. Additional searches of Medline were conducted, via PubMed, to establish details of the metabolic and pharmacological profile of caffeine and to review use of terminology that might help to define excessive levels of caffeine and other stimulants. In addition, selected grey literature was reviewed, including relevant books, monographs, technical and regulatory reports. Potential stimulant effects of taurine and ginseng were also researched using Medline, via PubMed.

Definitions were collated from the academic literature to provide a spectrum of values for “low”, “moderate”, “high” and “excessive” caffeine intake, per dose and per day. Regulatory and guidance limits for caffeine content (not necessarily for alcohol beverages) were also considered.

Appendix 2: References to caffeine levels in the research literature

A: Acute doses of caffeine

<u>Caffeine</u>		<u>Description/definition</u>	<u>Source</u>
12.5 - 50 mg	LOW	"... low doses of caffeine (12.5 to 50 mg) have been found to improve cognitive performance and mood [6]"	Smit & Rogers, 2000
40 – 60 mg	LOW	"...as little as 40–60 mg of caffeine can exert positive effects on cognitive function"	McLellan & Lieberman, 2012
80 mg	LOW	"Two separate studies examined the effect of a low dose of caffeine (80 mg) and taurine (1000 mg) in a beverage on the information processing of healthy volunteers."	Warburton, et al., 2001
200 mg	--	"... 200 mg doses have been found to improve cognitive task speed and accuracy and increase alertness among young adults."	Anderson & Horne, 2006
~ 75 mg	MODERATE	"Evidence suggests that moderate levels of caffeine (about 75 mg) improve several aspects of cognitive performance including attention, reaction time, visual searching, psychomotor speed, memory, face recognition, and serial subtraction"	Curry & Stasio, 2009
70 - 100 mg	--	"exhibit [a] linear pharmacokinetics"	Bonati, et al., 1982
20 - 200 mg	LOW-TO-MODERATE	"Low-to-moderate doses (e.g., 20–200 mg) of caffeine produce positive subjective effects"	Juliano, et al., 2011
200 – 400 mg	MODERATE	Moderate doses of caffeine generally stimulate the nervous system, increase sleep latency, reduce total sleeping time, and improve various motor skills impaired by fatigue.	Dorfman & Jarvik, 1970
200 - 350 mg	MODERATE	"moderate doses of caffeine"	Temple, et al., 2010
100 – 500 mg	NORMAL	"In normal doses (100 – 500 mg), [caffeine] potently stimulates the cerebral cortex, promoting wakefulness and improving some aspects of psychomotor performance."	Osborne & Rogers, 1983
210 mg	ADVERSE EFFECTS	"Based on data up to 1999, (Smith <i>et al.</i> , 2000) concluded an adverse effect level of 210 mg in adults (3 mg/day for a 70 kg adult) based on observations of increased anxiety."	Smith, et al., 2000
308 mg for a 70kg individual.	FAIRLY HIGH	"Alcohol (0.65 g/kg) consumption significantly reduced the number of inhibitions from baseline, and this detrimental effect was compensated for by a fairly high dose of caffeine (4.4 mg/kg)."	Attwood, et al., 2012
> 200 mg	HIGHER	"At higher acute doses (> 200 mg), caffeine is more likely to produce negative subjective effects such as anxiety, jitteriness, and gastrointestinal disturbances"	Huntley & Juliano, 2012
250 - 500 mg	HIGHER	"For higher doses (250 to 500 mg), the clearance of caffeine is significantly reduced and its elimination half-life is prolonged, indicating nonlinearity."	Kaplan, et al., 1997
> 200 mg or 3 mg/kg	LARGER	"larger doses, which typically exceed 200 mg or about 3 mg/kg, required to enhance physical performance when the dose is ingested about 1 h before exercise"	McLellan & Lieberman, 2012

<u>Caffeine</u>		<u>Description/definition</u>	<u>Source</u>
> 400 mg	HIGH	"High doses (>400 mg) ... lead to feelings of anxiety, nausea, jitteriness and nervousness."	Garrett & Griffiths, 1997
200 mg	HIGH	"200 mg caffeine facilitated performance on the relatively more difficult cancellation (addition and multiplication) tasks than the digit cancellation task."	Loke, 1988
500 mg	EXCESSIVE	500 mg appears to be an excessive amount if laboratory results are to be generalized to the social use of caffeine	Fudin & Nicastro, 1988
10,000 mg	LETHAL	"The acute lethal dose in adult humans has been estimated to be 10 g/person."	Nawrot, et al., 2003
10,500 – 14,000 mg for a 70 kg person	LETHAL	"Caffeine toxicity is dose dependent, and fatalities have been reported at very high dosages of greater than 150-200 mg/kg" body weight.	Duchan, 2013

B: Daily caffeine intake

<u>Caffeine</u>		<u>Description/definition</u>	<u>Source</u>
< 120 mg/day	LOW	"... caffeine can reinforce flavour liking in overnight deprived moderate caffeine consumers (e.g. average of 250 mg/day) but not in low consumers (<120 mg/day)...."	Tinley, et al., 2003
70 – 76 mg/day	AVERAGE (Global)	Caffeine consumption from all sources can be estimated to around 70 to 76 mg/person/day worldwide.	Fredholm, et al., 1999
40 mg/day (of 320 mg/l caffeine ED)	"MEAN CHRONIC"	Scientific Committee on Food of the European Commission (DG SANCO), classified ED consumption levels into "mean chronic" (125 ml/day), "high chronic" (350 ml/day) and "acute" (750 ml/day).	EC Scientific Committee on Food, 2003
< 50 mg/day	LOW	"low caffeine consumers" (adolescents)	Temple, et al., 2010
average of 250 mg/day	MODERATE	"... caffeine can reinforce flavour liking in overnight deprived moderate caffeine consumers (e.g. average of 250 mg/day) but not in low consumers (<120 mg/day)...."	Tinley, et al., 2003
300 mg/day	MODERATE	"... moderate caffeine consumption of 300 mg/day is safe and can even have beneficial health implications as part of a healthful diet and physically active lifestyle."	International Food Information Council, 1998
≤ 400 mg/day (for a 70 kg person)	MODERATE	"a moderate daily caffeine intake of ≤ 400 mg (equivalent to 6.5 mg/kg bw/d for a 70-kg person) was not associated with any adverse effects"	Nawrot, et al., 2003
< 200 mg/day	MODERATE	"high-caffeine consumers (>200 mg/day) are more likely than moderate-caffeine consumers (<200 mg/day) to respond to caffeine"	Attwood, et al., 2007
112 mg/day (of 320 mg/l caffeine ED)	"HIGH CHRONIC"	Scientific Committee on Food of the European Commission (DG SANCO), classified ED consumption levels into "mean chronic" (125 ml/day), "high chronic" (350 ml/day) and "acute" (750 ml/day).	EC Scientific Committee on Food, 2003
280 mg/day (for a 70 kg person)	AVERAGE (USA)	"In the United States, adults consume on average 4 mg/kg body weight/d of caffeine, which equates to 280 mg/d for a 70-kg person"	Barone & Roberts, 1996

<u>Caffeine</u>		<u>Description/definition</u>	<u>Source</u>
210 – 238 mg/day	AVERAGE (N. America)	"Caffeine consumption reaches 210 to 238 mg/day in the US and Canada."	Fredholm, et al., 1999
< 400 mg/day	MODERATE	"...moderate daily caffeine intake at a dose level up to 400 mg/day (equivalent to 6mg/kg body weight/day in a 65-kg person) is not associated with adverse effects"	Nawrot, et al., 2003
193 mg/day	AVERAGE (USA)	"...the average intake in caffeine consumers" (equivalent to 1.2 mg/kg/day). An analysis of the Continuing Survey of Food Intakes by Individuals (CSFII) in the US.	Frary, et al., 2005
> 200 mg/day	HIGH	"high-caffeine consumers (>200 mg/day) are more likely than moderate-caffeine consumers (<200 mg/day) to respond to caffeine"	Attwood, et al., 2007
240 mg/day (of 320 mg/l caffeine ED)	"ACUTE"	The Scientific Committee on Food of the European Commission (DG SANCO), classified ED consumption levels into "mean chronic" (125 ml/day), "high chronic" (350 ml/day) and "acute" (750 ml/day).	EC Scientific Committee on Food, 2003
> 400 mg/day	DECREASED RISK OF DEATH	"... significantly decreased (by 10%) the risk of dying from any cause (relative risk ratio [RR] 0.90, 95% confidence interval [CI] 0.85–0.94)"	Paganini-Hill, et al., 2007
> 400 mg/day	AVERAGE (Sweden/ Finland)	"Caffeine consumption [is] more than 400 mg/person/day in Sweden and Finland, where 80 to 100% of the caffeine intake comes from coffee alone".	Fredholm, et al., 1999
> 50 mg/day	HIGH	"high caffeine consumers" (adolescents)	Temple, et al., 2010
> 500 mg/day	SIGNIFICANT HEALTH RISK	"It is now widely believed that habitual daily use of caffeine > 500-600mg (four to seven cups of coffee or seven to nine cups of tea) represents a significant health risk and may therefore be regarded as 'abuse'."	Nawrot, et al., 2003
> 1000 mg/day	NO RISK	"routine daily consumption of up to 1000 mg of caffeine posed no risks to human health"	Bonita, et al., 2007

Appendix 3: Global regulations for caffeine content of soft drinks and energy drinks

<u>Country/Region</u>	<u>Regulations</u>	<u>Source</u>
European Union	No maximum caffeine content specified, but drinks containing more than 150 mg/l must be labelled 'High caffeine content', followed by the quantity of caffeine expressed in mg/100ml. This wording must appear in the same field of vision as the name of the drink (in effect until 12 December 2014).	Commission Directive 2002/67/EC of 18 July 2002 on the labelling of foodstuffs containing quinine, and of foodstuffs containing caffeine.
	Regulation (EU) No. 1169/2011 came into effect on 13 December 2014 and extends the labeling required for beverages where caffeine is added "for its physiological effects" to the following: "High caffeine content. Not recommended for children or pregnant or breast-feeding women". This applies to beverages intended for consumption without modification, containing at least 150 mg/l of caffeine. For further details, please refer to section 3.4. of the main report.	Regulation (EU) No. 1169/2011
Argentina	For soft drinks, a maximum of 200 mg/kg (200 mg/l) (with a declaration on the label near the name). Includes caffeine sourced from guarana.	Argentine Food Code CAPÍTULO XII – Bebidas hídricas, agua y agua gasificada.
	In 2012, Argentina imposed a 32mg/100ml caffeine limit on energy drinks and required that labels advise not consuming with alcohol. Further, the law stipulated that the phrase "high caffeine content" should be used when the product exceeded a caffeine content of 20 mg/100 ml.	Expediente N° 1-0047-2110-2454-03-1 de la Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (Argentina Ministry of Health, 2012)
Australia/ New Zealand	A maximum of 145 mg/kg (145 mg/l) for cola type soft drinks.	Australia New Zealand Food Standards Code, FSANZ
	Formulated caffeinated beverages (including energy drinks) must contain no less than 145 mg/L and no more than 320 mg/L of caffeine.	
	"Warnings are mandatory on energy drinks where caffeine levels are higher than 145mg/kg."	
Brazil	For energy drinks, a maximum of 350 mg/l.	Portaria nº 868, de 1998, Ministry of Health & Resolução RDC nº 273, de 22 de Setembro de 2005
	A maximum of 4 g/l of taurine is also permitted.	
Canada	For energy drinks, a maximum content of 400 mg/l, not to exceed 180 mg per container presented as a single-serve container.	Health Canada
Chile	A maximum of 180 mg/l for soft drinks containing caffeine.	Clasificación: Resolución de Segunda Instancia N° 125, Article 481.
China	A maximum of 0.15 g/kg (150 mg/l) for cola type carbonated drinks.	Ministry of Health (Standards for uses of food additives, GB2760-2011, implemented June 20, 2011)
Colombia	A maximum of 32 mg/100ml (320 mg/l) for energy drinks,	Ministry of Social Protection

<u>Country/Region</u>	<u>Regulations</u>	<u>Source</u>
	The law also permits a maximum of 400 mg/100ml of taurine.	Resolución 4150 de 2009
India	A maximum of 145 ppm (145 mg/l) for carbonated non-alcohol beverages.	Ministry of Health & Family Welfare, (Food Safety and Standards Authority of India)
Mexico	A maximum of 33 mg/100ml (330 mg/l) for energy drinks.	Mexican Official Standard NOM-218-SSA1-2011, Goods and services. Non-alcohol flavored drinks, their frozen concentrated products to prepare and beverages with added caffeine.
Russia	Energy drinks are regulated within a caffeine content of 150 – 400 mg/l and permitted in containers no larger than 330ml. Draft Federal Law N 192666-6 would ban “low-alcohol and non-alcohol energy drinks”.	Federal law.
South Africa	Formulated caffeinated beverages that contain more than 150 mg/L caffeine must be labeled “high caffeine content” in the same field of vision as the name.	Foodstuffs, Cosmetics and Disinfectants Act No. 54 of 1972 » Regulations » Soft Drinks » Amendment, 17 April 2012.
United Arab Emirates	No more than 32 mg/100ml (320 mg/l) permitted for energy drinks.	Emirates Authority for Standardization and Metrology (ESMA) - UAE.S/GSO 1926:2009: “Requirements of Handling Energy Drinks”.
United States	A maximum of 0.02% (approximately 200 mg/l) for cola type beverages is Generally Recognized As Safe (GRAS), but this ruling does not apply to alcohol beverages. The FDA is currently assessing the safety of caffeinated energy drinks.	FDA, 2009