GLOBAL ACTIONS:
Commitments to Reduce Harmful Drinking

STIMULANTS ADDED TO ALCOHOL BEVERAGES
Research Review and Discussion
June 2013
Contents

1. Background ......................................................................................................................................... 4

2. Energy drinks and caffeinated alcohol beverages ............................................................................... 4
   2.1. Terminology .................................................................................................................................. 4
   2.2. Energy drinks (ED) ....................................................................................................................... 5
   2.3. Caffeinated alcohol beverages (CAB) ............................................................................................ 6

3. Caffeine ............................................................................................................................................... 7
   3.1. Pharmacokinetics .......................................................................................................................... 7
   3.2. Physiological and behavioural effects ............................................................................................ 8
   3.3. Toxicity ......................................................................................................................................... 9
   3.4. Global regulations and restrictions ............................................................................................... 10

4. Alcohol mixed with caffeine or with energy drinks (AmED) .............................................................. 11
   4.1. Prevalence of AmED ..................................................................................................................... 11
   4.2. Association of AmED with higher alcohol intoxication and risk taking ....................................... 11
   4.3. Antagonistic effects of caffeine on measures of alcohol impairment ......................................... 12
   4.4. The role of expectancy .................................................................................................................. 14
   4.5. Influence of sensation-seeking or impulsive personality .............................................................. 14
   4.6. Metabolic effects of AmED ........................................................................................................... 14
   4.7. Committee on Toxicity of Chemicals (COT) statement on alcohol and caffeine interactions ....... 15

5. Additives other than caffeine ............................................................................................................ 16
   5.1. Guaraná ....................................................................................................................................... 16
   5.2. Taurine ........................................................................................................................................ 16
   5.3. Ginseng ....................................................................................................................................... 17

6. Summary and discussion points ........................................................................................................ 18
   6.1. Consensus on caffeine levels ....................................................................................................... 18
   6.2. Alcohol and caffeine interactions ............................................................................................... 19
   6.3. Stimulants other than caffeine .................................................................................................... 21
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.

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 and establishing a consensus on appropriate levels.

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:

<table>
<thead>
<tr>
<th>ED</th>
<th>Energy Drink</th>
<th>Premixed non-alcohol beverage containing caffeine and other stimulants.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmED</td>
<td>Alcohol mixed with Energy Drink</td>
<td>Hand-mixed beverage, prepared ad hoc.</td>
</tr>
<tr>
<td>CAB</td>
<td>Caffeinated Alcohol Beverage</td>
<td>Premixed, ready-to-drink (RTD) beverage, containing caffeine, sometimes with other stimulants as well.</td>
</tr>
</tbody>
</table>

The term “stimulant” is applied in a broad sense, to define substances associated with demonstrable or claimed improvements in cognitive, psychomotor or physical performance, increased alertness or wakefulness, or ergogenic (energy-giving) properties.
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 GBP £1.8 billion by 2016, a 95% increase on 2008 estimates (Mintel, 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, but 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)
- 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])
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 75 mg and 50 mg, 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, chronic ED consumption (12% in adults and adolescents) or high, acute ED consumption (11% for adults, 12% for adolescents) (Nomisma-Areté consortium, 2013). Prevalence of mixing alcohol with energy drinks was also reported to be similar for adults (56%) and adolescents (53%) in this study.

Considering mean daily intake of energy drinks, the Scientific Committee on Food of the European Commission (DG SANCO; European Commission, 2003), has classified consumption into “mean chronic” (125 ml/day), “high chronic” (350 ml/day) and “acute” (750 ml/day). 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)

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 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.

For the purposes of this report, research on the health and behavioural effects of AmED is considered pertinent to the effects of premixed CAB, since both involve the concurrent consumption of alcohol and caffeine.
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, 1998; 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 dimethylations (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, 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 (56 g alcohol for a 70 kg 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: 50 g 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 A2A 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-IV (APA, 1994) and 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 effects 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
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).

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 6 mg/kg dose (Bruce et al., 2000). However, ergogenic effects are subject to wide individual variation, due to factors such as 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 more than 200 mg. 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). James (1997) highlights the methodological hurdle this presents in studies of caffeine and performance, since most people would not normally abstain from caffeine.

With regard to daily intake of caffeine, there is also considerable variability in the data (see Appendix 1B). 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 ≤ 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 of 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 ≤ 300 mg per day and that children should consume ≤ 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 A2A 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 1999 and 2003, the EU Scientific Committee on Food (SCF) considered that 350 mg of caffeine (for a 70 kg person) could, in some people, result in transient changes, such as increased anxiety, irritability or nervousness, particularly if they were normally low caffeine consumers (EC Scientific Committee on...
Food, 2003). There is some consensus that acute doses over 400 mg can produce feelings of anxiety, nausea, jitteriness and nervousness, and higher doses are frequently associated with dysphoria (Garrett & Griffiths, 1997). However, intake is 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 500 mg 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.

3.4. GLOBAL REGULATIONS AND RESTRICTIONS

In the USA, the Food and Drug Administration (FDA) has approved caffeine as “Generally Recognised As Safe” (GRAS) for non-alcohol, cola-type beverages, in concentrations no higher than 200 parts per million, or 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, 2012b).

The FDA is reported to be assessing the safety of caffeinated energy drinks. Pertaining to this, in March 2013, a group of scientists concluded, in a letter to FDA Commissioner Margaret A. Hamburg, “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). In September 2009, some of the same scientists had raised concerns 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 concluded, “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 other 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 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”, and 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.

For further details, see Appendix 2, “Global regulations for caffeine content of soft drinks and energy drinks”.

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; Rosheim & Thombs, 2011), particularly in college student populations (Levy & Tapsell, 2007; O’Brien et al., 2008; Reissig et al., 2009). For example, 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 reported 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).

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 observed that the specific practice of combining caffeinated energy drinks with alcohol is associated with higher levels of intoxication, which can lead to increases in risk behaviour and alcohol-related harms (Ferreira et al., 2006; Marczinski & Fillmore, 2006; Miller, 2008; O’Brien et al., 2008; Reissig et al., 2009; Arria et al., 2010; Thombs et al., 2010; Woolsey et al., 2010; Arria et al., 2011; Berger et al., 2011; Howland et al., 2011; Peacock et al., 2012).

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. 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 recent editorial (2011), “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.”

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, but results have been varied (Nash, 1966; Fudin & Nicastro, 1988; Ferreira et al., 2006; Marczinski et al., 2006). As one research team noted, “given the variability of results regarding the perception of impairment, further studies are required to clarify the effects of energy drink when combined with alcohol on the subjective perception of intoxication” (Alford et al., 2012).

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 (Oborne & 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 65 g doses of caffeine (in coffee) over several hours with a single 200 mg 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 105 g of alcohol, with a mean of just under 50 g (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. Oborne & 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, 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 EXPECTANCY

Fillmore and colleagues have demonstrated that task performance can be affected 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 suggest 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). In one study, Fillmore and Vogel-Sprott (1995) showed that alcohol-induced impairment was reduced by the administration of caffeine, whether or not caffeine was expected.

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 those with high impulsivity benefited from it, with the opposite effect occurring in the evening (Revelle et al., 1980). More recently, researchers have 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, 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.

4.6. METABOLIC EFFECTS OF AMED

Concerns have been raised about the dehydrating effects of energy drinks, particularly in the exercise and fitness research literature, and there are additional concerns about their use in combination with alcohol. The principal issue is the high caffeine content of some products. Since caffeine and alcohol are both diuretics, with the potential to draw water and nutrients out of the body by stimulating urine.
output, it is believed that a “double dehydration” or hypohydration effect could occur if they are consumed together or in close proximity (Stookey, 1999).

Some researchers have questioned a diuretic effect of caffeine at low to moderate levels of consumption. Armstrong (2002) noted that, whilst caffeine stimulates a mild diuresis similar to that caused by water, there is no evidence of a debilitating effect from fluid-electrolyte imbalance and little evidence that caffeine doses of 100–680 mg have a significant effect on urine output when compared to water. In contrast, Maughan and Griffin (2003) observed that 250–300 mg of caffeine does cause short-term stimulation of urine output in caffeine-deprived individuals, but that tolerance significantly diminishes this effect in regular caffeine consumers, and that at lower caffeine doses there is no diuretic effect.

The extent of diuresis due to alcohol is also dependent on the amount consumed (Eggleston, 1942), and the threshold for increasing urine output is around 4% alcohol by volume (Shirreffs & Maughan, 1997), consistent with the majority of commercially available alcohol drinks. However, there is evidence that when the body is already dehydrated, the diuretic action of alcohol becomes blunted in an attempt to restore fluid balance (Hobson & Maughan, 2010).

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, Rosseheim 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.

4.7. COMMITTEE ON TOXICITY OF CHEMICALS (COT) STATEMENT ON ALCOHOL AND CAFFEINE INTERACTIONS

In December 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.”
5. 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; Marczinski 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.

5.1. 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). Guarana 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.

5.2. 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 125 ml and 350 ml 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 1,000 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.

### 5.3. 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 1,125 mg per day (Lee & Son, 2011).

6. Summary and discussion points

6.1. CONSENSUS ON CAFFEINE LEVELS

Referring to the research extracts in Appendix 1A, 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. Moderate doses of between 200 mg 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.**

<table>
<thead>
<tr>
<th>low</th>
<th>low-to-moderate</th>
<th>moderate</th>
<th>higher</th>
<th>excessive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mg</td>
<td>100 mg</td>
<td>200 mg</td>
<td>300 mg</td>
<td>400 mg</td>
</tr>
</tbody>
</table>

Appendix 1B 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 be regarded as moderate, whilst levels of intake above 500...
mg are regarded as high and increasingly less healthy. In the United States, the FDA (2013) has cited 400 mg of caffeine per day as being not generally associated with dangerous, negative effects, which is consistent with the findings of one extensive research review (Nawrot et al., 2003).

Looking at regulations applying in various countries, the maximum permitted caffeine content for cola type beverages and other soft drinks falls between 145 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.

6.2. ALCOHOL AND CAFFEINE INTERACTIONS

To establish a maximum level of caffeine for premixed alcohol beverages, the potential for enhanced effects of caffeine in the presence of alcohol should be taken into account, as well as possible antagonistic effects of caffeine on measures of performance and behaviour impaired by alcohol consumption. In addition, a number of market-specific reference points may preclude the application of a universal caffeine limit. For example, in addition to regulations that may be in place, there may be differences in advice on sensible drinking; health information on caffeine and other stimulants; beverage alcohol strengths and serving sizes; and relevant sociocultural factors.

The following notes summarise the key points emerging from the research review.

Metabolic research

- There is some evidence that the pharmacokinetics of caffeine may be impacted at very high doses, above 500 mg. In essence, metabolism would become saturated at that level, slowing down the elimination of caffeine and potentially prolonging its effects. However, at the lower doses associated with most beverages, caffeine elimination follows first-order kinetics.

- There is solid evidence of prolonged exposure to caffeine in the presence of alcohol. Research suggests that co-ingestion with around 50 g of alcohol can increase the elimination half-life of caffeine by up to 72% and its clearance by around 37%. This may be of significance in setting a caffeine limit for beverages containing both alcohol and caffeine.

- Although concerns have been raised about a “double dehydration” effect from combining alcohol and caffeine, reviews of the research literature suggest that low to moderate doses
(under 250 mg) of caffeine would not add to the diuretic effect of alcohol. In addition, in individuals who are already dehydrated, alcohol diuresis may become blunted to help restore fluid balance.

- Experimental studies suggest that mixing alcohol with caffeinated energy drinks containing up to 400 mg of caffeine is not associated with higher levels of blood alcohol.

- Energy drinks sweetened with sugars are reported to slow gastric emptying, reducing peak blood alcohol levels when compared to those sweetened artificially, implying that the effects of caffeine on alcohol intoxication may be enhanced when artificially sweetened mixers are combined with alcohol.

**Behavioural and experimental research**

- A majority of survey-based research has focused on the effects on college-aged students of mixing alcohol with energy drinks, particularly in the USA, but European research has found similar prevalence in adults and adolescents for mixing alcohol with energy drinks. Further research is required to assess effects and behaviours in different demographic groups.

- A number of studies have observed that the practice of combining caffeinated energy drinks with alcohol is associated with perceived higher levels of intoxication, which can lead to increases in risky behaviours. However, there is no direct scientific evidence of a causal relationship.

- There is some evidence that caffeine can mask the subjective experience of intoxication when alcohol has also been consumed, but results have been varied and several researchers have concluded that further research is required to clarify the effects.

- Reports of increased intoxication and risk behaviour are largely based on observations of the effects of combining alcohol with energy drinks. There is, currently, relatively little research reflecting consumption of premixed caffeinated alcohol beverages per se.

- A majority of AmED studies on subjective experience are based on retrospective survey data and on self-reports, which can suffer from measurement problems. Significantly, most retrospective survey studies have not examined simultaneous consumption of alcohol and caffeine.

- There have been very few field-based studies in natural drinking environments, in which acute alcohol intoxication might be assessed objectively following AmED consumption. There has also been little 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.

- Some studies of psychomotor and cognitive performance have reported antagonism of the effects of alcohol by caffeine relative to alcohol on its own, whilst others have found a
worsening of the effects, but the majority of research shows no significant reduction of alcohol-induced impairment or mixed results. The effects of caffeine may be restricted to countering impairment of psychomotor task performance.

- 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, but others have found no evidence to support this.

- Since most people do not abstain from caffeine, experimental studies often fail to reflect typical, cumulative caffeine levels. Subjects may be given single large doses of caffeine or alcohol, rather than doses consistent with typical drinking patterns or beverage contents. Typically, caffeine would be consumed during the day in coffee, tea and other beverages, reaching a peak level in the early evening, after which additional consumption of caffeine with alcohol would be adding to caffeine already in the bloodstream.

- When studying relatively small numbers of participants in experimental settings, particularly in between-subjects designs, significant individual variability, in relation to caffeine consumption, caffeine metabolism and responses to caffeine, could influence outcomes. Although most researchers attempt to address potential confounding factors, there is considerably variability in approach.

- Research suggests that expectancy could play a role in the outcome of AmED studies, as task performance may be affected if the subject is told whether or not to expect caffeine.

- There is some evidence that individuals with sensation-seeking or impulsive traits are drawn to energy drinks, heavy alcohol consumption and risky behaviours, although at least one study has reported AmED effects on intoxication and risk behaviour after correction for these traits.

- Drawing clear conclusions from the current experimental data is difficult, because performance tasks, doses of caffeine (or energy drinks) and alcohol, and methodologies used are not directly comparable and meta-analysis of the data is compromised.

- In December 2012, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) noted uncertainties in the current research but concluded, “the current balance of evidence does not support a harmful toxicological or behavioural interaction of caffeine and alcohol.”

### 6.3. STIMULANTS OTHER THAN CAFFEINE

- Guaraná seed extract contains between 2% and 15% caffeine, so caffeine derived from guaraná should be considered as part of the total caffeine content of premixed caffeinated beverages.
Based on current research and regulatory decisions, addition of taurine to beverages at a concentration of up to 4 g/l would appear to be safe. Ginseng also demonstrates no adverse effects at the levels typically used in energy drinks and may have some beneficial effects in relation to alcohol impairment.

References


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


FDA (2012b). Subchapter B - Food For Human Consumption (Continued); Part 170 - Food Additives, Subpart A - General Provisions; § 170.3 Definitions. 21 CFR §§ 170.3.


## Appendix 1: References to caffeine levels in the research literature

### A. Acute doses of caffeine

<table>
<thead>
<tr>
<th>Caffeine dose</th>
<th>Description/definition</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5–50 mg</td>
<td>“low doses of caffeine (12.5 to 50 mg) have been found to improve cognitive performance and mood [6]”</td>
<td>Smit &amp; Rogers, 2000</td>
</tr>
<tr>
<td>40–60 mg</td>
<td>“as little as 40–60 mg of caffeine can exert positive effects on cognitive function”</td>
<td>McLellan &amp; Lieberman, 2012</td>
</tr>
<tr>
<td>80 mg</td>
<td>“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.”</td>
<td>Warburton et al., 2001</td>
</tr>
<tr>
<td>200 mg</td>
<td>“200 mg doses have been found to improve cognitive task speed and accuracy and increase alertness among young adults.”</td>
<td>Anderson &amp; Horne, 2006</td>
</tr>
<tr>
<td>~ 75 mg</td>
<td>“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.”</td>
<td>Curry &amp; Stasio, 2009</td>
</tr>
<tr>
<td>70–100 mg</td>
<td>“exhibit [a] linear pharmacokinetics”</td>
<td>Bonati, et al., 1982</td>
</tr>
<tr>
<td>20–200 mg</td>
<td>“Low-to-moderate doses (e.g., 20–200 mg) of caffeine produce positive subjective effects.”</td>
<td>Juliano et al., 2011</td>
</tr>
<tr>
<td>200–400 mg</td>
<td>Moderate doses of caffeine generally stimulate the nervous system, increase sleep latency, reduce total sleeping time, and improve various motor skills impaired by fatigue.</td>
<td>Dorfman &amp; Jarvik, 1970</td>
</tr>
<tr>
<td>200–350 mg</td>
<td>“moderate doses of caffeine”</td>
<td>Temple et al., 2010</td>
</tr>
<tr>
<td>Caffeine dose</td>
<td>Description/definition</td>
<td>Source</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>100–500 mg</td>
<td>NORMAL</td>
<td>Oborne &amp; Rogers, 1983</td>
</tr>
<tr>
<td></td>
<td>“In normal doses (100 – 500 mg), [caffeine] potently stimulates the cerebral cortex, promoting wakefulness and improving some aspects of psychomotor performance.”</td>
<td></td>
</tr>
<tr>
<td>210 mg</td>
<td>ADVERSE EFFECTS</td>
<td>Smith et al., 2000</td>
</tr>
<tr>
<td></td>
<td>“Based on data up to 1999, Smith et al. (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.”</td>
<td></td>
</tr>
<tr>
<td>308 mg for a 70 kg individual</td>
<td>FAIRLY HIGH</td>
<td>Attwood et al., 2012</td>
</tr>
<tr>
<td></td>
<td>“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).”</td>
<td></td>
</tr>
<tr>
<td>&gt; 200 mg</td>
<td>HIGHER</td>
<td>Huntley &amp; Juliano, 2012</td>
</tr>
<tr>
<td></td>
<td>“At higher acute doses (&gt; 200 mg), caffeine is more likely to produce negative subjective effects such as anxiety, jitteriness, and gastrointestinal disturbances.”</td>
<td></td>
</tr>
<tr>
<td>250–500 mg</td>
<td>HIGHER</td>
<td>Kaplan et al., 1997</td>
</tr>
<tr>
<td></td>
<td>“For higher doses (250 to 500 mg), the clearance of caffeine is significantly reduced and its elimination half-life is prolonged, indicating nonlinearity.”</td>
<td></td>
</tr>
<tr>
<td>&gt; 200 mg or 3 mg/kg</td>
<td>LARGER</td>
<td>McLellan &amp; Lieberman, 2012</td>
</tr>
<tr>
<td></td>
<td>“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”</td>
<td></td>
</tr>
<tr>
<td>&gt; 400 mg</td>
<td>HIGH</td>
<td>Garrett &amp; Griffiths, 1997</td>
</tr>
<tr>
<td></td>
<td>“High doses (&gt;400 mg) . . . lead to feelings of anxiety, nausea, jitteriness and nervousness.”</td>
<td></td>
</tr>
<tr>
<td>200 mg</td>
<td>HIGH</td>
<td>Loke, 1988</td>
</tr>
<tr>
<td></td>
<td>“200 mg caffeine facilitated performance on the relatively more difficult cancellation (addition and multiplication) tasks than the digit cancellation task.”</td>
<td></td>
</tr>
</tbody>
</table>
### Caffeine dose

<table>
<thead>
<tr>
<th>Caffeine dose</th>
<th>Description/definition</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg</td>
<td>EXCESSIVE 500 mg appears to be an excessive amount if laboratory results are to be generalized to the social use of caffeine.</td>
<td>Fudin &amp; Nicastro, 1988</td>
</tr>
<tr>
<td>10,000 mg</td>
<td>LETHAL “The acute lethal dose in adult humans has been estimated to be 10 g/person.”</td>
<td>Nawrot et al., 2003</td>
</tr>
<tr>
<td>10,500–14,000 mg for a 70 kg person</td>
<td>LETHAL “Caffeine toxicity is dose dependent, and fatalities have been reported at very high dosages of greater than 150-200 mg/kg” body weight.</td>
<td>Duchan, 2013</td>
</tr>
</tbody>
</table>

### B. DAILY CAFFEINE INTAKE

<table>
<thead>
<tr>
<th>Caffeine dose</th>
<th>Description/definition</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 120 mg/day</td>
<td>LOW “Caffeine can reinforce flavour liking in overnight deprived moderate caffeine consumers (e.g. average of 250 mg/day) but not in low consumers (&lt;120 mg/day).”</td>
<td>Tinley et al., 2003</td>
</tr>
<tr>
<td>70–76 mg/day (Global)</td>
<td>AVERAGE Caffeine consumption from all sources can be estimated to around 70 to 76 mg/person/day worldwide.</td>
<td>Fredholm et al., 1999</td>
</tr>
<tr>
<td>40 mg/day (of 320 mg/l caffeine ED)</td>
<td>“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).</td>
<td>EC Scientific Committee on Food, 2003</td>
</tr>
<tr>
<td>&lt; 50 mg/day</td>
<td>LOW “low caffeine consumers” (adolescents)</td>
<td>Temple et al., 2010</td>
</tr>
<tr>
<td>average of 250 mg/day</td>
<td>MODERATE “Caffeine can reinforce flavour liking in overnight deprived moderate caffeine consumers (e.g. average of 250 mg/day) but not in low consumers (&lt;120 mg/day).”</td>
<td>Tinley et al., 2003</td>
</tr>
<tr>
<td>Caffeine dose</td>
<td>Description/definition</td>
<td>Source</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>300 mg/day</td>
<td>MODERATE</td>
<td>“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.”</td>
</tr>
<tr>
<td>≤ 400 mg/day (for a 70 kg person)</td>
<td>MODERATE</td>
<td>“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.”</td>
</tr>
<tr>
<td>&lt; 200 mg/day</td>
<td>MODERATE</td>
<td>“High-caffeine consumers (&gt;200 mg/day) are more likely than moderate-caffeine consumers (&lt;200 mg/day) to respond to caffeine.”</td>
</tr>
<tr>
<td>112 mg/day (of 320 mg/l caffeine ED)</td>
<td>“HIGH CHRONIC”</td>
<td>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).</td>
</tr>
<tr>
<td>280 mg/day (for a 70 kg person)</td>
<td>AVERAGE (USA)</td>
<td>“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”</td>
</tr>
<tr>
<td>210 – 238 mg/day</td>
<td>AVERAGE (N. America)</td>
<td>“Caffeine consumption reaches 210 to 238 mg/day in the US and Canada.”</td>
</tr>
<tr>
<td>&lt; 400 mg/day</td>
<td>MODERATE</td>
<td>“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.”</td>
</tr>
<tr>
<td>193 mg/day</td>
<td>AVERAGE (USA)</td>
<td>“… 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.</td>
</tr>
<tr>
<td>Caffeine dose</td>
<td>Description/definition</td>
<td>Source</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>&gt; 200 mg/day</td>
<td>HIGH</td>
<td>Attwood et al., 2007</td>
</tr>
<tr>
<td>240 mg/day (of 320 mg/l caffeine ED)</td>
<td>“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).</td>
<td>EC Scientific Committee on Food, 2003</td>
</tr>
<tr>
<td>&gt; 400 mg/day</td>
<td>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)”</td>
<td>Paganini-Hill et al., 2007</td>
</tr>
<tr>
<td>&gt; 400 mg/day</td>
<td>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.”</td>
<td>Fredholm et al., 1999</td>
</tr>
<tr>
<td>&gt; 50 mg/day</td>
<td>HIGH “high caffeine consumers” (adolescents)</td>
<td>Temple et al., 2010</td>
</tr>
<tr>
<td>&gt; 500 mg/day</td>
<td>SIGNIFICANT HEALTH RISK “It is now widely believed that habitual daily use of caffeine &gt; 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’.”</td>
<td>Nawrot et al., 2003</td>
</tr>
<tr>
<td>&gt; 1,000 mg/day</td>
<td>NO RISK “routine daily consumption of up to 1000 mg of caffeine posed no risks to human health”</td>
<td>Bonita et al., 2007</td>
</tr>
</tbody>
</table>
Appendix 2: Global regulations for caffeine content of soft drinks and energy drinks

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Regulations</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union</td>
<td>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/100 ml. This wording must appear in the same field of vision as the name of the drink (in effect until 12 December 2014). Regulation (EU) No 1169/2011 will come into effect on 14 December 2014 and extends the labelling 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 will apply to beverages intended for consumption without modification, containing at least 150 mg/l of caffeine.</td>
<td>European Commission Directive 2002/67/EC of 18 July 2002 on the labelling of foodstuffs containing quinine, and of foodstuffs containing caffeine.</td>
</tr>
<tr>
<td>Argentina</td>
<td>For soft drinks, a maximum of 200 mg/kg (200 mg/l) (with a declaration on the label in the vicinity of the name). Includes caffeine sourced from guarana.</td>
<td>Argentine Food Code CAPÍTULO XII – Bebidas hídricas, agua y agua gasificada.</td>
</tr>
<tr>
<td>Australia/ New Zealand</td>
<td>A maximum of 145 mg/kg (145 mg/l) for cola type soft drinks. 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.”</td>
<td>Australia New Zealand Food Standards Code, FSANZ</td>
</tr>
<tr>
<td>Brazil</td>
<td>For energy drinks, a maximum of 350 mg/l. A maximum of 4 g/l of taurine is also permitted.</td>
<td>Portaria nº 868, de 1998, Ministry of Health &amp; Resolução RDC nº 273, de 22 de Setembro de 2005</td>
</tr>
<tr>
<td>Country/Region</td>
<td>Regulations</td>
<td>Source</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Canada</td>
<td>For energy drinks, a maximum content of 400 mg/l, not to exceed 180 mg per container presented as a single-serve container.</td>
<td>Health Canada</td>
</tr>
<tr>
<td>Chile</td>
<td>A maximum of 180 mg/l for soft drinks containing caffeine.</td>
<td>Clasificación: Resolución de Segunda Instancia Nº 125, Artículo 481.</td>
</tr>
<tr>
<td>China</td>
<td>A maximum of 0.15 g/kg (150 mg/l) for cola type carbonated drinks.</td>
<td>Ministry of Health (Standards for uses of food additives, GB2760-2011, implemented June 20, 2011)</td>
</tr>
<tr>
<td>Colombia</td>
<td>A maximum of 32 mg/100ml (320 mg/l) for energy drinks, The law also permits a maximum of 400 mg/100ml of taurine.</td>
<td>Ministry of Social Protection Resolución 4150 de 2009</td>
</tr>
<tr>
<td>India</td>
<td>A maximum of 145 ppm (145 mg/l) for carbonated non-alcohol beverages.</td>
<td>Ministry of Health &amp; Family Welfare, (Food Safety and Standards Authority of India)</td>
</tr>
<tr>
<td>Mexico</td>
<td>A maximum of 33 mg/100ml (330 mg/l) for energy drinks.</td>
<td>Mexican Official Standard NOM-218-SSA1-2011, Goods and services. Non-alcoholic flavored drinks, their frozen concentrated products to prepare and beverages with added caffeine.</td>
</tr>
<tr>
<td>Russia</td>
<td>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”.</td>
<td>Federal law</td>
</tr>
<tr>
<td>Country/Region</td>
<td>Regulations</td>
<td>Source</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>South Africa</td>
<td>Formulated caffeinated beverages that contain more than 150 mg/l caffeine</td>
<td>Foodstuffs, Cosmetics and Disinfectants Act No. 54 of 1972 » Regulations » Soft Drinks » Amendment, 17 April 2012.</td>
</tr>
<tr>
<td></td>
<td>must be labeled “high caffeine content” in the same field of vision as the</td>
<td></td>
</tr>
<tr>
<td></td>
<td>name.</td>
<td></td>
</tr>
<tr>
<td>United Arab</td>
<td>No more than 32 mg/100ml (320 mg/l) permitted for energy drinks.</td>
<td>Emirates Authority for Standardization and Metrology (ESMA) - UAE.S/GSO</td>
</tr>
<tr>
<td>Emirates</td>
<td></td>
<td>1926:2009: “Requirements of Handling Energy Drinks”.</td>
</tr>
<tr>
<td>United States</td>
<td>A maximum of 0.02% (200 mg/l for cola type beverages is Generally Recognized</td>
<td>FDA, 2009</td>
</tr>
<tr>
<td></td>
<td>as Safe (GRAS). The FDA is currently assessing the safety of caffeinated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>energy drinks.</td>
<td></td>
</tr>
</tbody>
</table>