COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COT Statement on the interaction of caffeine and alcohol and their combined effects on health and behaviour

Introduction

1. The Committee was asked by the Food Standards Agency to comment on concerns that caffeine in energy drinks may interact with alcohol[1] in causing adverse behavioural or toxic effects.

Background

2. Since 2004, energy drinks have been the fastest growing sector of the drinks market in the UK, with an average growth of 12% per year (BSDA, 2011). The popularity of consuming energy drinks mixed with alcoholic beverages has also increased, especially amongst young males. Moreover, individuals who consume high quantities of both energy drinks and alcohol, are perceived to engage in a greater degree of risk-taking. This has raised concerns about the health effects of caffeine and alcohol in combination. In particular, a phenomenon described as "wide awake drunk" has been postulated, in which the stimulatory effect of caffeine prevents consumers of alcohol from realising how intoxicated they are, thereby increasing the potential for toxic injury and adverse behavioural effects (Reissig et al, 2009). In a report by the Scottish Prisons Service, "Buckfast Tonic Wine", which contains substantial quantities of caffeine as well as 15% alcohol by volume, was linked with violence in young offenders in Scotland. Among a sample of 172 young offenders, 43% admitted consumption of Buckfast Tonic Wine before their most recent offence (Scottish Prisons Service, 2009). Most energy drinks contain levels of caffeine approximately equivalent to those found in coffee (approximately 80mg caffeine per 250ml can, although drinks with smaller volumes and higher caffeine concentrations have appeared on the market in recent years) along with other substances such as sugar, taurine and glucuronolactone.

3. The Scientific Committee on Food (SCF), which advised the European Commission before the creation of the European Food Safety Authority (EFSA), looked at the safety of energy drinks in 1999 and 2003 (SCF, 1999; SCF, 2003). As part of their second assessment, the SCF examined the evidence for a toxic interaction between caffeine and alcohol. They concluded that most studies

[1] In this document, the term alcohol will refer to ethanol present in alcoholic beverages.

suggested that caffeine would not exacerbate the adverse effects of alcohol, and that at lower blood alcohol levels, caffeine may improve performance of simpler tasks (SCF, 2003).

4. The SCF also looked at evidence for interactions between alcohol and other constituents of energy drinks such as taurine and glucuronolactone. They observed that both taurine and alcohol inhibit the release of the antidiuretic hormone vasopressin, and therefore might act in concert to increase loss of water and sodium from the body, leading to a short-term risk of dehydration. In a 13-week study in rats, taurine was shown to cause behavioural effects in all dose groups tested (300, 600 and 1000 mg/kg bw/day), including persistent increased activity, occasional chewing of limbs, and in the 1000mg/kg bw group only, a possible decrement (not statistically significant) in motor performance on a rotarod[2]. The lowest dose was equivalent to 6 times the mean acute intake from energy drinks (50mg/kg bw). The SCF concluded that some alcohol–taurine interactions were possible, including "behavioural interactions", but these were neither marked nor consistent in human and animal studies. The SCF was of the opinion that focused neurological studies should be carried out on taurine, and concluded that glucuronolactone would not be expected to interact with alcohol or other constituents of energy drinks.

5. The COT was asked to consider the literature published since the SCF opinion of 2003, and to advise on the potential for interactions between caffeine and alcohol.

Current European legislation on caffeine

6. Under European Directive *2002/67/EC on the labelling of foodstuffs containing quinine and foodstuffs containing caffeine*, beverages containing more than 150 mg/l caffeine (other than those based on coffee or tea) must carry the statement 'High caffeine content' in the same field of vision as the name of the product, followed by a reference in brackets to the caffeine content expressed in mg per 100ml. Under the new Food Information Regulation (EU 1169/2011), which comes into effect on the 13 December 2014, beverages containing more than 150 mg/l caffeine (other than those based on coffee or tea) must carry the statement '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 to the caffeine content expressed in mg per 100ml.

Consumption of caffeine

7. Caffeine (1,3,7-trimethyl xanthine) is probably the most widely used psychoactive substance worldwide (Benowitz, 1990). Its molecular structure is shown in Figure 1:

[2] Animals are trained to stay on a rotating bar which gradually accelerates. Animals that fall off receive a foot-shock. The speed of the rotating bar at which the animals fall off is taken as the performance score. Rotarod trials occur before and after treatment to compare performance.

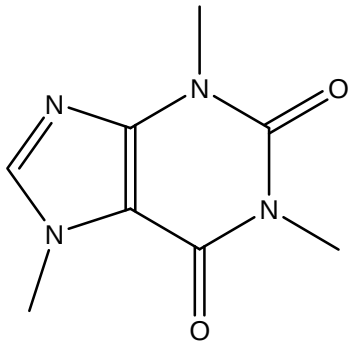

Figure 1: Caffeine

8. In 2004, the Dietary Caffeine and Health Study estimated a mean caffeine intake of 241mg/day in 6,000 individuals from the Bristol area who completed a questionnaire quantifying consumption of coffee, tea, chocolate products, cola drinks and energy drinks (Heatherley et al, 2006b; Heatherley et al, 2006a). This level of intake is similar to those indicated by a UK survey of consumption of coffee, tea and colas, carried out in 1988 – 3.98 mg/kg body weight per day (i.e. 279 mg/day for a 70 kg person) for the general population and 3.43 mg/kg body weight per day (i.e. 240 mg/day for a 70 kg person) for pregnant women (Barone and Roberts, 1996). In terms of instant coffee, this would be equivalent to 2-2.5 average sized mugs (260ml), assuming an average content of 100 mg caffeine per mug. The survey did not address other sources of caffeine such as chocolate, cold and flu remedies, headache treatments and energy drinks. In a more recent study, mean caffeine intakes were found to be 238 mg/day in women before they became pregnant, and reduced to 159 mg/day during pregnancy (CARE Study Group, 2008).

9. Recently, estimates of caffeine intake in the UK were derived from the rolling National Diet and Nutrition Survey (NDNS)[3]. These were based on the first two years of the survey and applied to respondents who reported consuming foods containing caffeine in 4-day food diaries (in which quantities were gauged approximately and not by weighing). The intake assessment was restricted to foods within 35 NDNS food groups that potentially contained caffeine (these included coffee, tea, cocoa, energy and soft drinks and dietary supplements). The caffeine content of dietary constituents was estimated from various sources, including information received from food manufacturers and earlier MAFF surveys (MAFF, 1998). The mean (± standard deviation) total caffeine intakes of men and women aged 19-64 were estimated to be 130 (±88) and 122 (±87) mg/d respectively. The corresponding figures for older men and women in the 65+ age range were 143 (±94) and 131 (±88) mg/d. Boys and girls in the age range of 11-18 years had lower intakes (46 (±43) and 44 (±45) mg/d) (Fitt et al, 2012). A breakdown of caffeine intake from caffeinated beverages in all NDNS respondents who reported consumption of such products indicated that coffee contributed more caffeine (49.5

[3] The NDNS provides detailed, quantitative information on food consumption, nutrient intakes, nutritional status and related characteristics. The NDNS is, in its current form, a four year rolling survey. The sample size for the survey is 500 adults and 500 children per year, covering people of all ages from 1½ years upwards living in private households. People living in institutions are not covered, and pregnant and lactating women are also excluded. The survey includes boosted samples in Scotland, Wales and Northern Ireland to enable cross-country comparisons. So far, only results from the first two years of the survey have been published (Department of Health, 2011).

(±32.3) mg/d) than tea (36.2 (±11.3) mg/d) and energy and soft drinks (34.5 (±21.4) mg/d). The inclusion of a larger range of products containing caffeine (e.g. chocolate products and energy drinks) in the recent analysis of NDNS data, as well as differences in the dietary assessment methods and in the assumed caffeine content of dietary constituents, may account for the differences in estimation of caffeine intake between different studies. High level intakes were not reported in these studies.

Biochemistry and psychopharmacology of caffeine

10. Caffeine is completely absorbed in the small intestine and the peak blood concentration occurs around 1-2 hours after ingestion. Caffeine is distributed throughout total body water and enters the brain quickly after absorption, but rate of metabolic clearance is variable, the half-life ranging from 2.3 to 9.9 hours in adults following single doses of caffeine (Arnaud, 2011), with a mean half-life of 4.3 hrs being reported in healthy non-smoking adult males (Seng, 2009). Extensive inter-individual variation occurs in caffeine metabolism due to factors such as alcohol and smoking habits, pregnancy, genetic polymorphisms and level of caffeine consumption. At low doses (<5mg/kg bw or 3-4 cups of coffee), pharmacokinetics can be represented accurately using a one-compartment model with first order absorption (Csajka et al, 2005). Metabolism of caffeine proceeds through three main pathways illustrated in Figure 2 (percentages refer to the mean proportion of caffeine converted to each metabolite). Some of the metabolites of caffeine themselves have pharmacological activity (Casarett et al, 1996).

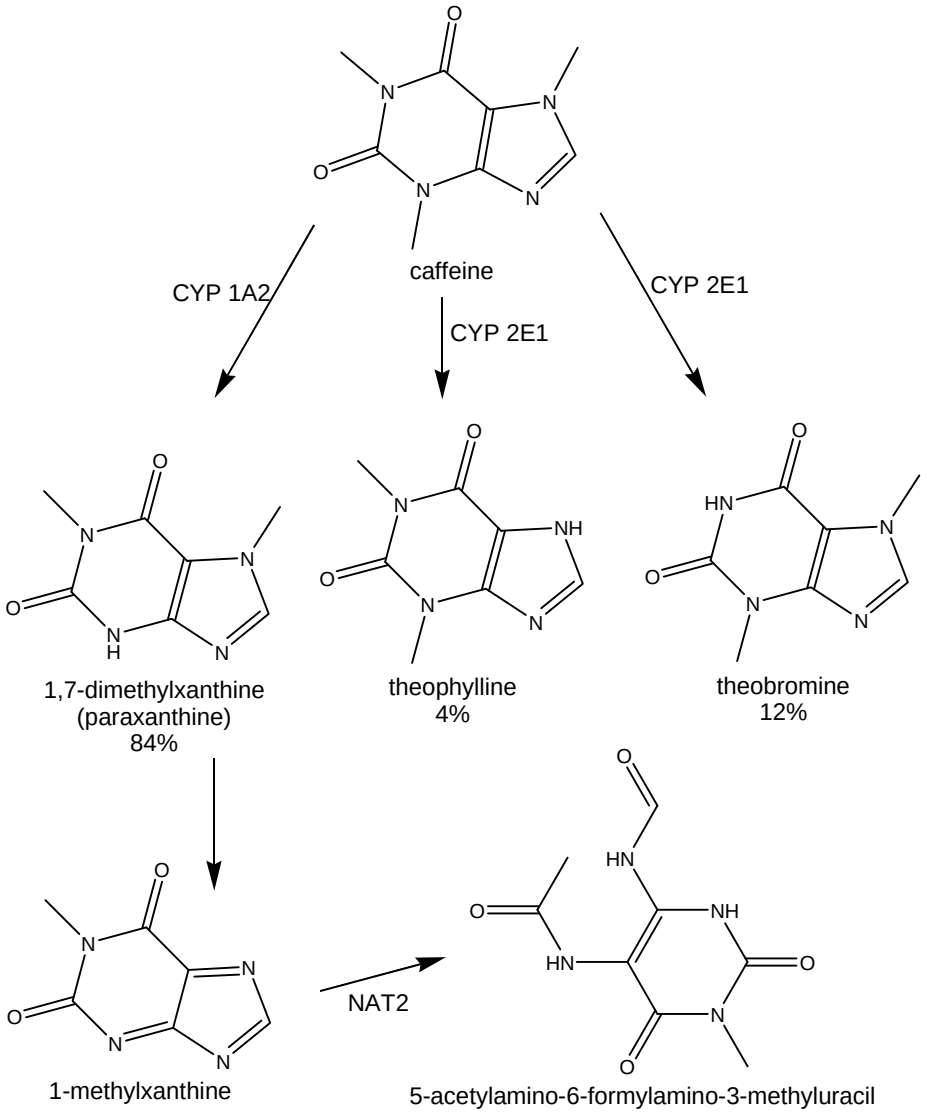

Figure 2: Metabolism of caffeine

11. Caffeine's primary biologically relevant mechanism of action is as a non-specific adenosine antagonist. Adenosine receptors are found throughout the body, and adenosine acts presynaptically to inhibit neuronal release of several neural transmitters, reduces spontaneous firing of neurons, produces sedation and has anticonvulsant activity (Benowitz, 1990). The pharmacologically active dose of caffeine can vary considerably between individuals as tolerance is rapidly developed to its effects. However, levels of 2-3 mg/kg bw have been shown to stimulate central nervous system activity in humans (FDA, 1978).

12. Adenosine is involved in a number of fundamental processes such as ATP-related energy production and RNA synthesis, but it is also released in response to metabolic stress and acts to protect the brain by suppressing neural activity (Latini and Pedata, 2001). Adenosine A_{2A} receptors are largely concentrated in the basal ganglia region and may be involved in the dopamine system (which is involved in reward and arousal). Adenosine may also be involved in the sleep-wake cycle (Basheer et al, 2004; Latini and Pedata, 2001).

13. Caffeine may also have secondary effects that are not related to adenosine, since it acts also as a competitive non-selective phosphodiesterase inhibitor, allowing the build up of cyclic AMP in cells and therefore modulation of many biological processes (Essayan, 2001).

14. In the central nervous system, caffeine acts primarily as a stimulant, increasing arousal and vigilance, reducing fatigue and decreasing motor reaction times in some tasks. At higher doses, caffeine can induce insomnia, anxiety, tremors, and seizures (Benowitz, 1990). The ADORAA2A 1083TT genotype of the adenosine A_{2A} receptor has been associated with lower caffeine intakes, suggesting a genetic link to the degree of caffeine consumption (Cornelis et al, 2007).

15. Studies carried out in adults showed improvements in aerobic endurance, anaerobic performance, choice reaction time, concentration and immediate-recall memory following consumption of an energy drink (80 mg caffeine, equivalent to 1.1 mg/kg bw for a 70 kg adult; (Alford et al, 2001), and 0.58, 1.70 or 1.75mg/kg bw (Howard and Marczinski, 2010)) in comparison with controls consuming a dummy energy drink or water. Following a mental depletion task (designed to require significant concentration on a number of tasks at one time), caffeine was found to increase aggression compared to placebo, but no effects were observed in groups which did not undertake the mental depletion task. In contrast, during a second experiment when a no pill control group was included along with the caffeine and placebo groups, no difference was observed in aggression between the caffeine and no-pill control groups, following the mental depletion task (Denson et al, 2011).

Consumption of alcohol

16. Alcohol is widely consumed in the UK with at least one alcoholic drink being reported as consumed in the week before interview by 68% of men and 54% of women in the 2009 General Lifestyle Survey carried out by the Office for National Statistics. In the same report, mean weekly consumption of alcohol in the 12 months before interview was 16.3 units for men and 8.0 units for women, equivalent to 2.33 g/kg bw for a 70kg man and 1.33 g/kg bw for a 60kg woman (Office of National Statistics, 2009). However, these data were for the total population, including those who did not drink alcoholic beverages, and the mean consumption of those who did drink alcohol would have been higher. During the week before interview, 37% of male participants exceeded the recommended limit for men of 4 units (32 g alcohol[4]) in a single day, and 29% of female participants exceeded the corresponding limit for women of 3 units (24 g alcohol).

Biochemistry and psychopharmacology of alcohol

17. Alcohol is rapidly absorbed from the stomach and intestine, and distributed widely through simple diffusion from blood into tissues. It is metabolised to acetaldehyde, primarily through the action of alcohol dehydrogenase (ADH) using the co-enzyme nicotinamide adenine dinucleotide (NAD), but also by CYP 2E1. Acetaldehyde is converted to acetic acid, through the action of the NAD-dependent enzyme acetaldehyde dehydrogenase (AcDH) (Casarett et al, 1996) (see Figure 3).

[4] www.drinkaware.co.uk. One unit of alcohol equals 8g pure alcohol.

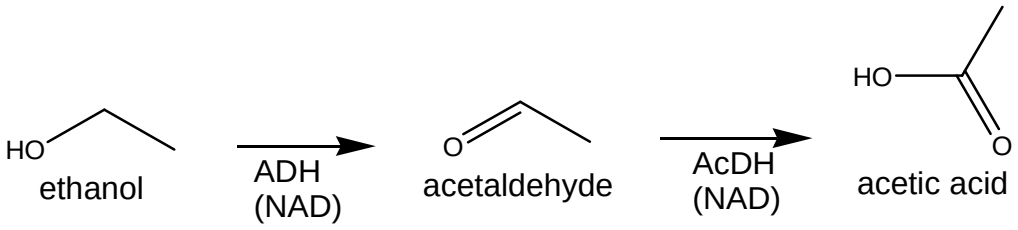

Figure 3: Metabolism of ethanol

18. Alcohol is a central nervous system depressant, but its mode of action has not been fully elucidated. It is thought to act in the central nervous system (CNS) by binding to the GABA-A receptor, which mediates rapid inhibitory neurotransmission throughout the CNS. The outward signs of alcohol intoxication, such as impaired sensory and motor function, slowed cognition and stupefaction, are a result of this receptor-binding activity (Kumar et al, 2009).

19. A major effect of alcohol is to impair inhibitory responses. It is thought that behaviour is governed by two distinct systems: one that activates a response and one that inhibits a response. As an example, in tests for behavioural inhibition, participants are required to respond appropriately to “go” signals on a computer, but when a “stop” signal is observed then they should inhibit their response. The impaired ability to inhibit responses when under the influence of alcohol has received much attention because of the social implications of excessive consumption (Marczinski and Fillmore, 2003). Doses of 0.62 g/kg bw absolute alcohol (43.4 g for a 70 kg adult) have been shown to reduce response inhibition using “stop/go” software as described above under laboratory conditions (Fillmore and Vogel-Sprott, 1999). The neuronal pathways directly responsible for the effects on response-inhibition are not clear.

20. Studies looking at the effects of lower doses of alcohol on attention tasks indicate that attention concentrated on a single source of information is not impaired by alcohol, but in divided attention tasks, especially those where two tasks follow each other closely, reaction time is increased (Moskowitz and Burns, 1971).

Co-consumption of alcohol, caffeine and other psychoactive substances

21. Accurate estimates of the extent to which alcohol and caffeine are consumed together are not available. One of the reasons for this is that drinks containing alcohol and caffeine are often sold separately and mixed by the consumer rather than being formulated in a single product – for example rum with cola or energy drinks with vodka.

22. Four studies looking at the energy drink and alcohol consumption of university students in the US and Canada showed an association between consumption of energy drinks and alcohol. Some of these studies investigated alcohol-related adverse incidents, and showed that high consumers of both energy drinks and alcohol were at greater risk of such incidents than consumers of alcohol alone (Arria et al, 2011; O'Brien et al, 2008; Price et al, 2010; Velazquez et al, 2011). One Canadian study found a significant association of combined energy drink and alcohol consumption with risk-taking behaviours, including consumption of illicit drugs

(Brache and Stockwell, 2011). In another study, general caffeine consumption in 12-13 year olds in high school was significantly associated with the use a year later, not only of caffeine, but also of nicotine and alcohol (Collins et al, 2011).

23. In a field study of 1255 bar patrons, individuals who consumed alcohol mixed with energy drinks were at three-fold increased risk of leaving a bar highly intoxicated and four-fold increased risk of intending to drive, when compared to other patrons who consumed alcohol but not mixed with energy drinks. The mean quantity of alcohol consumed by individuals who drank only alcohol was 95.3g, as compared with 108.3g for those who also consumed energy drinks but not mixed with the alcohol, and 152.2g for those who consumed alcohol mixed with energy drinks. Group sizes for those consuming energy drinks and alcohol were small (46 consumed both but not mixed and 45 consumed both mixed) (Thombs et al, 2010).

24. In contrast, in a survey of 1503 Dutch students, those who consumed alcohol with an energy drink consumed less alcohol than those who drank alcohol alone, although the difference did not reach statistical significance ($p=0.056$). Those who consumed alcohol with a cola beverage consumed significantly more alcohol than those who consumed alcohol alone ($p=0.001$) or those who combined energy drinks with alcohol ($p=0.001$). The group sizes for those consuming cola and energy drinks with alcohol were small; 45 and 24 respectively (Penning et al, 2011).

25. There has been some suggestion that high intake of caffeine might be a marker for the use of other drugs, both legal and illegal, and also for other addictive behaviours such as excessive gambling and excessive use of the internet (Arria et al, 2010; Istvan and Matarazzo, 1984; Kaminer, 2010; Pallanti et al, 2006).

26. Studies based on a cohort of male and female mono- and dizygotic twin pairs, looked at caffeine, smoking, alcohol and drug consumption habits. These investigations suggested that the association between high consumption of caffeine and alcohol depended on familial factors, which were primarily genetic. Modelling indicated two genetic factors – one linked to illicit drug use and the other to use of legal drugs including caffeine and alcohol (Hettema et al, 1999; Kendler et al, 2006; Kendler et al, 2007; Kendler et al, 2008). However, this finding has yet to be independently confirmed.

27. In a cohort of male di- ($n=183$) and monozygotic ($n=173$) twins, heavy consumption of alcohol and heavy smoking were significantly associated [phenotypic Pearson correlation $r=0.22$ ($p<0.001$)], as were heavy smoking and heavy coffee consumption [phenotypic Pearson correlation $r=0.28$ ($p<0.001$)]. In contrast, heavy consumption of coffee and alcohol were more weakly related [phenotypic Pearson correlation $r=0.14$ ($p<0.001$)] (Swan et al, 1997). Further comparisons between di- and monozygotic twins suggested that co-consumption of coffee and alcohol had a genetic basis, and co-consumption of alcohol, coffee and nicotine is determined in part by genetic predisposition (Swan et al, 1996).

28. In a population of 1925 patients who had voluntarily sought treatment for substance abuse disorders, a statistically significant relationship was found between the frequencies of using caffeine, nicotine and alcohol, but there was no significant association of exposure to caffeine and nicotine with exposure to other substances of abuse such as heroin, cannabis and glue (Kozlowski et al, 1993).

29. In a sample of 105 Israeli alcoholics undergoing treatment, caffeine and alcohol consumption were significantly correlated ($p<0.05$). When the sample was subdivided into those with (n=62) and those without (n=43) a family history of alcoholism (defined as at least one primary family member meeting the DSM-IV criteria for alcohol dependence) no differences were observed between the two groups in alcohol or caffeine consumption (Amit et al, 2004)

30. The balance of evidence suggests that higher intake of caffeine is associated not only with higher alcohol intakes but also with use of other psychoactive substances. There is limited evidence that the relationship may be determined, at least in part, by genetic predisposition. It appears that, at least in some population groups, there is a correlation between high consumption of alcohol and of energy drinks specifically. However, it is unclear whether this is because consumption of energy drinks causes people to drink more alcohol, or because people who are inclined to more risky behaviour tend generally to consume larger quantities of psychoactive substances, including caffeine and alcohol.

Health effects of co-consumption of alcohol and caffeine

31. It has been suggested that when consumed together, energy drinks and alcohol might interact in several ways (Weldy, 2010):

- Carbonation tends to increase the absorption of alcohol (although some non-carbonated energy drinks are available, the majority of sales are of carbonated products)
- Diluted alcohol is emptied from the stomach into the faster absorbing small intestine more quickly than alcohol at higher concentrations.
- Caffeine blunts the sedative effects of alcohol
- Caffeine prevents sleep, allowing greater opportunity for consumption of alcohol before loss of consciousness
- At low blood alcohol levels, caffeine appears to decrease some of the physical and mental impairment resulting from alcohol, although at higher blood alcohol levels no such effects are observed.
- Energy drink ingredients give the consumer a false sense of physical and mental competence and decrease their awareness of impairment by alcohol.

Does caffeine counteract the neuro-cognitive effects of alcohol consumption?

32. There is some evidence that caffeine can ameliorate some of the neuro-cognitive effects of alcohol, but the findings have not been consistent in all studies, and the underlying mechanisms are unclear. In a review of the data published up to 1988, the authors concluded that because of variation in the doses of caffeine and alcohol administered, the behavioural effects assessed, and other aspects of study design, it was not possible to determine whether there was a counteracting effect of caffeine (Fudin and Nicastro, 1988).

33. A number of studies published since the SCF opinion of 2003 have investigated the effects of combined alcohol and caffeine consumption on various aspects of neurological function. Doses ranged from 1.1 to 5.6 mg/kg bw for caffeine and 0.18 to 1.07 g/kg bw for alcohol. Many of these studies used driving simulators and doses of approximately 2-3 cups of coffee or 1-2 cans of energy drink with 1-2

standard measures of vodka. Results have been inconsistent, with some studies finding that caffeine did not antagonise the physiological effects of alcohol and others suggesting that some important aspects of alcohol intoxication were ameliorated, especially effects on motor reaction time, mean tracking performance and memory reaction time (Alford et al, 2012; Attwood et al, 2011; Azcona et al, 1995; Burns and Moskowitz, 1990; Ferreira et al, 2004; Ferreira et al, 2006; Fillmore et al, 2002; Fillmore and Vogel-Sprott, 1999; Hasenfratz et al, 1993; Howland et al, 2011; Kerr et al, 1991; Marczinski et al, 2011; Marczinski et al, 2012a; Marczinski et al, 2012b; Marczinski and Fillmore, 2003; Marczinski and Fillmore, 2006). Conflicting results have also been obtained in studies designed to test perceived degree of alcohol intoxication with and without caffeine. The most direct subjective ratings of intoxication[5] were no different when alcohol was consumed with and without caffeine. Where conflicts have been found, these were in less direct subjective[6] measures (Alford et al, 2012; Ferreira et al, 2006; Marczinski and Fillmore, 2006). A recent review concluded that the available literature did not support the argument that energy drinks mask the effects of alcohol intoxication and increase alcohol consumption (Verster et al, 2012). A more detailed description of the primary studies can be found in Annex 1.

34. In conclusion, the heterogeneity of methods and neurological end-points in reported studies prevents firm conclusions on whether caffeine counteracts the acute neuro-cognitive effects of alcohol. It should be noted that because of ethical constraints, the levels of alcohol consumed in these studies were relatively low.

Case reports of deaths and acute illness following consumption of caffeine alone or in combination with alcohol

35. Through a literature search, the National Programme on Substance Abuse Deaths has identified seven cases from the UK in which a coroner named caffeine alone (five cases) or in combination with alcohol (two cases) as a factor contributing to death. In another case report, the parents had linked the death of their son to caffeine consumption (Corkery, 2012). One study in the peer-reviewed literature describes acute renal failure following consumption of three litres of energy drink mixed with one litre of vodka (Schoffl et al, 2011).

36. Analysis of phone calls to the New South Wales Poisons Information Service over a seven year period revealed that of 297 calls concerning caffeinated energy drinks, 73% related to recreational exposures (others concerned accidental consumption by children or deliberate self-poisoning). The median age of the cases was 17 years. Co-ingestion of other substances was reported in 46% of calls relating to recreational exposure, most frequently alcohol (23% of recreational users) and other caffeine-containing products such as cola and caffeine tablets (20%). Features of serious toxicity such as hallucinations, seizures and cardiac ischaemia were described in 21 calls. Among the callers, 128 people sought or were advised to

[5] Examples of direct subjective measures on intoxication include participants being asked how many drinks they had consumed, for an estimate of blood alcohol or being asked to rate their level of intoxication on a scale ranging from least ever to most ever.

[6] Examples of less direct subjective measures of intoxication include participants being asked how competent they felt to drive a car or how fatigued they felt.

seek, urgent medical attention, of whom 70 had co-consumed other substances (Gunja and Brown, 2012).

37. Although some of the cases described in this section suggest acute toxic effects of caffeine and/or alcohol, they do not allow firm conclusions about the contribution of either substance or of whether caffeine increases the acute toxicity of alcohol.

Serious cardiac outcomes

38. In its opinions of 1999 and 2003, the SCF noted anecdotal reports of serious cardiac outcomes in young people following consumption of energy drinks with alcohol, but observed that the reports were incomplete and that consumption of energy drinks and alcohol often occurred in combination with other drugs, thus limiting the conclusions that could be drawn. The Committee identified one paper on cardiac effects of co-consumption of alcohol and caffeine that had been published since the SCF opinion (Wiklund et al, 2009). However, because of the small size of the study that it described, it did not allow useful conclusions.

The role of expectations

39. The Committee noted evidence that individuals' expectations of behavioural effects following consumption of alcohol and/or caffeine may lead them to behave differently when exposed (Fillmore et al, 2002; Fillmore and Vogel-Sprott, 1995; Harrell and Juliano, 2009). However, it was not clear how far psychological mechanisms of this sort contributed to behavioural outcomes following consumption of caffeine and alcohol in combination.

Conclusions

40. The increasing consumption of drinks containing caffeine mixed with alcohol has raised concerns about the physical and mental health effects of these psychoactive substances in combination. A phenomenon known as "wide awake drunk" has been suggested, in which the stimulatory effects of caffeine may prevent consumers of alcohol from realising how intoxicated they are, leading to increased risk of toxic injury and adverse behavioural effects such as increased risk-taking, violence and criminal activity.

41. The balance of evidence suggests that higher intake of caffeine is associated not only with higher alcohol intakes, but also with use of other psychoactive substances. There is limited evidence that the relationship may be determined at least in part, by genetic predisposition. It appears that, at least in some population groups, there is a correlation between high consumption of alcohol and of energy drinks specifically. However, it is unclear whether this is because consumption of energy drinks causes people to drink more alcohol, or because people who are inclined to more risky behaviour tend generally to consume larger quantities of psychoactive substances, including caffeine and alcohol.

42. A number of studies have suggested that caffeine can ameliorate some effects of alcohol, especially on motor reaction time, mean tracking performance and memory reaction time, but other investigations have failed to support this. The evidence that perceptions of alcohol intoxication are modified by caffeine is

conflicting. Overall, the heterogeneity of methods and neurological end-points in reported studies prevents firm conclusions on whether caffeine counteracts the acute neuro-cognitive effects of alcohol

43. Published case reports of deaths and acute illness following consumption of caffeine and alcohol in combination do not allow conclusions as to whether caffeine increases the acute toxicity of alcohol.

44. Individuals' expectations of behavioural effects following consumption of alcohol and/or caffeine may lead them to behave differently when exposed. However, it is unclear how far psychological mechanisms of this sort contribute to behavioural outcomes following consumption of caffeine and alcohol in combination.

45. Overall, the Committee concludes that the current balance of evidence does not support a harmful toxicological or behavioural interaction between 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.

COT statement 2012/04
December 2012

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Annex 1: Studies on the effects of alcohol and caffeine on neurological function.

Reference	Caffeine dose	Alcohol dose	Observed effects
Alford et al, 2012	0, 2.2 mg/kg bw (energy drink)	0, 0.79 g/kg bw	Recognition reaction time slowed by alcohol alone (p=0.02) but similar to baseline following alcohol and caffeine consumption. Word memory was impaired by alcohol regardless of whether or not caffeine was co-consumed (p=0.001). Stroop test error rate was not increased by alcohol alone and was actually improved in the alcohol and energy drink group (p=0.028). Stroop completion times were decreased by energy drink (p=0.004) and were decreased further still by alcohol mixed with energy drink (p=0.024)
Attwood et al, 2012	0,2 mg/kg bw (dissolved caffeine powder	0, 0.6 g/kg bw	Subjective measures of intoxication did not differ between test and control groups. Caffeine appeared to antagonise the effects of alcohol on omission errors in the stop-signal task (p=0.016) but had no effect on simple reaction time (p=0.34) or performance of go – no-go tasks (P=0.95) and worsened the accuracy on the Stroop test (p=0.019).
Azcona et al, 1995	0, 5.6 mg/kg bw (encapsulated caffeine powder)	0, 0.8 g/kg bw	Simple Reaction Time increased by alcohol and ameliorated by caffeine ($p < 0.05$).
Burns & Moscowitz, 1990	0, 2.93, 5.87 mg/kg bw (encapsulated caffeine powder)	0, 0.5, 0.99 g/kg bw	Alcohol had effects on alertness, tracking, visual search, reaction time and information processing. Caffeine ameliorated all but information processing (none of the results were statistically significant).
Ferreira et al, 2004	1.14 mg/kg bw (energy drink)	0.3 g/kg bw	Following a physical test on a cycle ergometer, no differences were observed in physical parameters between the alcohol group and the alcohol and energy drink group.
Ferreira et al, 2006	1.14 mg/kg bw (energy drink)	0, 0.18, 0.3 g/kg bw	Alcohol and energy drink consumed together did not reduce deficits in objective motor co-ordination (p=0.11) and visual reaction time (p=0.12) caused by alcohol alone.

Fillmore, Roach and Rice, 2002	0, 4 mg/kg bw (dissolved caffeine powder)	0.65 g/kg bw	Groups led to expect that caffeine would counteract the effects of alcohol showed greater impairment of performance in a pursuit rotor task than groups led to expect no such counteracting effect ($p=0.037$). No significant differences were found in subjective measures of intoxication between the groups consuming caffeinated and non-caffeinated drinks.
Fillmore & Vogel-Sprott, 1999	0, 4.4 mg/kg bw (dissolved caffeine powder)	0, 0.62 g/kg bw	No effects observed on reaction time. Mean number of inhibitions was significantly reduced following alcohol consumption compared to baseline whereas following alcohol and caffeine consumption number of inhibitions was higher than baseline ($p<0.002$).
Hasenfratz et al, 1993	0, 3.3 mg/kg bw (dissolved caffeine powder)	0, 0.7 g/kg bw	In a rapid information processing (RIP) task, mean reaction time and processing rate were improved by caffeine ($p<0.01$; $p<0.05$); the reaction time was increased by alcohol ($p<0.05$); the combination of alcohol and caffeine did not differ from baseline suggesting that caffeine was able to offset the alcohol induced performance decrements.
Howland et al, 2011	0, 5.47 (men), 5.63 (women) mg/kg bw (Dissolved caffeine powder)	0, 1.07 (men), 0.92 (women) g/kg bw	Alcohol significantly impaired driving and sustained attention/reaction time. Caffeine did not appear to antagonise the effects of alcohol. No significant differences were found in subjective measures of intoxication between the groups consuming caffeinated and non-caffeinated drinks.
Kerr, 1991	0, 5 mg/kg bw (encapsulated caffeine powder)	0, 0.18 g/kg bw	Caffeine appeared to antagonise the effect of alcohol on short term memory and choice reaction time (not statistically significant) and mean tracking performance ($p<0.05$). No effects were observed on critical flicker fusion (measures arousal).
Marczinski and Filmore, 2003	0, 2, 4 mg/kg bw (dissolved caffeine powder)	0, 0.65 g/kg bw	Alcohol impaired inhibitory and activational aspects of behavioural control. Caffeine antagonised response activation ($p=0.03$) but not inhibition ($p>0.81$).
Marczinski and Filmore, 2006	0, 2, 4 mg/kg bw (dissolved	0, 0.65 g/kg bw	Alcohol impaired the speed of reaction time and accuracy of response in go/no-go and auditory discrimination tasks. Caffeine antagonised

	caffeine powder)		the effects of alcohol on speed of reaction time ($p<0.02$), but not accuracy ($p>0.15$).
Marczinski et al, 2011.	0, 1.2 mg/kg bw (energy drink)	0, 0.65 g/kg bw	Alcohol impaired the inhibitory failures and response times compared to placebo in a cued go/no-go task. Caffeine ameliorated some impairment of response times ($p<0.05$) but not inhibition ($p>0.27$).
Marczinski et al, 2012a	0, 0.6 mg/kg bw (energy drink)	0, 0.36 g/kg bw	Subjective measurements of intoxication were not significantly different between those consuming alcohol alone and in combination with caffeine. Subjects consuming energy drink and alcohol were more likely to feel motivation to consume more alcohol at 10, 20, 40 and 60 mins after dosing ($p<0.01$) compared to baseline, whereas the alcohol alone group felt motivation only 10 and 20 minutes after dosing ($p=0.01$).
Marczinski et al, 2012b	0, 1.2 mg/kg bw (energy drink)	0, 0.65 (men), 0.57 (women) g/kg bw	Subjective measurements of intoxication were not significantly different between those consuming alcohol alone and in combination with caffeine, but there were non-significantly reduced perceptions of mental fatigue and stimulation in the caffeine and alcohol group compared with the alcohol alone group. Alcohol slowed dual task information processing and impaired simple and complex motor co-ordination. No antagonistic effects were observed from caffeine.

Annex Two: Search Criteria and databases used

As the Scientific Committee on Food (SCF) looked at alcohol and caffeine interactions in 2003, only references published after this time were included in the literature review. Some references that were not included by the SCF but published prior to 2003 came to light through searching the reference lists of later papers. When considered relevant, these were also reviewed. Because of the availability of human studies, animal studies were not considered unless they were considered particularly relevant.

Searches using Pubmed

Caffeine, alcohol, behaviour (limits 01/01/2003-present)

Caffeine, alcohol, interactions (limits 01/01/2003-present)

Energy drinks, alcohol, behaviour (limits 01/01/2003-present)

Energy drinks, alcohol, interactions (limits 01/01/2003-present)

Caffeine, alcohol, behaviour (limits 01/01/2003-present; human studies only)

Caffeine, alcohol, interactions (limits 01/01/2003-present; human studies only)

Energy drinks, alcohol, behaviour (limits 01/01/2003-present; human studies only)

Energy drinks, alcohol, interactions (limits 01/01/2003-present; human studies only)

Searches using Google Scholar

All in title: Caffeine, alcohol, (NOT rat, mice) (since 2003, articles excluding patents)

All in title: “Energy drinks”, alcohol, (NOT rat, mice) (since 2003, articles excluding patents)

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