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TOX/2012/10

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

The interaction of caffeine and alcohol and their combined effects on health and behaviour

Introduction

1. As part of its horizon scanning discussion at the meeting in February 2011, the Committee was asked to comment on concerns over the potential for interaction between the caffeine in energy drinks and alcohol[1] to result in adverse behavioural or toxic effects. Members agreed that a full review of the literature[2] should be considered with input from experts in experimental human psychology and psychopharmacology.

Background

2. Since the introduction of "Red Bull" in Austria in 1987, the sales of energy drinks have risen dramatically, with the average annual growth rate from 2002 to 2006 being 55% (Reissig et al, 2009). The popularity of energy drinks mixed with alcoholic beverages has also increased, especially amongst young males, with individuals who consume higher levels of energy drinks also consuming greater quantities of alcohol and seeming to engage in a greater degree of risk taking. These factors have given rise to concerns over the health effects of this combination of psychoactive substances in particular, a phenomenon described as "wide awake drunk" where the stimulatory effect of caffeine prevents the consumer from realising how intoxicated they are, with the potential for increased toxicological damage and adverse behavioural effects occurring (Reissig et al, 2009). In a report from the Scottish Prisons Service, other alcoholic beverages such as "Buckfast Tonic Wine", which contains significant quantities of caffeine (375-550 mg/L) and 15% alcohol by volume, have been associated with violence in young offenders in Scotland; with 43.4% of young offenders from a sample of 172 admitting consumption of Buckfast Tonic Wine prior to their most recent offence (Scottish Prisons Service, 2009; Wikipedia, 2011). Most energy drinks contain levels of caffeine approximately equivalent to the levels found in coffee along with other substances such as sugar, taurine and glucuronolactone.

3. The Scientific Committee on Food (SCF), who advised the European Commission prior to the creation of the European Food Safety Authority (EFSA), looked at the safety of energy drinks in 1999 (SCF, 1999). Additional information was submitted following the publication of their opinion in 1999 and a further opinion was issued in 2003. As part of their second assessment, the SCF looked at the evidence for an interaction between caffeine and alcohol. The Committee concluded that the majority of studies suggested that caffeine would not exacerbate the adverse effects of alcohol; at lower blood alcohol levels, and on simpler tasks, caffeine may improve performance (SCF, 2003).

4. The SCF also looked at the 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, which could act additively to increase water and sodium loss from the body in the short term increasing the risk of dehydration. In a 13-week study in rats, taurine has been shown to cause

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

[2] The search criteria and databases used can be found in annex 1.

behavioural effects in animal studies in all dose groups tested, with the lowest dose being equivalent to 6 times the mean acute intake for energy drinks of 50mg/kg bw for a 60kg adult. The SCF concluded that some alcohol–taurine interactions are possible, including behavioural interactions, but these are neither marked nor consistent in human and animal studies. The SCF were of the opinion that focused neurological studies should be carried out in this area. The SCF concluded that glucuronolactone would not be expected to interact with alcohol or other constituents of energy drinks.

5. In response to concern over the safety of alcohol mixed with high caffeine drinks and the uncertainties in the literature, the COT is asked to consider the literature published since the SCF opinion of 2003, and advise on the potential for interactions between caffeine and alcohol.

6. Literature published since 2003 has been reviewed with studies relevant to the combined effects of caffeine and alcohol on health and behaviour summarised below. The search terms used can be found in annex 1.

Current European legislation on caffeine

7. Under European Directive *2002/67/EC on the labelling of foodstuffs containing quinine and foodstuffs containing caffeine, b*everages 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 1169/2001), 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. This requirement comes into effect on the 13 December 2014.

8. Foods other than beverages where caffeine is added with a physiological purpose must carry the statement ’Contains caffeine. Not recommended for children or pregnant women’ in the same field of vision as the name of the product followed by a reference in brackets to the caffeine content in mg per 100 g or ml. In the case of food supplements, the caffeine content shall be expressed per portion as recommended for daily consumption on the labelling.

Legislative history and international opinion on energy drinks and caffeinated alcoholic drinks

9. France banned the sale of energy drinks in 1996 following advice from the French Health Authorities over the neuro-behavioural and thyroid effects of taurine and concerns over the renal effects of D-glucuronolactone. In 2004, the European Commission challenged this ban which was partially upheld by the European Court of Justice. Unable to prove a health risk, the French Health Authorities retracted their ban and energy drinks were permitted for sale in France in 2008. Similar bans in Denmark and Norway have also been revoked.

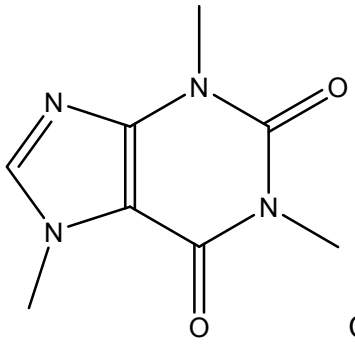
10. The United States Food and Drug Administration have concluded that there are insufficient data relating to the safety of alcoholic beverages with added caffeine to form the basis of a consensus among experts that these beverages are safe. Therefore, such products are marketed in violation of federal law. They also stated that other alcoholic beverages containing added caffeine may be subject to FDA action in the future if the available scientific data and information indicate that the use of caffeine in these products is

not generally recognised as safe (GRAS) (Food and Drug Administration, 2010). However, this position is based on legislation that is not relevant for the EU or UK.

Caffeine in beverages

11. Caffeine (1,3,7-trimethyl xanthine) is probably the most widely used psychoactive substance (Benowitz, 1990). The pharmacologically active dose can vary considerably between individuals as a tolerance is rapidly developed to the effects of caffeine, however levels of 2-3 mg/kg bw have been shown to stimulate central nervous system activity in humans (Food and Drug Administration, 1978). The structure of caffeine is shown in figure 1:

Figure 1: Structure of caffeine



Caffeine

12. In 2004, the Dietary Caffeine and Health Study estimated a mean caffeine intake of 241mg/day for 6,000 individuals from the Bristol area who filled out a questionnaire designed to measure consumption of coffee, tea, chocolate products, cola drinks and energy drinks (Food and Drug Administration, 1978; Heatherley et al, 2006b; Heatherley et al, 2006a). This level of intake is similar to that identified from a Ministry of Agriculture, Fisheries and Food (MAFF) survey of 1988 of consumption of coffee, tea and colas, from which the mean caffeine intake was estimated to be 3.98 mg/kg body weight per day (i.e. 239 mg/day for a 60 kg person) for the general population and 3.43 mg/kg body weight per day (i.e. 206 mg/day for a 60 kg person) for pregnant women. 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 MAFF survey did not include other sources of caffeine such as chocolate, cold and flu remedies, headache treatments and energy drinks (Committee on Toxicity of Food Consumer Products and the Environment, 2001; Ministry of Agriculture Fisheries and Food, 1998). Most energy drinks contain approximately 80mg caffeine per 250ml can although drinks with smaller volumes and higher caffeine levels have appeared on the market in recent years.

Human effects

Psychopharmacology and biochemistry of caffeine

13. Caffeine enters the brain quickly after absorption, and metabolism is variable with a half life ranging from 2 to 12 hours in healthy adults. Caffeine's primary biologically relevant mechanism is through its action 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).

14. Adenosine is involved in a number of fundamental processes such as ATP related energy metabolism and RNA synthesis but is also released in response to metabolic stress and acts to protect the brain by suppressing neural activity and increasing blood flow through adenosine receptors (Latini and Pedata, 2001). A2A 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).

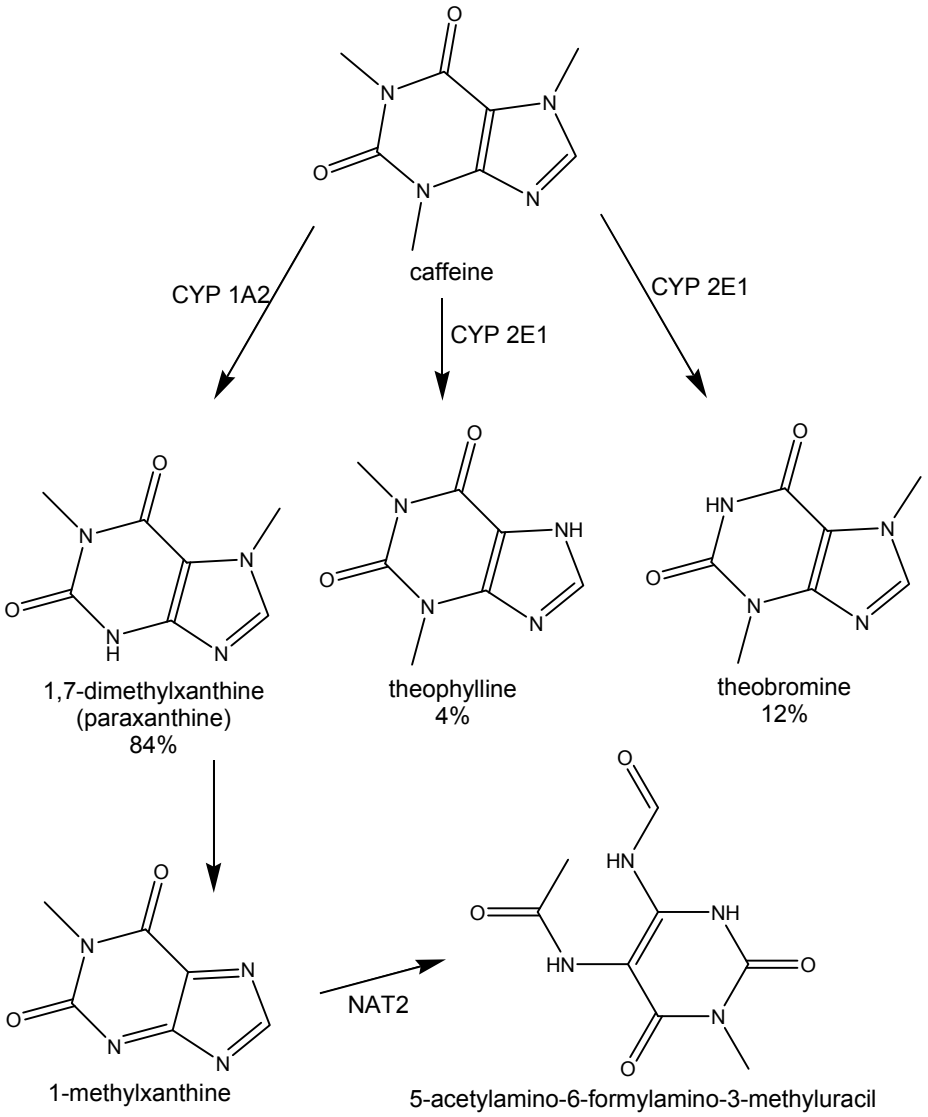
15. Caffeine has secondary effects that may not be related to adenosine, since caffeine is also a competitive non-selective phosphodiesterase inhibitor, allowing the build up of cyclic AMP in the cells (Essayan, 2001).

16. 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. In 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).

17. Studies carried out in adults showed improvements in aerobic endurance, anaerobic performance, choice reaction time, concentration and memory following consumption of an energy drink (80 mg caffeine or 1.33 mg/kg bw for a 60 kg adult; (Alford et al, 2001)) or (0.58, 1.70 and 1.75mg/kg bw (Howard and Marczinski, 2010)) compared to controls of a dummy energy drink or water. In a study of 133 Australian undergraduates, a 200mg caffeine tablet (3.3mg/kg bw for an average 60kg adult), placebo (sucrose) or no tablet were administered followed by a mental depletion task and a provocation task or a provocation task alone. Caffeine was found to increase aggression compared to placebo following the depletion task but not under no-depletion conditions. Consumption of the placebo tablet reduced aggression compared to both caffeine and the no-pill control following the depletion task suggesting that expectancies about the effects of caffeine in the absence of the pharmacological effects can reduce aggression when mentally depleted (Denson et al, 2011).

18. Metabolism of caffeine takes place through 3 main pathways that are shown in Figure 2 with the percentages indicating the proportion of caffeine metabolised to a particular metabolite.

Figure 2: Metabolism of caffeine



19. Some of the metabolites of caffeine pictured above also have pharmacological activity (Casarett et al, 1996).

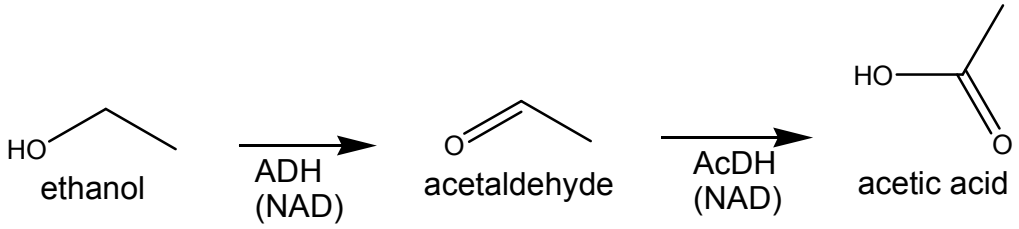
Consumption of alcohol

20. Alcohol is widely consumed in the UK with at least one alcoholic drink being consumed in the week prior to interview by 68% men and 54% of women in the UK during 2009 according to the General Lifestyle survey carried out by the Office of National Statistics. In the same report, mean weekly consumption of alcohol was 16.3 units for men and 8.0 units for women in the 12 months prior to interview, equivalent to 2.33 g/kg bw for an average 70kg man and 1.33 g/kg bw for an average 60kg woman (Office of National Statistics, 2009). However, these data are for the total population including those who do not drink alcoholic beverages and therefore mean consumption by consumers will be higher. The proportion of adults exceeding recommended limits of 4 units (40g alcohol) in one day in the week prior to interview was reported to be 37% for men and 3 units (30g alcohol) in one day in the week prior to interview was 29% for women.

Psychopharmacology and biochemistry of alcohol

21. Alcohol is rapidly absorbed from the stomach and intestine and distributed widely through simple diffusion from blood into tissues. Alcohol is converted to acetaldehyde primarily through the action of alcohol dehydrogenase using the co-enzyme nicotinamide adenine dinucleotide (NAD). Acetaldehyde is then converted to the corresponding carboxylic acid through the action of the NAD-dependent enzyme acetaldehyde dehydrogenase which is then released from the liver and oxidised peripherally (Casarett et al, 1996) (see figure 3).

Figure 3: Metabolism of ethanol



22. It is thought that behaviour is governed by two distinct systems: one that activates a response and one that inhibits a response. The impaired ability to inhibit a response under the influence of alcohol has received considerable attention because of the social implications of excessive consumption (Marczinski and Fillmore, 2003). Doses of 0.62 g/kg bw absolute alcohol (37.2 g for a 60kg adult) have been shown to reduce response inhibition under laboratory conditions (Fillmore and Vogel-Sprott, 1999).

23. Alcohol is a central nervous system depressant and its mode of action has not been fully elucidated. It is understood that alcohol acts 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). It is not clear if the binding of the GABA-A receptor is directly responsible for the effects on response inhibition.

24. Studies looking at the effects 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).

Health effects of co-consumption of alcohol with caffeine or energy drinks

25. In its opinions of 1999 and 2003, the SCF noted the existence of anecdotal reports of serious cardiac outcomes in young individuals but stated that these reports were incomplete and that consumption of energy drinks and alcohol often occurred in connection with other drugs; limiting the ability to draw conclusions. Since that time, a small study of 10 healthy adult volunteers has been carried out on the effects of alcohol and energy drinks on cardiac output. Subjects consumed a volume of energy drink containing 240mg caffeine (4 mg/kg bw assuming 60kg) alone or mixed with alcohol (0.4 g/kg bw) or no drink (no placebo). Each subject completed all three of the treatment regimens 1-3 months apart. Thirty minutes following consumption of the test substance, individuals performed a maximal bicycle ergometer exercise whilst undergoing an electrocardiogram (ECG) analysis. Post exercise recovery in heart rate was statistically significantly slower following alcohol and energy drink combined than following exercise alone ($p<0.02$). Heart rate variability was measured using the power of the high (PHF; 0.15-0.50 Hz) and low frequency (PLF; 0.04-0.15 Hz) components of the heart rate as well as the total spectral power (PTOT) the ratio of PLF/PHF was used as an indicator of sympathovagal balance (an indicator of heart rate variability). Before exercise the PLF/PHF ratio was statistically significantly higher following

consumption of energy drink alone (p=0.03) compared to the no-drink control group and heart rate was higher following energy drink/alcohol consumption compared to controls (p=0.01). Heart rate variability was decreased following exercise in all groups. Post-exercise heart rate was higher in both the energy drink and exercise group and the energy drink, alcohol and exercise group compared to the exercise alone group (p=0.001). The PLF/PHF ratio was lower following consumption of energy drinks than in controls (p=0.05). The energy drink and exercise group and the energy drink, alcohol and exercise group were not directly compared in this study but it appears that there were no significant differences between these two groups. The authors concluded that the healthy subjects developed blunted cardiac autonomic modulation after exercise when they had consumed energy drinks mixed with alcohol (but do not comment on the energy drink alone group which does not appear to be significantly different from the controls) and that although no arrhythmias were observed, predisposed individuals could have an increased risk for malignant cardiac arrhythmia in similar situations (Wiklund et al, 2009).

26. It has been suggested that the addition of energy drinks to alcohol may have several effects (Weldy, 2010):

- Carbonation tends to increase the absorption of alcohol (although some non-carbonated energy drinks are available, the majority of sales are carbonated)
- Diluted concentrations of alcohol are emptied from the stomach into the faster absorbing small intestine more quickly than higher concentrations.
- Caffeine keeps one awake and blunts the sedative effects of alcohol
- Lengthened time awake theoretically allows greater 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. 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 the awareness of impairment

Higher caffeine intake is associated with higher alcohol intake

27. The regular use of energy drinks has been strongly associated with an increased risk for alcohol dependence (Arria et al, 2011). In a study involving 1097 4th year college students from one large university in the US, the high frequency consumers of energy drinks (consumption on >52 days per year) were found to drink alcoholic beverages (not necessarily together) more frequently (on 141.6 vs 103.1 days per year) and were found to be at greater risk of alcohol dependence when compared to non users and low frequency users of energy drinks (Arria et al, 2011). Another study in 4,271 US college students asked to complete an online survey showed that consumption of alcohol mixed with energy drinks was significantly associated with increased heavy[3] episodic drinking (6.4 days vs 3.4 days on average in the past 30 days p<0.001) and twice as many episodes of weekly drunkenness (1.4 days/week vs 0.73 days/week, p<0.001). After adjusting for number of drinks consumed, students who reported consuming alcohol mixed with energy drinks, had a significantly higher prevalence of alcohol related consequences, including being taken advantage of sexually, taking advantage of another sexually, riding with an intoxicated driver, being physically hurt or injured and requiring medical treatment (p<0.05). It is not clear whether participants were reassured that their responses would be kept confidential; it may therefore be possible that alcohol consumption and related consequences were under-reported in this study (O'Brien et al, 2008, a copy of this paper can be found in annex 2). In a further study, 72 students and staff from a Canadian University selected because they were

[3] Defined as 4 or more alcoholic drinks in one drinking session for females and 5 or more for males.

consumers of energy drinks, were questioned about their alcohol and energy drink consumption both individually and combined. More alcohol was consumed when combined with energy drinks than when alcohol alone was consumed (Mean 8.6 vs 4.7, p=0.016) (Price et al, 2010).

28. College students from a large US university (n=585) completed an online survey on alcohol and energy drink consumption. For every one unit of energy drink consumed in the past 30 days, the likelihood of consuming alcohol in the past month increased by 80% (OR = 1.8), the likelihood of undertaking an episode of heavy drinking[4] in the past two weeks increased by 80% (OR = 1.8) and the likelihood of consuming energy drinks mixed with alcohol in the past month increased by 90% (OR = 1.9). An increased energy drink consumption was significantly associated with a higher quantity of alcohol consumed during a single event (p<0.001). For every one unit increase in energy drink consumption in the past week, the likelihood of consuming alcohol in the past two weeks increased by 70% (OR = 1.7), the likelihood of experiencing an episode of heavy drinking in the last two weeks increased by 80% (OR = 1.8) and the likelihood of consuming energy drinks mixed with alcohol in the past month increased 140% (OR = 2.4). An increased energy drink intake was significantly associated with a higher alcohol intake during a single drinking session (p<0.001). As alcohol use increased, past month energy drink use also increased from a mean of 0.9 days per month (no alcohol use) to 3.9 days per month (heavy drinkers with at least one episode of heavy drinking[4] in the past two weeks). Past week energy drink use increased from a mean of 0.4 times to 1.2 times per week (p<0.0001) (Velazquez et al, 2011).

29. A web-based survey of 465 Canadian college students (56% female) was used to investigate whether consumption of energy drinks mixed with alcohol is associated with heavy drinking, stimulant drug use and alcohol related consequences. Students who reported drinking alcohol mixed with energy drinks in the past 30 days scored higher on the risk taking measure than those who did not (p<0.001). Even after controlling for age, gender and risk taking propensity, consumers of energy drinks were statistically more likely to consume a larger number of drinks per day, consume alcohol on a greater number of days in the 30 days prior to interview, show an increased level of episodic drinking[4] and increased number of days intoxicated in a typical week compared to non-drinkers of energy drinks (p<0.001). After controlling for age and sex, consumption of alcohol mixed with energy drinks was significantly associated with consumption of amphetamines (p<0.001), cocaine and all stimulants (p<0.01). After controlling for heavy episodic drinking or risk taking propensity, this association was no longer statistically significant. After controlling for age and sex, drinkers of energy drinks were more likely to have driven home after drinking or been in a verbal fight (p<0.01); been in a car driven by someone who had been drinking, been hurt or injured or experienced one or more negative consequences (those previously mentioned plus being in a physical fight, requiring medical treatment, being taken advantage of sexually and taking advantage of someone else sexually) (p<0.001) than non-drinkers of energy drinks. After adjusting for age, sex and heavy episodic drinking the relationship was significant for being driven home by a driver who had been drinking or being hurt or injured (p<0.05) and one or more negative consequences (p<0.001). After adjusting for age, sex, heavy episodic drinking and risk taking propensity, the relationships were the same as previously plus driving home after drinking (p<0.05). It is not clear how blinded this study was and therefore there may be underreporting of consumption or consequences (Brache and Stockwell, 2011, a copy of this paper can be found in annex 2).

[4] Defined as 4 or more alcoholic drinks in one drinking session for females and 5 or more for males.

30. A study in high school pupils looked at caffeine consumption at 7th grade (age 12-13) and then use of caffeine, nicotine and alcohol a year later. Those pupils who had higher caffeine consumption at 7th grade were more likely to smoke and to consume greater quantities of alcohol a year later than those pupils who consumed lower levels of caffeine in 7th grade (Collins et al, 2011).

31. In a field study of 697 bar patrons, breath alcohol was assessed and a face to face interview and self-administered questionnaire were used to identify the type of drinks consumed. After adjusting for number of drinks consumed and other potential confounders, individuals who consumed alcohol mixed with energy drinks were at a 3-fold increased risk of leaving a bar highly intoxicated (breath alcohol ≥0.08g/210L) as well as a 4-fold increased risk of intending to drive compared to other drinking patrons who did not consume alcohol mixed with energy drinks (Thombs et al, 2010). In a study by the same authors using a proportion of the sample of bar patrons above, consumers of diet cola drink mixers were found to have a mean blood alcohol level that was significantly higher than those consuming regular (sucrose sweetened) cola and other, non-caffeinated mixers ($p<0.001$); no difference was observed between consumers of diet cola mixers and energy drink mixers ($p=0.108$). The authors cite several laboratory studies in which gastric emptying has been significantly slower following consumption of sucrose sweetened drinks when compared to artificially sweetened drinks that may go some way to explain why breath alcohol levels were lower in those consuming sucrose sweetened beverages (Rossheim and Thombs, 2011).

Does caffeine counteract the neuro-cognitive effects of alcohol consumption? (Copies of the papers in this section can be found in annex 2 including details of the tasks used to assess each parameter).

32. There is some evidence that caffeine can ameliorate some of the effects of alcohol but the mechanisms for this activity are still unclear. There are also several studies that discount this hypothesis. In a review of the data up until 1988, the authors stated that the variation in dose of both caffeine and alcohol along with performance indicators used and study design did not allow simple conclusions to be drawn in this area (Fudin and Nicastro, 1988).

33. Eight healthy male volunteers were given 0.8 g/kg bw alcohol (unclear if figure represents pure alcohol or alcoholic beverage) or placebo and/or 400 mg caffeine in a gelatine capsule (mean 5.6 mg/kg bw) or placebo (lactose) in a randomised cross over trial. The alcohol was administered in the form of an orange juice solution using peppermint to mask the placebo drink; it is not clear whether this was an adequate placebo but the authors claimed the study to be double-blind. Simple reaction time (SRT) was measured using the mean time taken to respond to visual stimuli (30 stimuli over 2 minutes). They showed an increase in SRT following alcohol consumption compared to baseline ($p<0.01$), that was ameliorated by caffeine. The results were not statistically significantly different between the alcohol with caffeine group and the placebo group. Statistically significant differences were not observed between any treatments in tests designed to measure reflex rate and arousal. Subjective feelings of “drunkenness” were elevated when alcohol (with or without caffeine) was consumed but not feelings of depression, anxiety or drowsiness (Azcona et al, 1995).

34. In a placebo controlled cross over trial in healthy male adults, 4.4 mg/kg bw caffeine or a placebo (lactose) given in the form of a capsule was administered along with 0.58 g vodka (40% ABV)/kg bw, (calculated to be 0.18 g/kg bw alcohol) mixed with orange juice in a 1:1.5 mixture. A placebo beverage consisted of orange juice and water with a vodka float to give an initial odour and taste of alcohol. It is not clear how effective this was as a placebo. A battery of tests designed to measure compensatory tracking, divided attention, visual backward masking and critical tracking were carried out. In these tests, caffeine was found to off-set many of the alcohol related impairments on alertness, tracking, visual search and

reaction time, but the rate of information processing when impaired by alcohol was not improved by caffeine administration (Burns and Moskowitz, 1990).

35. In a randomised cross-over study, 26 healthy male volunteers consumed 3.57 g/kg bw of an energy drink (calculated to be 1.14 mg/kg bw caffeine) mixed with 0, 0.6 or 1 g/kg bw vodka (calculated to be 0, 0.18 or 0.3 g/kg bw alcohol) or vodka alone. The authors stated that this trial was double blind using peach squash as a mask for the flavours of energy drink and vodka but no independent test of blindness appears to have been carried out and no placebo was given. Breath alcohol was not significantly different between the alcohol and energy drink group and the alcohol group. Tests of motor co-ordination and visual reaction time were carried out before and after consumption of the alcohol and/or energy drink. Consumption of energy drink and alcohol reduced perception of headaches, dry mouth, weakness and motor co-ordination compared with vodka alone. However the combination did not significantly reduce deficits caused by vodka on objective motor co-ordination and visual reaction time (Ferreira et al, 2006). In another study by the same authors, 14 healthy male volunteers consumed the same amounts and combinations of energy drink and vodka (although only the 1g/kg bw vodka dose was used). Following dosing, individuals completed a physical test on a cycle ergometer. Blood pressure, blood alcohol, oxygen uptake (VO_2), ventilator threshold, ventilation, glucose, insulin, dopamine, adrenaline, adrenocorticotropic hormone and cortisol were found to be similar between groups but heart rate, blood lactate and noradrenaline were statistically significantly higher and the respiratory exchange rate statistically significantly lower in the vodka and vodka plus energy drink groups compared to the energy drink group alone. No statistically significant differences were observed between results from the alcohol group and the alcohol plus energy drink group (Ferreira et al, 2004a).

36. In a placebo controlled study designed to measure inhibitory control, 35 healthy male volunteers were divided into 5 groups. The groups were given either 0.62 g/kg bw alcohol with a carbonated mixer (identity not specified) (A), the same dose of alcohol plus behavioural reinforcement (B), alcohol plus 4.4 mg/kg bw caffeine (C), alcohol plus caffeine plus behavioural reinforcement (B+C) or placebo (P) who received a non-alcoholic beverage with 5ml of alcohol on the surface of the drink and sprayed with alcohol mist to give a strong alcohol scent (in previous research, participants reported that this drink contained alcohol). Inhibitory control was measured using a go-stop choice reaction time task. The behavioural reinforcement involved financial incentives for an individual to exceed their baseline score following treatment. Drinking habits, baseline scores and breath alcohol concentrations did not differ between groups. Compared to before treatment, the mean number of inhibitions were significantly reduced in group A, but this reduction was completely reversed in groups B, C and B+C with these groups showing better inhibitory control compared to baseline. No effects were observed on reaction time (Fillmore and Vogel-Sprott, 1999).

37. In a double blind study of 10 female volunteers, 5 of whom were regular smokers and 5 non-smokers, participants were given 30 g 80% proof vodka (0.18 g/kg bw assuming a 60kg adult[5]) or placebo. The placebo drink consisted of 200ml orange juice diluted with 30g water and the rim of the glass smeared with vodka to give an initial olfactory cue. No independent test of blindness appears to have been carried out. Additionally a 300mg caffeine capsule (5 mg/kg bw assuming 60kg adult) or sucrose placebo and 2mg of nicotine polacrilex gum or placebo gum were given in all 8 possible combinations in a randomised order with volunteers acting as their own controls. Tasks to measure choice reaction time, compensatory tracking (to measure divided attention), critical flicker fusion (measures

[5] Calculated assuming 30g vodka is equal to 30ml and using calculator available at http://www.cleavebooks.co.uk/scol/ccalcoh4.htm. This is quite a low dose of alcohol, although the Authors consider this to be equivalent to 3 glasses of wine. There may be a typing error in this publication.

arousal) and short term memory were carried out before and 1, 2, 3 and 4 hours after treatment. One-way ANOVAs were carried out using the results from each task followed by Tukey's HSD post-hoc pair-wise test. Caffeine appeared to antagonise the effects of alcohol in short term memory and choice reaction time although these were not statistically significant. Caffeine appeared to antagonise the effects of alcohol on mean tracking performance to a statistically significant degree ($p<0.05$) (Kerr et al, 1991).

38. In a double blind study, 12 healthy young adult volunteers were given 0.65 g/kg bw alcohol or placebo and/or 2 or 4 mg/kg bw caffeine or placebo dissolved in a carbonated lemon mixer. Each individual received all combinations in a randomised order thus acting as their own controls. The placebo beverage consisted of the same volume of lemon soda with 3ml of alcohol floated on the surface and the glass sprayed with an alcohol mist. Previous studies by these authors have reported that volunteers believe that this placebo drink contains alcohol. Following dosing, individuals undertook a split attention task using prolonged reaction time to complete the second of two tasks as an indicator of performance. A 2 (gender) x 2 (alcohol dose) x 3 (caffeine dose) mixed design ANOVA of the scores from the task and T-tests showed that both doses of caffeine had a non-uniform counteracting effect on various aspects of performance impaired by alcohol. Speed of reaction was restored by caffeine, but not accuracy. Also participants reported feeling less intoxicated when caffeine was co-administered than when alcohol was administered alone despite the fact that aspects of their performance were equally impaired including accuracy (Marczinski and Fillmore, 2006).

39. In a study by the same authors, using the same number of participants and doses of alcohol and caffeine, a cued go/no-go task was used to assess performance. Using a 2 (alcohol dose) x 3 (caffeine dose) x 2 (cue) ANOVA it was found that the high dose of caffeine statistically significantly antagonised alcohol effects on response execution (results did not differ significantly from controls, $p>0.55$) but had no effect on inhibitory control ($p > 0.81$) (Marczinski and Fillmore, 2003).

40. In a randomised, double blind placebo controlled study, 56 healthy young adults were allocated to four groups to receive either A) vodka (0.65 g/kg bw alcohol), B) energy drink (1.2 mg/kg bw caffeine), C) vodka and energy drink (same doses as groups A and B) and D) placebo. Forty five minutes after dosing, participants started a 25 minute cued go/no go task to measure response activation and inhibition. A mixed design ANOVA, where alcohol and energy drink doses were treated as between subject factors and cue was treated as a within subject factor, followed by post-hoc 1 sample t-tests demonstrated that alcohol alone significantly slowed reaction time following the invalid no-go cue ($p=0.02$) but was unchanged from baseline following administration of placebo, energy drink or vodka and energy drink. For the valid go cue, mean reaction time was significantly faster when placebo, energy drink or vodka mixed with energy drink were administered ($p<0.05$) but unchanged from baseline when vodka was administered ($p=0.13$). Response inhibition failures increased from baseline for the invalid go cue condition under all dose conditions ($p<0.03$) indicating poorer inhibitory control and for the valid no-go cue response inhibition failures were significantly increased when vodka was administered alone ($p<0.05$) but unchanged from baseline when placebo, energy drink or vodka mixed with energy drink were administered ($p<0.27$). The authors concluded that energy drinks antagonised the effects of alcohol on reaction time but not those on reaction inhibition. Subjective ratings showed that energy drinks escalated reported levels of stimulation but did not alter the alcohol effects observed for other ratings such as level of intoxication and perceived ability to drive (Marczinski et al, 2011).

41. In a randomised double-blind placebo controlled study, 127 young adult volunteers were divided into 4 groups and received (1) caffeinated beer, (2) non-caffeinated beer, (3) caffeinated non-alcoholic beer or (4) non-caffeinated non-alcoholic beer. Alcohol

consumption was equivalent to 1.07 g/kg bw for men and 0.92 g/kg bw for women and caffeine consumption was on average 383 mg caffeine for men (5.47 mg/kg bw assuming 70kg) and 338 mg (5.63 mg/kg bw assuming 60kg) for women. Thirty minutes after dosing volunteers performed a driving simulator task and a sustained attention/reaction time task. The effects of alcohol were statistically significant on a number of variables tested in the driving simulator including speed variability, lane position variability, number of crashes and sustained attention/reaction time and were higher, but not statistically significantly so, in speed deviation. Caffeine produced no measurable counteraction on performance detriments produced by alcohol except on lane position variability where a small, non-statistically significant improvement was observed compared to those consuming non-caffeinated beer. Self estimates of breath alcohol concentration were used to assess the awareness of the degree of intoxication. From this the authors concluded that individuals who had consumed alcohol were able to identify their level of intoxication accurately whether or not they had consumed caffeine as well (Howland et al, 2011).

42. Twenty eight social drinkers of alcohol (between 5 and 35 units per week for females and 10-50 units per week for males) who were also light caffeine consumers (more than 1 caffeinated beverage per week but less than 2 per day) aged between 18 and 40 were recruited. Volunteers attended 5 afternoon sessions approximately a week apart with the first acting as a pre-study screening/baseline session. During subsequent sessions, volunteers were given either a placebo drink (tonic water plus lime cordial, chilled) or a drink containing alcohol (0.6g/kg), caffeine (2mg/kg) or both (drink volume not provided so cannot calculate approximate doses). Participants completed a number of computer tasks (Stroop test, Go/no go task, stop-signal task and a simple reaction time task) after consumption of the test drink and completed questionnaires both before and after drink consumption on alcohol craving, anxiety state alcohol intoxication and mood. Before leaving, volunteers were asked to state if they believed their drink contained alcohol. No difference was observed between the alcohol and caffeine alcohol groups in simple reaction time ($p=0.34$), go-no go errors ($p=0.67$) and Stroop test ($p>0.17$). In the stop signal task, more omission errors were seen following consumption of alcohol alone compared to placebo and caffeine and alcohol ($p=0.016$). Significantly more commission errors were observed after consumption of alcohol alone compared to consumption of alcohol and caffeine ($p=0.04$). Ratings of stimulation decreased over time in the alcohol and placebo conditions and increased following consumption of alcohol and caffeine although these were not statistically significant ($p>0.1$) (Attwood et al, 2011).

Caffeine and alcohol may interact through their effects on the adenosine receptor

43. Recently it has been proposed that the actions of alcohol are mediated via the adenosine A_2 receptor; with in vitro and in vivo studies showing an increase in extracellular adenosine following exposure to alcohol (Mailliard and Diamond, 2004; Sharma et al, 2010). Rats trained to self administer alcohol showed decreased alcohol consumption when given adenosine A_2 and dopamine D_2 receptor antagonists compared to controls; rats given an adenosine A_1 antagonist showed no differences in alcohol consumption from controls (Arolfo et al, 2004). Using measures of motor impairment in mice and rats, caffeine attenuated alcohol-induced motor inco-ordination and rapid development of tolerance to alcohol, along with an adenosine A_1 receptor antagonist and a dopamine D_1 receptor antagonist. Antagonists of the adenosine A_{2A} and dopamine D_2 receptors did not alter alcohol induced effects (Batista et al, 2005; Connole et al, 2004; Dar et al, 1987; Dar and Wooles, 1986). Evidence for a direct pharmacodynamic interaction between alcohol and caffeine is not available.

Expectation of effect may be related to actual effect

44. There is evidence to suggest that the expectation of behaviour of individuals following consumption of alcohol and / or caffeine can influence their actual behaviour. In a blinded trial of 50 healthy male volunteers receiving 0.56 g/kg bw alcohol, individuals were allocated to one of four treatment groups with 2 groups told they were receiving caffeine and 2 groups told that they were not. Of those told that they were receiving caffeine, one group was given 4.4mg/kg bw and the other received no caffeine. Of those told that they were going to receive no caffeine, one group was given 4.4mg/kg bw caffeine and the other received no caffeine. There was also a no treatment control group. Before the treatments, individuals were asked to rate their expected responses to the combination of caffeine and alcohol. All participants undertook a computerised pursuit rotor task that required psychomotor coordination. History of alcohol and caffeine consumption and blood alcohol levels did not differ between groups. Individuals receiving alcohol and caffeine showed improved performance compared to those who received alcohol alone regardless of the treatments expected. Expecting to receive caffeine showed no overall effects on impairment compared to the other groups. However, those who expected significant impairment of activity and received both caffeine and alcohol showed the greatest degree of impairment in the task (Fillmore and Vogel-Sprott, 1995).

45. In a randomised placebo controlled trial, 60 healthy adult coffee drinkers were given either 280 mg caffeine (4.6mg/kg bw caffeine assuming a 60kg adult) dissolved in decaffeinated coffee or decaffeinated coffee alone (placebo coffee). All volunteers were told that they were receiving coffee with a large dose of caffeine. Each dose group was divided in two with half told that caffeine improves performance and half told that it impairs performance and “makes learning less efficient”. Measures of sustained attention and psychomotor speed were taken as well as a measure of expectancies of the effect of caffeine on performance; performance was measured before and after coffee consumption. Individuals who consumed caffeine significantly improved their scores on all performance measures compared to baseline whereas those who did not consume caffeine did not demonstrate such improvements. According to the authors, individuals given placebo coffee and told that performance would be impaired by caffeine significantly reduced their reaction time (mean = -10.08ms, SE = 10.67, $p<0.05$) and improved their accuracy (mean = 2.67, SE = 2.33, $p<0.05$) and those given placebo coffee and told that caffeine would enhance their performance increased their reaction time significantly (mean = 20.62ms, SE = 10.67, $p<0.05$) and reduced their accuracy (M = -4.33, SE = 2.33, $p<0.05$). In those given coffee with caffeine no effects of expectation were observed. The authors comment that their results could be due to the reversal of withdrawal effects as volunteers were asked to avoid caffeine for at least 17 hours prior to participation therefore the validity of this study is questionable (Harrell and Juliano, 2009).

“Polysubstance use” and genetic factors

46. There has been some suggestion that high caffeine use may be a marker for the use of other drugs, legal or not, and other addictive behaviours such as excessive gambling or internet use (Kaminer, 2010; Pallanti et al, 2006).

47. Data were collected on three consecutive annual interviews from 1097 college students from a large US university (same sample as Arria et al, 2011). Results indicated that the number of energy drink consumers increased as participants passed through college (22.6% respondents in year 2 vs 36.5% in year 3). Energy drink users from year 2 were significantly more likely to have initiated consumption of medical prescription stimulants for non-medical use ($p<0.001$) and prescription analgesics ($p<0.05$) but not other drugs such as marijuana (Arria et al, 2010).

48. In a meta-analysis of alcohol, caffeine and tobacco use, the authors concluded a moderate to strongly significant relationship between alcohol and tobacco use and tobacco and caffeine use, but only a weak relationship between caffeine and alcohol use (Istvan and Matarazzo, 1984).

49. In four studies using a cohort of male and female mono- (n=774) and dizygotic (n=809) twin pairs, structured clinical interviews were carried out to ascertain level of caffeine consumption; lifetime histories of major depression, generalised anxiety disorder and panic disorder, alcohol and nicotine dependence, adult anti-social behaviour and cannabis/cocaine abuse/dependence. In one of the studies, maximal lifetime caffeine intake, caffeine associated toxicity[6] and dependence were significantly and positively associated with the psychiatric and substance use disorders studied including alcohol dependence. When controlling for genetic and family environmental factors using monozygotic twins these associations were found to be positive but not significant. The authors suggested that most of the observed associations are not causal and that familial factors, which are in part genetic, predispose to both caffeine intake, toxicity and dependence and the risk for a broad array of internalising and externalising disorders (Kendler et al, 2006). The second study used a number of models to attempt to identify the genetic and environmental factors affecting high caffeine intake and its links to use of other substances of abuse, either legal or not. The best fitting model used two genetic factors and one individual environmental factor with the first genetic factor linked to cocaine and cannabis dependence and the other alcohol and nicotine dependence. The second best fitting model included one illicit drug genetic factor for cannabis and cocaine and another legal drug factor for alcohol, caffeine and nicotine. In both models, large substance-specific genetic effects were found for nicotine and caffeine (Kendler et al, 2007). The third study used multivariate structural equation modelling to determine the sources of covariation between the use of caffeine, alcohol and tobacco. Shared genetic risk factors across the three substances accounted for between 7 and 28% of the total variance and 12-56% of the genetic variance. The authors concluded that common familial environmental factors appear to play little or no role and that underlying genetic and individual environmental risk factors produce liability to polysubstance use in general and that substance-specific factors also play an important etiologic role (Hettema et al, 1999). The final study by this group looked at the effect of age on the covariance of alcohol, caffeine and other substances. They concluded that use of these substances earlier in life was strongly influenced by social and familial environmental factors whereas later use was influenced by genetic factors (Kendler et al, 2008).

50. 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 ($p<0.001$); tetrachoric correlation 0.29 ($p < 0.001$)] and heavy smoking and heavy coffee consumption [phenotypic Pearson correlation r=0.28 ($p<0.001$); tetrachoric correlation 0.29 ($p<0.001$)] were significantly associated, whereas heavy coffee consumption and heavy alcohol consumption were not [phenotypic Pearson correlation r=0.14 ($p<0.001$); tetrachoric correlation -0.04 ($p<0.01$)]. Common genetic factors accounted for 35% to 78% of the total genetic variance in heavy substance use, but a substantial amount of genetic variance remained specific to the three substances. No mention of caffeine sources other than coffee is made (Swan et al, 1997). Comparisons between di- and monozygotic twins showed that there was a statistically significant likelihood that coffee and alcohol consumption had a genetic basis (intrapair correlations between mono- and dizygotic twins 0.47 vs 0.32 for alcohol and 0.34 vs 0.17 for coffee) and that using a number of models to determine the best fit, co-consumption of alcohol, coffee and nicotine were also found to have a genetic basis (Swan et al, 1996).

[6] Defined by the authors as "feeling ill, shaky or jittery after drinking caffeinated beverages".

51. From a population of 1925 patients who had voluntarily sought treatment for substance abuse disorders, a statistically significant relationship was found between the frequencies of use of caffeine, nicotine and alcohol, but not between caffeine and nicotine and other substances of abuse such as heroin, cannabis and glue (Kozlowski et al, 1993).

52. In a sample of 105 Israeli alcoholics undergoing treatment, caffeine and alcohol consumption were statistically significantly correlated ($p<0.05$). When the sample was sub-divided into those with (n=62) and those without (n=43) a family history of alcoholism (defined as 1 primary family member meeting the DSM-IV criteria for alcohol dependence) no differences between the two groups were observed in alcohol or caffeine consumption (Amit et al, 2004; Kozlowski et al, 1993).

Case reports following consumption of caffeine alone or in combination with alcohol

53. The National Programme on Substance Abuse Deaths have identified eight case studies in the UK, through a literature search, in many of which the coroner has named caffeine alone or in combination with alcohol as a contributing factor to death (Corkery, 2012, see annex 3).

54. Analysis of phone calls to the New South Wales Poisons Information Service over a 7 year time period revealed that of 297 calls related to caffeinated energy drinks, 217 (73%) were a result of recreational exposure to energy drinks and the median age was 17 years. Co-ingestion of other substances was reported in 46% of calls with the most popular substances to be co-ingested being alcohol and other caffeine containing products. Twenty one calls reported signs of serious toxicity such as hallucinations, seizures and cardiac ischemia. At least 128 people sought or were advised to seek urgent medical attention of which 57 had not co-consumed other substances (Gunja and Brown, 2012).

55. A 17yr boy consumed 3 litres of energy drink combined with 1litre of vodka over the course of one evening containing a total of 4600mg of taurine and 780mg of caffeine mixed with 380g of alcohol. The next day after completing two 100m races, he began hyperventilating and vomiting. Following admission to hospital he suffered acute renal failure but had sufficiently recovered after 10 days to be discharged (Schoffl et al, 2011).

Animal studies

56. Due to the number of human studies on alcohol and caffeine, only studies using animals dosed with both alcohol and caffeine and using tests to determine measures of animal behaviour have been briefly outlined below:

57. Four groups of 16 Albino Swiss mice were administered an energy drink via gavage at doses of 0, 3.57, 10.71 and 17.86 ml/kg bw (equivalent to 0, 1.14, 3.42, and 5.7 mg/kg bw caffeine) in a range finding exercise. This was then repeated using four different doses of alcohol, 0.5, 1.0, 1.5 and 2.5 g/kg bw combined or not with 10.71 ml/kg bw of energy drink (equivalent to 3.42 mg/kg bw caffeine). Following dosing, animals were placed in a cage and activity measured using the number of interruptions of a light beam. All doses of energy drink administered alone were found to increase activity compared to controls. Total locomotor activity in 45 minutes was significantly different in all energy drink groups compared to controls ($p<0.01$) but an incremental relationship with dose was not observed. The 0.5 and 1.0 g/kg bw doses of alcohol significantly reduced the stimulatory effect of the energy drink at 15-30 minutes following dosing and tended to reduce this effect at 30-45 minutes. The alcohol dose of 1.5 g/kg significantly reduced the stimulatory effect of the energy drink at all time periods. The 2.5 g/kg bw alcohol dose significantly reduced the locomotor activity when administered alone compared to the control group at 30 and 45 minutes and this depressant effect was reduced by the co-administration of the energy drink. In the first 15 minutes

following co-administration of 2.5g/kg bw alcohol and 10.71ml/kg bw, locomotor activity was significantly increased compared to controls (Ferreira et al, 2004b).

58. Eight groups of six Long-Evans rats were allocated to the following treatments (figures in brackets indicate estimated maximum caffeine consumption in mg/kg bw/day):

Adequate diet – rat chow				Marginal diet – rice krispies			
32g rat chow		16g rat chow		23g rice krispies		11.5g rice krispies	
0.75mg/ml caffeine (68.5)	0.33 mcg/ml quinine	0.75mg/ml caffeine (88.5)	0.33 mcg/ml quinine	0.75mg/ml caffeine (36)	0.33 mcg/ml quinine	0.75mg/ml caffeine (50)	0.33 mcg/ml quinine

59. Caffeine and quinine were dissolved in the drinking water and alcohol solution. Rats received a 16-day acclimatisation phase with access to both 10% ethanol and tap water (which continued for the duration of the study) followed by a 24-day baseline phase with allotted diets in place; a-28 day caffeine or quinine phase then an 8-day baseline phase. In rats fed an inadequate diet, caffeine was found to significantly increase consumption of alcohol ($p<0.01$) in relation to quinine. No such effect was observed in animals fed an adequate diet (Gilbert, 1979).

60. Twenty one male Wistar rats were randomly assigned to one of 3 groups in which animals were given i.p. injections daily of either saline (control), or caffeine at levels of 5 or 10 mg/kg bw. For one hour each day during the acclimatisation and test phases and 30 minutes after each i.p. injection, all animals were given the choice of 10% alcohol or water. The test period lasted 20 days over which the alcohol consumption was observed. Animals given 5mg/kg bw caffeine increased their alcohol consumption significantly ($p<0.05$) compared to control animals and those receiving 10mg/kg bw caffeine. Animals given 10 mg/kg bw were not significantly different from controls. A subsequent experiment by the same authors used 40 male Wistar rats. The same protocol was followed except that animals were only exposed to caffeine during the test period and not in the acclimatisation period where they were all given saline injections. During the test phase, rats were administered either saline (control) or 2.5, 5 or 10 mg/kg bw caffeine. Animals given 5mg/kg bw caffeine showed a significantly higher ethanol intake compared to controls and the 2.5 and 10 mg/kg bw groups. Again, higher doses of caffeine were not associated with an increase in ethanol consumption (Kunin et al, 2000).

61. Adult male Long Evans rats were used (8 per group) in a model of cerebral ischemia to measure the effects of caffeine and alcohol on cerebral infarction. Animals were administered 0.65g/kg bw ethanol and 10 mg/kg bw caffeine with one group receiving ethanol first followed by caffeine 2 hours later and the other group receiving caffeine followed by ethanol. Reversible cerebral ischemia was induced for 180 minutes following which animals were sacrificed and the brains sectioned and analysed via computerised imaging software. In animals receiving ethanol first followed by caffeine, infarct volume was higher (121.4 +/- 32.6 mm^3) that in those receiving caffeine first (41.8 +/- 15.8mm^3). A similar experiment with 9 rats per group received the same doses of ethanol and caffeine but administered together by gavage. A saline solution was used as a control. Infarct volumes were higher in the saline controls (161.2 +/- 12.3 mm^3) compared to animals receiving caffeine and ethanol (88.5 +/- 16.0 mm^3) (Aronowski et al, 2003).

Summary

62. The increasing consumption of energy drinks containing caffeine mixed with alcohol has raised concerns over the physical and mental health effects of this combination of

psychoactive substances. The phenomenon known as “wide awake drunk” has been described where the stimulatory effects of caffeine prevent the consumer from realising how intoxicated they are, with the potential for increased toxicological damage and adverse behavioural effects occurring including increased risk taking, violence and criminal activity.

63. A body of work has looked into the physiological effects of the combination of caffeine and alcohol. Many of these studies have used driving simulators and doses of approximately 2-3 cups of coffee and 1-2 standard measures of vodka. Results were mixed, with some studies concluding that caffeine did not antagonise the physiological effects of alcohol and other studies showing that some key aspects of alcohol intoxication were ameliorated, especially motor reaction time, mean tracking performance and memory reaction time. In some studies the perception of degree of intoxication appeared to be altered by caffeine with individuals consuming alcohol and caffeine perceiving themselves to be less intoxicated that those consuming an equivalent amount of alcohol alone.

64. Surveys carried out in college aged adults showed an increased propensity for risk taking in groups who consume higher levels of caffeine and alcohol combinations compared to those consuming lower levels of these substances. Expectation of effect may shape the subjective and behavioural response to alcohol and to caffeine.

65. A large number of studies have looked at the use of caffeine and how this is associated with the use of other substances of abuse. There seems to be an association between severity of alcoholism and caffeine and nicotine use. Analysis of studies in monozygotic twins has shown that these effects do not appear to be causal with familial factors, partly genetic, predisposing for a higher intake of caffeine and dependence. Excessive consumption of caffeine also appears to be associated with an increased risk for a wide range of psychiatric disorders.

66. A significant number of studies have been carried out in human subjects, but some animal studies are available.

Questions for the Committee:

i. Are members able to come to any conclusions on the possible health effects of combined alcohol and caffeine consumption?

ii. Do members feel that the studies on the physiological effects of alcohol and caffeine indicate a direct interaction between the two substances and can they comment on whether there is sufficient information to conclude that there is a chemical interaction or whether the two substances have competing effects on different neural pathways.

iii. Can members comment on the described “wide-awake drunk” phenomenon and can it be concluded that the potential for adverse effects from alcohol and caffeine combined is higher than when consumed individually.

iv. Can the Committee comment on the importance of “expectation of effect” on the actual effect of alcohol or caffeine when consumed together.

v. What conclusions are the Committee able to draw on the perceived association between caffeine consumption and the use of other legal and illegal stimulant drugs?

vi. From the evidence available, are members able to identify potential data gaps.

Secretariat
March 2012

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

The interaction of caffeine and alcohol and their combined effects on health and behaviour

Annex One: 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 have been included in the literature review. Some references that were not included by the SCF but published prior to 2003 have come to light through searching the reference lists of published papers. When considered relevant, these have been included in this paper. Due to the availability of human studies, most animal studies have not been included in the paper unless considered extremely 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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March 2012

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

The interaction of caffeine and alcohol and their combined effects on health and behaviour

This annex contains 15 published papers.

NOTE: For copyright reasons these papers are not included in the paper on the COT website. They are in the public domain and individuals can obtain them by application to appropriate sources.

O'Brien, M C, McCoy, T P, Rhodes, S D, Wagoner, A, and Wolfson, M (2008) Caffeinated cocktails: energy drink consumption, high-risk drinking, and alcohol-related consequences among college students. Acad.Emerg.Med **15** (5) 453-460

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Azcona, O, Barbanoj, M J, Torrent, J, and Jane, F (1995) Evaluation of the central effects of alcohol and caffeine interaction. Br.J Clin Pharmacol. **40** (4) 393-400

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Howland, J, Rohsenow, D J, Arnedt, J T, Bliss, C A, Hunt, S K, Calise, T V, Heeren, T, Winter, M, Littlefield, C, and Gottlieb, D J (2011) The acute effects of caffeinated versus non-caffeinated alcoholic beverage on driving performance and attention/reaction time. Addiction **106** (2) 335-341

Attwood, A S, Rogers, P J, Ataya, A F, Adams, S, and Munafo, M R (2011) Effects of caffeine on alcohol-related changes in behavioural control and perceived intoxication in light caffeine consumers. Psychopharmacology (Berl) (Online only)

Secretariat
March 2012

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

The interaction of caffeine and alcohol and their combined effects on health and behaviour

This annex contains a submission from the Director of the National Program for Substance abuse deaths outlining a number of case reports where caffeine either alone or in combination with alcohol has been named by the Coroner as contributing in some way to the cause of death.

Secretariat
March 2012

Committee on Toxicity review of behavioural and other effects of caffeine and alcohol

UK fatalities associated with caffeine

Background and methodology

Fatalities due to caffeine are not monitored in the UK. The National Programme on Substance Abuse Deaths is aware of caffeine being used as a 'cutting' agent in street drugs and 'legal highs' (see also Cole et al, 2011). The results of recent research undertaken by Davies et al (2011) in respect of the caffeine content of 'legal highs' may be worth consideration. Six novel psychoactive products ('legal highs') that were not declared to contain caffeine were purchased from different Internet suppliers; one additional product was supplied by the UK police force. Analysis of these seven products, which weighed approximately 1 g each, contained only caffeine as the active pharmacological compound. There was significant variation in the percentage caffeine content (<2 to 96%), with four powders containing very significant caffeine contents of 87-96%. The authors conclude that individuals are at risk of significant caffeine toxicity related to the high caffeine content of some novel psychoactive substances. Clinicians, including clinical pharmacologists, need to be aware of this to ensure that the management of acute recreational drug toxicity is appropriate and that over-correction of any hypokalaemia does not occur.

There seems to have been only a few possible cases in the UK where caffeine may have had a role in causing or contributing to death. None of these cases were reported to np-SAD as they do not meet our case criteria (Controlled Drug present in post-mortem toxicology, psychoactive drug causing or contributing to death; history of drug use or addiction - see Ghodse et al, 2010); one case does now appear to meet our criteria and will be added to the database.

However, through searches of Medline and the Internet it was possible to identify several deaths where caffeine was thought to have possibly played a part. The search terms used included: 'death', 'fatality', 'caffeine', 'inquest', 'coroner', 'poisoning', 'overdose'. Searches were restricted to the UK. This compilation is not exhaustive but does cover a range of possible associations between the ingestion of caffeine and fatalities. The cases are dealt with by date of inquest.

Case 1

In August 2002, Dr Lawrence Addicott, HM Coroner for Cardiff and Vale of Glamorgan, recorded a verdict of suicide in the case of James Bird, a chemistry student aged 20, who was found dead on 31 January in his halls of residence at Cardiff University. He had left handwritten notes in his room, one of which gave calculations showing how much caffeine was required to kill someone. He had also visited Internet websites looking at the effects of caffeine. Supermarket receipts found at the scene showed that on 24 January the deceased had bought 4 boxes of Pro Plus, each containing 96 tablets. The pathologist reported that the blood level of caffeine was 150mg/100ml (1500mg/L), sufficient to cause death.
http://www.guardian.co.uk/education/2002/aug/30/highereducation.uk/print
http://www.telegraph.co.uk/news/1405785/Student-died-overdosing-on-caffeine.html

Case 2

In April 2004, Mr Stanley Hooper, HM Coroner for South Yorkshire East, recorded a verdict of accidental death in the case of Lee Foster, aged 21, whose car suddenly swerved off a motorway link road and crashed at nearly 90mph into a barrier at 3 am. He was not wearing his seat-belt and was thrown from the car. He had spent the evening out, in December 2003, with friends but had not apparently consumed any alcohol or drugs, but had drunk 4 cans of "Red Bull". Mr Hooper his "irrational" driving which had happened "dramatically and very quickly" shortly before the crash. He continued: "This young man was driving in a manner that was quite out of character. One cannot say it was definitely the caffeine in his body but there is no other explanation that is apparent."
http://www.thestar.co.uk/news/caffeine_death_crash_warning_1_321252

Case 3

In April 2008, Mr Nicholas Gardiner, HM Coroner for Oxfordshire, recorded a verdict of natural causes in the case of Alfredo Duran, aged 40, who collapsed in an aisle in the supermarket where he had completed his regular night shift. Paramedics were summoned to the scene in September 2006 but were unable to resuscitate him. Colleagues said that they usually found at least 4 empty cans of Red Bull when the deceased worked. The pathologist said that the amount of caffeine (unstated in media reports) found at post mortem could have triggered a cardiac arrest because the deceased had an enlarged heart. He said: "For an individual with this condition, the risk of problems with the heart is increased by stimulants such as caffeine and may be triggered by levels which would have no effect on people with a normal heart. My feeling is, given the evidence available, it was a cardiac arrest, possibly contributed to by sub-toxic caffeine ingestion." The Coroner described the deceased as a healthy man and likened his death to Sudden Adult Death Syndrome, but recorded the cause of death as "unascertained".
http://www.metro.co.uk/news/144543-man-killed-by-4-cans-of-red-bull-a-day
http://www.telegraph.co.uk/news/uknews/1902897/Drinking-Red-Bull-could-have-killed-man.html
http://www.mirror.co.uk/news/uk-news/did-red-bulls-kill-shift-worker-304608

Case 4

In March 2010, Mr Alan Walsh, HM Deputy Coroner for West Manchester, recorded a verdict of accidental death in the case of Neil Molyneux, aged 33, who died at home on 9 January. After his mother had retired to bed at 23:30, it appears that the deceased had made himself and consumed a milkshake containing what he thought was a protein supplement. His mother was awoken at 03:30 by a banging noise and went to her son's bedroom where she found their pet dog thrashing about on the floor. Her son said the dog was having a fit and told her to go back to bed. She found the dog dead later in the morning. When she returned from work she found her son lying on his bed in the usual position in which he slept, and recognised that he was dead. The deceased had apparently found the "protein supplement" at a relative's home which the deceased had rented out, and had intended to use it in combination with working out in the hope that it would assist in his recovery from an injury. The contents of the container holding the "supplement" were found on analysis to contain 95% caffeine; more than 30 times the typical amount found. It appears the dog had licked the jug used to make the milkshake. The Coroner found the cause of death to be a caffeine overdose, saying: "[the deceased] took this powder without any indication that it would harm him, his death was sudden and unexpected and his actions had unintended consequences. Caffeine is not an illegal substance but anybody who takes it must be aware that it poses grave danger to their health and could result in their death.
http://www.wigantoday.net/news/local-news/man_is_killed_by_massive_caffeine_overdose_1_16764

Case 5

In August 2010, Mr Peter Bedford, HM Coroner for Berkshire, recorded a narrative verdict in the case of Sean/Shaun Biggs, aged 21, who died in hospital on 1 January 2010. The deceased, together with a number of friends, went out to celebrate New Year. They first consumed vodka and Red Bull purchased from a local shop, and then went a pub and a restaurant. Later in the evening, he had an argument with one of his friends and had become very irate. Shortly afterwards he collapsed in his bedroom, feeling cold to the touch. He was taken to hospital where he later died. The post mortem blood alcohol level was found to be 76mg/dL; caffeine was also detected but was not sufficient to be quantified. The coroner concluded that the deceased had died from Sudden Adult Death Syndrome and suffered a natural, sudden cardiac arrest. The deceased's father was reported as saying that his son's confrontation could have caused an adrenalin surge, and that the energy drink was also a contributory factor.
http://www.getreading.co.uk/news/s/2092873_dads_fears_over_energy_drinks
http://www.gethampshire.co.uk/news/s/2075986_shaun_biggs_dad_denies_sons_death_was_natural

Case 6

In February 2009 Mr Geoffrey Saul, HM Coroner for the East Riding of Yorkshire & Hull, recorded a verdict of natural causes in the case of Chloe Leach, aged 21, who died in September 2008 from cardiac arrhythmia (Long QT Syndrome); she was also epileptic. Media reports suggest that she had consumed 4 cans of Red Bull energy drink before collapsing at a club in Hull, and that the caffeine could have pushed her heart over the 'upper limit of normal' into abnormal. Following a conversation between the compiler and Mr Saul, the latter has now provided us with some details of the case, including the statements from the toxicologist and pathologist involved in the case.
http://www.upi.com/Top_News/2009/02/03/Caffeine-blamed-for-students-death/UPI-47841233720345/

The toxicologist states that the deceased was understood to have consumed 2 'Red Bulls', 2 vodkas, and 2 'Red Bull' and vodka combined. The toxicology results were: blood alcohol level of 153mg/dL on admission to hospital, and 143mg/dL at post mortem (PM). On admission there was a blood Lamotrigine (anti-epileptic) concentration of 3.5mg/l, PM blood concentration of 1.9mg/l and PM gastric concentration of 0.5g/l; these are consistent with therapeutic use. The PM blood caffeine level was 7.2mg/l. This level is likely to indicate the consumption of more than 1 to 2 cans of Red Bull or Coca Cola, and would be consistent with the possible 4 to 6 cans of Red Bull that had been ingested on the evening prior to death.
The deceased's mother suffered from Long QT Syndrome. If the deceased had not been previously tested, there was a possibility she also had undiagnosed Long QT Syndrome. The toxicologist was of the opinion that "caffeine will have had the effect of increasing the risk of arrhythmias". He concluded that:
1. ... [T]he caffeine is likely to have had a more than minimal contribution to the risk of arrhythmias in an individual who may have suffered with Long QT Syndrome.
2. [he] had not been provided with evidence that [the deceased] ... did indeed suffer with Long QT Syndrome, but there is a family history of such a condition.
3. Arrhythmias in Long QT Syndrome may also be precipitated by stressful environments, excessive physical activity and loud noises.
4. [The deceased] also suffered with epilepsy and although her anti-epileptic medication was within the therapeutic range, there was an increased risk of epilepsy with increased stressful response and sudden loud noises.
5. It is therefore [his] ... overall opinion that although there may well be an increased risk of death due to caffeine and possible Long QT Syndrome, [he] ... cannot exclude from the information provided ... that epilepsy has not had a more than minimal contribution to the mechanism of death.

Evidence given by the Consultant Neuropathologist indicated that an earlier ECG performed on the deceased showed a QT interval at the upper limit of normal. Her mother had a similar diagnosis, but combined with "ventricular bigeminy and unimorphological ventricular ectopics". There was, in addition, T-wave inversion in the antero-lateral leads". One of the deceased cousins died at the same age of "myocardial insufficiency secondary to cardiomegaly". It appears that the deceased had not had a seizure.

The pathologist concluded: "It is not unreasonable to suppose, therefore, that [the deceased] ... was a victim of a familial syndrome of epilepsy in association with a prolonged QT interval. This syndrome can result in polymorphic ventricular arrhythmias (torsade de pointes) and these arrhythmias can result in recurrent syncopes, seizures and sudden death. Given the history of sudden death in two cousins at the age of 21, and cardiac arrest in her mother, it may be prudent to refer other family members for genetic counselling to confirm or refute the presence of the long QT or other syndrome in this extended family. Other causes of death are not excluded but, on the basis of probability, it is likely that death was due to a pre-existing cardiac condition known to be associated with sudden cardiac death. The fatal arrhythmia may well have been induced as a consequence of alcohol/caffeine combinations that are known to trigger arrhythmias in this condition. ... I suggest the cause of death be given as: 1a: Cardiac Arrhythmia, 1b: Long QT Syndrome, 2: Epilepsy". This wording was accepted by the coroner and recorded as the official cause(s) of death.

Case 7

In May 2009 Mr Peter Watts, assistant deputy coroner for West Manchester, recorded an open verdict in the case of Tyler Johns, aged 11 of Bolton, who was found hanging in his bedroom by his mother, death was later confirmed at hospital as due to hanging. Media reports suggest that his behaviour had become bad after drinking 'energy' drinks, to the extent he had been sent home from school for being disruptive on the day of his death. Apparently an empty 1 litre caffeine drink was found near his body. Media reports suggest that his father thought the drinks had contributed to his son's death.
http://www.dailymail.co.uk/news/article-1178249/Energy-drinks-killed-son-says-devastated-father.html

Mrs Jennifer Leeming, HM Coroner for West Manchester, spoke with the compiler on 17 January about this case. She had read through the parents' statement, and concluded that the deceased's intake of caffeine-based energy drinks had at the very least contributed to his bad behaviour. It had set in train a series of events which culminated in his death. As the contents of the energy drink had apparently been poured down the sink, there was probably no toxicology testing for caffeine. The Coroner has promised to provide np-SAD with an appropriate form of words than be used relating to the link (if any) between energy-drink consumption and the death of the deceased.

Case 8

In October 2010, Dr Chapman the then Coroner for Nottinghamshire, recorded a verdict of accidental death in the case of Michael Lee Bedford, aged 23 of Mansfield, who died in hospital on 9 April from toxic caffeine poisoning. At a party he had apparently consumed alcohol and taken an amount (reported as two teaspoons) of a product bought legally on the Internet. He was sick and was taken outside for air and given some water. He was singing songs and slurring his words. He was later found collapsed, apparently having fallen. A bag of white substance was found near his head; its label read "Ingredients: 100% Caffeine". Apparently, the recommendation is not to exceed one-sixteenth of a teaspoon. Information provided to np-SAD by the Nottinghamshire coroner shows that the post mortem toxicology results were: Ethanol – blood 129mg/dL, urine 171mg/dL; cocaine – blood <0.02mg/L; Benzoylecgonine (cocaine metabolite) – blood 0.02mg/L; caffeine – blood 251mg/L, stomach contents 48(g?) (total). The official cause of death was "1a. Toxic caffeine overdose; 2. Other drug abuse."
http://www.bbc.co.uk/news/uk-england-nottinghamshire-11645363
http://healthland.time.com/2010/11/02/a-man-dies-after-overdosing-on-caffeine/
http://www.thisisnottingham.co.uk/Strong-caffeine-products-banned-says-grandmother-Notts-boy-overdosed/story-12264014-detail/story.html

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This is a background paper for discussion. It does not reflect the views of the Committee and should not be cited.

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1 March 2012

Note

The family of Chloe Leach (Case 6) have enquired if they can be provided with a copy of the evidence submitted to the Committee. It has been indicated to Mr Saul that we could provide a copy of this submission, but that were are unsure of the status of any other evidence submitted.

Acknowledgements

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