DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
College Park, MD 20740

Scientific Memorandum

Date: October 28, 2010

From: [redacted] Senior Toxicologist, Senior Science & Policy Staff, Office of Food Additive Safety (OFAS), HFS-205

[redacted] ORISE Fellow, Division of Biotechnology & GRAS Notice Review, OFAS, HFS-255

Through: [redacted] Director, Divi[redacted]AS Notice Review, OFAS, HFS-255 [redacted]

[redacted] Acting Director, Office of Food Additive Safety, HFS-200 [redacted]

To: [redacted] Caffeinated Alcoholic Beverages (CABs)

Subject: Review of the safety of caffeine added to alcoholic beverages

I. Background

The combined consumption of alcohol[1] and caffeine including in the form of caffeinated alcoholic beverages, has increased in recent years (Centers for Disease Control and Prevention, 2010). There is a growing body of scientific literature that suggests that caffeine (a central nervous system (CNS) stimulant) consumed in combination with alcohol (primarily a depressant) can lead to a decreased level of perceived intoxication, potentially allowing drinkers to drink for longer periods and consuming greater amounts of alcohol. Despite the reduced perception of intoxication, the drinker remains intoxicated as caffeine does not affect the blood or breath alcohol concentration. The individual is therefore more likely to engage in risky behaviors such as driving, thereby resulting in an increased number of driving accidents, or other alcohol related incidents. The behavioral effects associated with the combined consumption of ethanol and caffeine, as well as the increasing number of caffeinated alcoholic beverage products (some of which contain unknown quantities of additional caffeine from herbal ingredients such as guarana), are an emerging risk to public health and safety that is of considerable concern to the Center for Food Safety and Applied Nutrition (CFSAN).

CFSAN has been evaluating the safety of caffeine by itself for many years. In the past, CFSAN had reviewed the literature on caffeine several times (e.g., in 1978, 1986, 1992). The purpose of this

[1] Throughout this memorandum, the term "alcohol" will be used to refer to the two carbon alcohol known as ethanol or alternatively as ethyl alcohol.

memorandum is to consider relevant toxicological, pharmacological, and behavioral studies in order to assess CFSAN's concerns about the public health and safety issues that may be associated with co-consumption of caffeine and alcohol.[2]

This memorandum is also to provide data to assist CFSAN in addressing the health and safety concerns that were expressed in a letter to the Food and Drug Administration (FDA) dated September 25, 2009, from 17 States Attorneys General, one U.S. Territory Attorney General, and one City Attorney, associated with the consumption of caffeinated alcoholic beverages.

Scope of this memorandum

CFSAN is aware of the extensive scientific literature pertaining to either caffeine or alcohol consumed alone. This memorandum is not intended to be a comprehensive review of the vast literature on caffeine or alcohol.[3] Rather, this memorandum is intended to review the limited information, particularly in humans, in the scientific literature regarding the effects elicited by the co-consumption of caffeine and alcohol. The available human data mostly rely on results of interviews, questionnaires and surveys of college students, and are predominantly acute effects. Research on the co-consumption of caffeine and alcohol is still evolving; the scientific community does not fully understand the mechanism of the interaction of caffeine and alcohol, and what the possible chronic effects may be. However, the data currently available show an emerging risk to public health and safety.

Unlike traditional toxicological studies conducted in animals, which provide the basis for most food safety evaluations, many of the concerns raised in the available literature regarding the consumption of caffeine with alcohol are based on studies that address adverse behavioral outcomes in humans. Behavioral effects in animals are incorporated via observations into most safety assessments and when concerns are identified, more specific tests in animals are conducted. It is much rarer to base food ingredient safety assessments on studies of complex behavioral effects observed in humans. Using the results of studies that involve complex human behavior in a food additive safety evaluation is novel, but appropriate to the consideration of a public health and safety concern, as both caffeine and alcohol affect the CNS and thus would be expected to have effects on behavior.

This memorandum will first discuss briefly the pharmacology, mechanism of action, metabolism, and adverse effects of caffeine and alcohol when consumed alone. The brief summary of effects from ingestion of caffeine or alcohol alone in the following sections will provide a basis for comparison with the effects now reported from co-exposure to these substances. Moreover, it will focus on what is generally known about the adverse outcomes (e.g., effects on the CNS) resulting from the consumption of the combination of caffeine and alcohol, including a consideration of any resulting unsafe human behavior, especially in vulnerable subpopulations such as young adults (18–24 years of age) and inexperienced alcohol consumers. This memorandum will not consider the disease of alcoholism, and a separate memorandum will discuss the chemistry (including estimated daily exposure).

---

[2] In this memorandum, the following phrases are used synonymously to describe the ingestion of caffeine and alcohol: "co-consumption," "co-administration," "combined consumption," "co-exposure," and "co-ingest" or co-ingestion."

[3] CFSAN is aware that much of the caffeine-related literature is not specific to the co-consumption of caffeine and alcohol. In light of special public health concerns raised by caffeinated energy drinks in general, CFSAN currently has a contract underway for collection and preliminary review of the literature on the safety of caffeine as well as a contract for an updated exposure estimate for caffeine.

II. Pharmacology and Toxicology of Caffeine and Alcohol

This section will briefly describe the mechanism of action, metabolism, physiological and adverse effects of caffeine and alcohol as single entities, with a focus on CNS effects that are well-documented in humans, in order to give context to the discussion of the pharmacological and toxicological effects associated with the co-administration of caffeine and alcohol.

A. Caffeine

Mechanism of action

Caffeine is a CNS stimulant and acts predominantly by antagonizing adenosine receptors located in the brain, blood vessels, kidneys, heart, and the gastrointestinal tract (Fisone et al., 2004). Caffeine non-selectively blocks A1 and A2 subtypes of adenosine receptors in the brain and competitively inhibits the actions of adenosine at concentrations found in consumers of caffeine from dietary sources. Caffeine releases norepinephrine, dopamine, and serotonin in the brain, and increases circulating catecholamines (Benowitz, 1990; Nawrot et al., 2003). Genetic studies suggest that the mechanism by which caffeine produces its stimulant effects is by blockade of the A2a receptor (Huang et al., 2005). Evidence in the literature suggests that caffeine's weak psychomotor stimulant property is primarily due to caffeine's ability to counteract the inhibitory control exerted by adenosine A2a receptors on striatal dopamine D2 transmission (Fisone et al., 2004). In animals, circulating plasma caffeine concentrations as low as 100 μmol (equivalent to plasma concentrations of caffeine in humans achieved after drinking 1–3 cups of coffee) suppress most of the pharmacological effects of adenosine in the brain (Chawla et al., 2008).

Other mechanisms discussed in the literature include, calcium (Ca) mobilization, prostaglandin antagonism and phosphodiesterase inhibition by caffeine. At high plasma concentrations (0.5–1 mmol), caffeine is reported to interfere with the uptake and storage of Ca by the sarcoplasmic reticulum in striated muscles. This action can account for observations that such concentrations of caffeine increase the strength and duration of contractions in the skeletal and cardiac muscles. However, the extent to which caffeine is able to alter Ca binding and transport is unclear (Chawla et al., 2008). Caffeine is also reported to act by potentiation of the inhibitors of prostaglandin synthesis, and as a competitive inhibitor of cyclic nucleotide phosphodiesterase isozymes in various tissues, including the brain. However, the affinity of caffeine for phosphodiesterases is low and a high plasma concentration of caffeine is required to attain significant effects (Fisone et al., 2004).

Absorption, Distribution, Metabolism and Excretion (ADME)

Caffeine is absorbed rapidly and completely from the gastrointestinal tract, through the small intestine, into the portal circulation. Plasma caffeine concentration increases in a dose-dependent manner and reaches peak plasma concentrations within 30 to 60 minutes after ingestion (Grosso et al., 2005; Benowitz, 1990). Caffeine is metabolized in the liver by cytochrome P450 1A2 (CYP1A2) enzyme to paraxanthine which is the primary metabolite of caffeine in humans (see figure 1 of the Chemistry Memorandum, DiNovi and Cheng). The metabolites undergo additional demethylation and oxidation in the liver to other metabolites (e.g., 8-hydroxyparaxanthine, 1-methylxanthine, 1-methylurate, and 5-acetylamino-6-formylamino-3-methyluracyl). Caffeine and its primary metabolites (including other dimethyl xanthines e.g., theobromine and theophylline) readily enter all body tissues and freely cross the blood-brain, placental, and blood-testicular barriers. The paraxanthine metabolites appear in the urine as fast as they are formed due to active renal tubular

secretion. Only 0.5 percent to 2 percent of the ingested caffeine is excreted in the urine due to 98 percent renal tubular reabsorption (Grosso et al., 2005).

In a pharmacokinetics study by Cheng et al. (1990), normal subjects were administered single doses of 70, 200, or 300 milligrams (mg) of caffeine. The results show that caffeine clearance decreased with increasing dose (1.52, 1.14, and 1.08 milliliters/minute/kilogram (mL/min/kg)), and half-life of caffeine increased (4.5, 6.0, and 6.4 hours) for caffeine doses 70, 200, and 300 mg respectively. Serum caffeine levels peaked at less than 2 hours after dosing and decreased to near zero within 24 hours for all dose levels. However, the rates of metabolism and elimination of caffeine are variable. Studies cited in reviews by Grosso et al. 2005, and Benowitz, 1990 demonstrate this variability. They report that the average half-life of caffeine in healthy adults ranges from 2 to 6 hours, but can be as long as 12 hours in some individuals.

Caffeine metabolism has also been studied in special populations and reports show that the rate of metabolism of caffeine is slow during later stages of pregnancy, with long term use of oral contraceptives, alcohol consumption, and in individuals with liver disorders. The rate of caffeine metabolism in the newborn is low resulting in a slow rate of elimination. However, the rate of caffeine metabolism increases with age. Cigarette smoking is reported to accelerate caffeine metabolism (Grosso et al., 2005; Benowitz, 1990; Chawla et al., 2008).

The wide variability in the rate of caffeine metabolism is primarily due to variations in CYP1A2 enzyme activity. Some of the variability in CYP1A2 enzyme activity is due to genetic polymorphisms in the CYP1-A2 gene which can cause increased or decreased induction of the enzyme. An adenine to cytosine (A→C) substitution at nucleotide position 734 in the CYP1A2 gene decreases the enzyme inducibility and activity. Carriers of the variant CYP1A2*1F allele (A/C or C/C) are reported to be slow caffeine metabolizers, whereas individuals homozygous for the CYP1A2*1A allele (A/A) are rapid caffeine metabolizers (Palatini et al., 2009).

CNS Effects

Caffeine is described as the most widely consumed CNS stimulant, increasing wakefulness and enhancing mental focus and improving performance. Doses of caffeine ranging from 50 to 300 mg per day (mg/d) have been reported to be associated with effects on mood, such as feelings of increased energy, alertness, motivation and concentration (Chawla et al., 2008; Strain, 2002). However, depending on an individual's sensitivity, lower doses of caffeine may also have CNS stimulating effect. For example, Quinlan et al. (2000) (discussed below) report increased energetic arousal at caffeine doses as low as 25 mg/d.

Chawla et al. (2008) in their review state that in humans, sleep seems to be the physiological function most sensitive to the effects of caffeine, generally a caffeine dose greater than 200 mg is required to affect sleep significantly. Excessive consumption of caffeine (doses of 1,000–1500 mg or about 10–15 cups/d of coffee) may lead to a state of intoxication known as caffeinism, which is characterized by restlessness, agitation, excitement, rambling thought and speech, and insomnia (Winston et al., 2005).

Two studies illustrate the effects of caffeine alone on the CNS. Quinlan, et al. (2000) conducted two cross-over design, single-dose studies using tea and coffee containing moderate levels of caffeine. In the first study, 17 habitual coffee consumers, who had abstained from coffee for 3 or 16 hours, were given caffeine doses of 37.5 or 75 mg/d in a single serving of 300 mL of tea (equivalent to levels in one or two cups of tea), or caffeine doses of 75 or 150 mg in a single serving of 300 mL of coffee (equivalent to levels in 1 or 2 cups of coffee). The subjects were observed for 2 hours after dosing.

The results show that the tea and coffee produced mild autonomic stimulation and elevation in mood. In the second Quinlan, et al. study, the subjects consumed decaffeinated tea with 25, 50, 100, or 200 mg of added caffeine. The results show that caffeine at all dose levels increased energetic arousal in the subjects. These data demonstrate that doses of caffeine as low as 25 mg can stimulate the CNS. In a repeated dose study by Lieberman et al. (1987), using an intensified dosing regimen, 20 healthy males were administered caffeine capsules at dose levels of 32, 64, 128, or 256 mg/d, after a 12-hour fast during 6 sessions. The results show a dose-related elevation of the plasma concentration of caffeine, with the 32 mg dose (typical of the level in one serving of a cola beverage) elevating plasma concentrations from 0.30 micrograms/milliliter (µg/mL) to 0.85µg/mL. In this third study, caffeine alone significantly improved performance in visual reaction time and auditory vigilance tests.

The results of these three foregoing studies illustrate the effects of caffeine alone on the CNS.

Adverse Effects

The effects of caffeine in humans depend on multiple factors, such as an individual's rate of metabolism of caffeine, sensitivity, amount ingested, and frequency of consumption. Daily consumption of about two to three cups of coffee (200–300 mg/d of caffeine) is not associated with serious deleterious effects in non-sensitive healthy adults. However, individuals in sensitive sub-populations (e.g., pregnant women or children) may experience some adverse effects associated with caffeine consumption (Chawla et al. 2008).

Acute effects of caffeine in humans reported in the literature include increased systolic or diastolic blood pressure, decreased heart rate, sleep disturbance, tremor, diarrhea, emesis, and tremor at dose levels ranging from 3.3 mg/kg to 12 mg/kg (Benowitz, 1990; Motl et al, 2004; Humayun et al., 1997; Swampillai et al., 2006; Nawrot et al., 2003). The acute lethal dose of caffeine in adults has been estimated to be 10 grams (g)/person, but survival of a patient who ingested 24 g was also reported (Nawrot et al., 2003).

Caffeine consumption has been associated with increased risk of cardiovascular disease, including increased blood pressure. However, there are insufficient data to draw definite conclusions regarding this risk. In a widely cited review, Nawrot et al. (2003), cite acute studies that indicate that caffeine induces an increase in systolic (5–15 mmHg) and /or diastolic (5–10 mmHg) blood pressure, most consistently at doses greater than 250 mg/person in adults. An effect on blood pressure was most pronounced in the elderly, in individuals with hypertension, and in caffeine-naïve individuals. The risk of hypertension associated with acute caffeine consumption varies according to CYP1A2 genotype, with carriers of slow CYP1A2*1F allele at increased risk (Palatini et al., 2009). The results of a meta-analysis of case-control studies showed that consumption of coffee (≥4 cups/day) was associated with an increased risk of nonfatal myocardial infarction only among individuals with slow caffeine metabolism (carriers of the CYP1A2*1F allele) (Cornelius et al., 2006).

In their review, Nawrot et al. (2003) addressed several studies on general toxicity (children included), genotoxicity, cardiovascular, behavioral, reproductive and developmental toxicity, and bone and calcium balance associated with caffeine consumption. Overall, Nawrot et al. concluded that there is evidence indicating that in the general population of healthy adults, moderate caffeine intake up to a dose level of 400 mg/day (equivalent to 6 mg per kilogram body weight per day (mg/kg bw/d) in a 65 kg person) is not associated with adverse effects such as general toxicity, cardiovascular effects, effects on bone status and calcium balance (with consumption of adequate calcium), changes in adult behavior, increased incidence of cancer, or effects on male fertility. They further concluded that the data they reviewed show that women of reproductive age and children are 'at risk' subgroups who may require specific advice on moderating their caffeine intake. They suggested that women of

reproductive-age should consume ≤300 mg caffeine per day, while children should consume ≤2.5 mg/kg bw/d. They also stated that the literature shows evidence supporting the existence of caffeine withdrawal in some individuals, with variability in the severity of symptoms. Symptoms reported when regular caffeine consumption is abruptly stopped (i.e., withdrawal symptoms) include headache, drowsiness, irritability, depression, and impaired concentration. Withdrawal symptoms occur generally from 12 to 24 hours (or from 3–6 hours in some individuals) after cessation of caffeine consumption and reach a peak at 20 to 48 hours. Withdrawal symptoms may occur in regular consumers of caffeine at doses as low as 100 mg/d, and the symptoms can be resolved after resumption of caffeine consumption (Chawla et al., 2008; Satel, 2006; Griffiths et al., 2000).

Conclusion

The studies above show that caffeine, a widely consumed pharmacologically active food ingredient, is a CNS stimulant and has behavioral effects. There is variability in individual response to caffeine; however, acute symptoms such as nervousness, irritability, sleep disorder, and tremor have been reported to be associated with caffeine consumption in humans. Withdrawal symptoms, primarily headache, following cessation of caffeine have also been reported.

B. Alcohol

Mechanism of Action

The effects of alcohol on the CNS are complex and involve many different neurotransmitter systems. The current literature suggests that ligand-gated ion channels (LGICs) and voltage-gated calcium channels are important targets for alcohol because their function, type and numbers are altered by short- and long-term exposure to alcohol. In particular, the gamma-aminobutyric acid type A ($GABA_A$), *N*-methyl-D-aspartate (NMDA), glycine (Valenzuela et al., 1998), neuronal nicotinic (Cardoso et al., 1999), and 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptors (Lovinger, 1999) are LGICs that have been shown to be differentially modulated by alcohol (Davies, 2003). Additionally, alcohol, when administered acutely, has been shown to block voltage-gated calcium channels at pharmacologically relevant concentrations (Widmer et al., 1998; Wang et al., 1994). However, it is likely that some targets play more important roles than others in mediating the effects of alcohol in the CNS. Specifically, a large body of work ranging from biochemical to genetic studies points to the importance of $GABA_A$ receptors in mediating the effects of alcohol in the CNS (Davies, 2003). The $GABA_A$ receptor is an ionotrophic (ion channel) receptor that binds gamma-aminobutyric acid (GABA). Upon activation, the $GABA_A$ receptor selectively allows the flow of chloride ions through its membrane channel resulting in an inhibitory effect on neuronal excitability. Within the CNS, alcohol acts as a positive allosteric modulator, meaning that alcohol binds to the $GABA_A$ receptor at a site other than the GABA binding site and so increases in the inhibitory actions of GABA (Davies, 2003).

Absorption, Distribution, Metabolism, and Excretion

Alcohol is a small polar molecule that is completely soluble in water. These properties allow for alcohol to move through the same transmembrane channels that allow the passage of water. Thus, when an alcoholic beverage is consumed, it is quickly absorbed by passive diffusion in the stomach and proximal small intestines (Ferreira et al., 2008). Alcohol then enters the blood circulation where it is distributed throughout the body to the tissues in proportion to the water content in the tissues (Ramchandani et al., 2001).

Ninety to ninety-five percent of the alcohol that is consumed undergoes normal metabolism in the liver (Wiberg et al, 1971). The rate of alcohol metabolism depends, in part, on the amount of metabolizing enzymes in the liver, as well as enzymatic activity; these factors vary among individuals and appear to have genetic determinants (Benet et al., 1996). Alcohol is metabolized into acetaldehyde by alcohol dehydrogenase. Acetaldehyde is then rapidly converted to acetate by acetalaldehyde dehydrogenase and acetate is eventually metabolized to carbon dioxide and water. Alcohol can also be metabolized in the liver by the cytochrome P450 oxidase enzyme system, specifically the CYP2E1 isozyme. The liver can metabolize only a certain amount of alcohol per hour, regardless of the amount that has been consumed. Since alcohol is metabolized more slowly than it is absorbed, consumption needs to be controlled to prevent accumulation in the body and intoxication. Less than 10 percent of consumed alcohol remains un-metabolized and disappears from the body by excretion, permitting alcohol concentration to be measured in breath and urine (Wiberg et al., 1971).

CNS Effects

Alcohol can be a depressant or a stimulant depending on the dose. In general, moderate consumption of alcohol produces symptoms of intoxication, including slurred speech, unsteady walk, disturbed sensory perception, and a decrease in reaction time (Eckardt et al., 1998). At relatively high concentrations, alcohol produces general anesthesia and a highly intoxicated person will fall asleep, be very difficult to wake, and unable to move voluntarily when awake. The resulting effects of excessive alcohol consumption include brain damage, as evidenced by brain imaging, as well as related neurologic deficits such as impairments in working memory, cognitive processing of emotional signals, executive functions, visuospatial abilities, and gait and balance (Cargiulo, 2007). Although alcohol is not a potent substance in comparison to other substances, it is possible to consume enough to cause toxicity or death.

The effects of chronic alcohol consumption on the CNS include tolerance and physical dependence. These characteristics play a role in impeding the ability of a chronic alcohol consumer to stop drinking. Chronic alcohol consumption can also have adverse effects on mental health; specifically, it can cause psychiatric disorders (Dunn and Cook, 1999).

Physiological Effects

The effects of alcohol in humans are well-documented (Katzung, 2001). After the consumption of one standard drink, the blood alcohol concentration (BAC) peaks within 30 to 45 minutes. A single serving of a strong spirit contains as much as 12 g of alcohol and can cause the concentration of alcohol in the blood to reach 5–10 millimole/liter (mmol/L) (Katzung, 2001). Thus it is possible to consume large amounts of alcohol in a single sitting and quickly reach these blood concentrations. Relatively low concentrations of alcohol produce a feeling of stimulation (BAC equivalent to 2 mmol/L – 9 mmol/L), whereas higher concentrations of alcohol have depressant properties (BAC equivalent to 17 mmol/L – 25 mmol/L) (Martin et al., 1993). The information from Grilly (2002) supports the information from Martin (1993). At low BACs, there is a feeling of euphoria. When the concentration of alcohol in the blood increases, motor function is impaired and speech becomes slurred (Grilly, 2002). With a BAC between 200 milligrams/deciliter (mg/dL) and 300 mg/dL (i.e., between 43 mmol/L and 65 mmol/L), vomiting can occur and the subject can fall into a stupor (Grilly, 2002). Having a BAC higher than 200 mg/dL or 300 mg/dL can result in coma, and at an even higher BAC (500 mg/dL or 109 mmol/L), there is the potential for respiratory failure and death (Grilly, 2002).

Adverse Effects

Alcohol dependence and excessive alcohol intake are associated with multiple physical and mental health problems that carry significant morbidity and mortality. In fact, alcohol is implicated in approximately 100,000 deaths a year in the United States (Meister, 2000). Some of the health problems and deaths can be attributed to acute effects of excessive alcohol (e.g., injuries and deaths due to alcohol-related driving accidents), but many more can be attributed to the insidious effects of chronic, excessive consumption and alcohol dependence (Cargiulo, 2007). Excessive alcohol intake has direct adverse effects on the nervous and cardiovascular systems, as well as the liver, and has been linked to specific cancers (Cargiulo, 2007). Additionally, alcohol dependence is associated with psychiatric morbidity and an increased risk of suicide, and the children of women who drink while pregnant may be born with fetal alcohol spectrum disorders (Cargiulo, 2007).

Conclusion

Depending on the dose, alcohol can have a depressant or a stimulant effect on the CNS. At moderate doses (≤ two drinks/day for men age 65 years-old or less and ≤ one drink/day for women of all ages), alcohol can impair judgment, coordination and balance. Alcohol consumption is associated with a dose-related increase in the risk of acute injury, and contributes to traffic-related injuries and deaths. Excessive alcohol consumption is associated with brain damage, increased risk of heart disease, and liver disease (Cargiulo, 2007).

III. Data on the Effects of Caffeine and Alcohol Combination

A. Background:

If one surveys the scientific literature on the effects of alcohol and caffeine most studies have been conducted on each of the substances administered alone. There is a relatively clear understanding of their respective effects at a given dose. The scientific literature reviewed below, however, demonstrates that when these two substances are given simultaneously, complex and unpredictable new responses and effects have been observed and measured, which raises legitimate public health concerns given the widespread availability of manufactured combinations of these agents. In the sections below the results of recent studies on the combined effects of these substances are reviewed and interpreted. However, the available data are limited and there are no studies to address the possible effects of chronic, high co-exposure to these two substances. Additional study is needed to evaluate accurately the nature and extent of the adverse effects associated with the co-consumption of caffeine and alcohol.

A. Absorption, Distribution, Metabolism and Excretion (ADME) of the Caffeine and Alcohol Combination

The metabolism of caffeine and alcohol consumed alone are each well-understood (see Section II). In humans, both caffeine and alcohol are metabolized in the liver. Alcohol is metabolized by the CYP2E1 isoenzyme to acetaldehyde which in turn is converted to acetate and eventually to carbon dioxide and water. Caffeine is metabolized by the CYP1A2 isoenzyme into paraxanthine and other methylxanthines. However, there is a lack of adequate ADME data on the metabolism of the combination of caffeine and alcohol as evidenced by a search of the current literature.

In human studies, co-administration of caffeine (2–7 mg/kg) with alcohol (0.6–1 g/kg) had no significant effect on alcohol metabolism as indicated by results of blood/breath alcohol concentration (BAC) (Maczinski et al., 2006; Rush et al., 1993; Ferreira et al., 2006). In contrast, a study by

George et al. (1986) suggests that alcohol (50 g/d) intake significantly prolongs the half-life of caffeine by 72 percent and decreases the clearance of caffeine by 36 percent. Differential metabolic responses may help explain some of the outcomes resulting from co-exposure.

B. Summary of Human data

1. ***Behavioral Effects Measured with Caffeine and Alcohol:***

Miller, KE. Wired: Energy drinks, jock identity, masculine norms, and risk taking. J Am College Health, 56, 481–489, 2008.

The authors designed this study to examine whether there are links among various factors, including: sports-related (jock) identity, masculine norms, and risk-taking, and amount of energy drink consumption in both men and women undergraduate students.

The data collected from questionnaire responses of 795 undergraduate students were used by the author to conduct a linear regression analysis of the students' responses to determine (if any) association of energy drink consumption frequencies with the socio-demographic characteristics described above.

The responses of the 795 students indicated that 39 percent of participants consumed at least 1 energy drink in the past 30 days, with more frequent use by men (2.49 days/month) than women (1.22 days/month). Twenty-six (26) percent of the students reported mixing energy drinks with alcohol at least once. Strength of jock identity was positively associated with frequency of consumption of both energy drinks and energy drinks mixed with alcohol, and this is mediated by conformity to masculine norms and risk-taking behavior.

The author concludes that sports-related identity, masculinity, and risk-taking are components of the emerging portrait of a toxic jock identity, which may signal an elevated risk for health-compromising behaviors.

CFSAN concludes that the measurements in this study do not provide context for the overall consumption of energy drinks alone, and mixed with alcohol beyond the past 30 days measured in the survey. However, it does shed some light on the growing trend among college campuses and a possible driving factor.

O'Brien MC, McCoy T, Rhodes SD, Wagoner A, and Wolfson M. Caffeinated cocktails: Get wired, get drunk, get injured. Acad Emerg Med 15, 453–460, 2008.

The principal investigators designed their study to determine the relationship between energy drink use, high-risk drinking behavior, and alcohol-related consequences. A 2006 (Fall) web-based survey was conducted with a stratified random sample of 4,271 college students (61 percent female) from 10 universities in North Carolina (average age 20.4 years-old)

Data from the survey indicate that of the 4,271 students, 697 (24 percent of those who drank in the past 30 days) consumed alcohol mixed with energy drinks (AmED) in the test period. In multivariable analyses, consumption of AmED was associated with increased heavy episodic drinking and episodes of weekly drunkenness compared to those who did not consume AmED. Consumers of AmED reported higher prevalence of alcohol-related adverse consequences, including taking advantage of another or being taken advantage of sexually, riding with an intoxicated driver, being physically injured, and requiring medical treatment.

The authors concluded that almost one-quarter of current college student drinkers reported mixing alcohol with energy drinks, and that these students are at increased risk for alcohol-related adverse consequences. The authors suggest that further research is necessary to understand this association.

CFSAN concludes from these results that students who consume AmED are at increased risk for alcohol-related adverse consequences, even after adjusting for the amount of alcohol consumed.

Thombs DL, O'Mara RJ, Tsukamoto M, Rossheim ME, Weiler RM, Merves ML, and Goldberger BA. Event-level analysis of energy drink consumption and alcohol intoxication in bar patrons. Addictive Behaviors 35, 325–330, 2010.

In this study the authors attempted to assess event-level associations between energy drink (ED) consumption, alcohol intoxication, and intention to drive a motor vehicle in patrons exiting bars at night. This was an alcohol field study of 802 participants, 71.7 percent of them patrons exiting seven drinking establishments between 10 p.m. and 3 a.m., on 3 nights in a bar district near a U.S. college. Anonymous interview and survey data and breath alcohol concentration (BAC) readings were obtained.

The results from logistic regression analyses show that compared to other drinking patrons who did not consume alcohol mixed with ED, patrons who consumed alcohol mixed with ED were at a three-fold increased risk of leaving the bar intoxicated (i.e., BAC $\geq$0.08), and at a four-fold increased risk of intending to drive upon leaving the bar district.

The authors concluded that this field study contributes to the growing body of literature indicating that this drinking behavior (mixing alcohol with ED) has negative health and safety consequences for young adults.

CFSAN interprets that the three studies reviewed immediately above by Thombs et al., O'Brien et al., and Miller collectively raise concerns about the increased risks of negative behavioral outcome and adverse physical consequences when young adults consume energy drinks mixed with alcoholic beverages compared to youths who drink, but without concurrent ED consumption.

Oteri A, Salvo F, Caputi AP, and Calapai G. Intake of energy drinks in association with alcoholic beverages in a cohort of students of the School of Medicine of the University of Messina. Alcohol Clin Exp Res 31:1677–1680, 2007.

The study's objective was to determine students' use of ED alone or mixed with alcoholic beverages in a group of medical students (450–500) who responded to an anonymous questionnaire.

The students' responses indicated that: 1) 56.9 percent declared using ED; 2) 48.4 percent of total sample (218) declared using ED plus alcohol, and of these, 116 used both ED alone and ED plus alcohol (usually gin or vodka); one-third of these 116 have also consumed more than three cocktails of ED plus alcohol in the past month; and 3) the group consuming ED alone and ED plus alcohol appeared more motivated to justify the use of EDs.

CFSAN agrees with the authors' conclusions that based on their data: 1) consumption of ED plus alcohol is very popular among students; 2) consumption of ED plus alcohol is dangerous because it prevents the consumer from feeling (masks) some adverse effects associated with alcohol intoxication; 3) subjects may end up consuming more alcohol, which may, in turn, increase the chance of alcohol dependence and car accidents.

Marczinski CA, and Fillmore MT. Dissociative antagonistic effects of caffeine on alcohol-induced impairment of behavioral control. Exp Clin Psychopharmacol 11:228–236, 2003.

The study's objective was to examine the effects of caffeine and alcohol, separate and combined, on fundamental aspects of behavioral control in healthy adults using a cued go/no go (response/failure to inhibit a response) reaction time (RT) task.

Participants were 12 healthy volunteers (6 men, 6 women; mean age: 23.8 years-old), their mean drinking frequency = 2.6 times/week, mean dose per occasion = 0.8 g/kg (equivalent to four bottles of beer containing 5 percent alcohol for a 70 kg person), caffeine = 2.4 mg/kg/d (equivalent to one mug of strong coffee for a 70 kg person). They were instructed to abstain from alcohol for 24 hours, caffeine for 8 hours, and food for 4 hours prior to each test session. Caffeine (0, 2.0, and 4.0 mg/kg), or alcohol (0 and 0.65 g/kg which produces an average peak BAC of 90 mg/100 mL approximately 60 minutes after drinking), or both were administered in a randomized double-blind design across participants. Participants' cued go (green)/no go (blue) task performance was tested 30 minutes after drinking (i.e., during the ascending period of the blood alcohol curve).

Additional measurements included: biphasic alcohol effects scale (BAES) to provide subjective rating of the levels of stimulation and sedation, and a beverage rating scale to report their perceived intoxication, BAC (from 30, 50, 65, and 90 minutes after drinking/session), and RT.

The following results were reported:

1. Overall, RTs were higher for no go cues compared with go cues.
2. Compared to vehicle, alcohol significantly increased failures of response inhibition scores for go cues, unaffected by caffeine alone and in combination with alcohol.
3. Compared with vehicle, alcohol alone increased RTs for go and no go cues, alcohol plus caffeine (2 mg/kg) further increased RTs for no go cues
4. Compared with vehicle, caffeine alone significantly decreased RTs for go cues at 4 mg/kg, and RT for no go cues decreased but not significantly.
5. Caffeine (4 mg/kg) plus alcohol decreased RTs for no go cues, and alcohol plus caffeine (2, 4 mg/kg) decreased RTs for go cues, but the decrease was not significant.
6. Caffeine alone caused a dose-related increased stimulation, and decreased sedation compared with vehicle.
7. Participants consuming caffeine (0, 2.0, or 4.0 mg/kg) plus alcohol (0.65g/kg) reported greater stimulation (24.3, 29.7, and 31.2 respectively) and less sedation (21.6, 15.8, and 16.2 respectively) compared to the alcohol only group.

The authors concluded that the findings in this study highlight potential differences in how activational and inhibitory aspects of behavioral control might respond to various drugs. The authors stated that the study findings contribute to the understanding of how drugs of abuse can disrupt behavioral control in humans.

CFSAN concludes that the data from this study indicate that caffeine doses tested (2.0 and 4.0 mg/kg) have stimulating properties and 0.65 g/kg alcohol impaired both response execution and response inhibition. Caffeine at 4 mg/kg selectively antagonized alcohol-induced impairment of response execution (RT), but had no antagonizing effect on the response inhibition due to alcohol. These data suggest that events while operating a car, for example, where an immediate response is required to prevent an accident (like the RT), are delayed by alcohol alone and that delay is somewhat attenuated by a high dose of caffeine. In contrast, response inhibition reaction time, (when withholding of a response is required) was increased by alcohol and further increased by addition of caffeine.

Curry K, Stasio MJ. The effects of energy drinks alone and with alcohol on neuropsychological functioning. Hum Psychopharmacol Clin Exp 24:473–481, 2009.

The objective of this study was to examine the neuropsychological performance after consumption of a commercially available caffeinated alcoholic beverage (*Orange Sparks,* 6 percent alcohol by volume (ABV)) compared to the consumption of an energy drink (*Green Monster*) or control beverage (diet *7-Up*).

Twenty-seven (27) healthy female college students (non-smokers, the majority of whom currently consume alcohol and caffeinated drinks, with a mean age of 21.6 years-old) participated in the study. Participants abstained from caffeine for one hour prior to study time then blindly ingested 16 ounces (oz) of the following test beverages: control, or one serving regular energy drink (RED) or caffeinated alcoholic beverage (RED + A). Post-test assessments, using a repeatable battery for the assessment of neuropsychological status (RBANS), began 45 minutes after ingestion of the respective beverages. The RBANS consists of 12 subtests that yield standardized scores in the following five cognitive domains: immediate memory, delayed memory, visuospatial/constructional, attention, and language.

The following results were reported:

1. Participants who consumed RED alone tended to have higher, though not statistically significant, attention scores, compared to the control group.
2. Participants who consumed RED + A drink had significantly lower visuospatial/constructional scores than those in placebo group; there was no significant difference between RED and the RED + A groups.
3. Compared to the control group, the RED + A group showed a decrease in language scores.

The authors concluded that consumption of 16 oz of an alcoholic energy drink containing 6 percent alcohol by volume negatively influenced performance on a global measure of cognitive functioning.

CFSAN notes that the present study does not include an alcohol-only group, so direct comparison of effects due to alcohol versus caffeine or alcohol versus alcohol plus caffeine could not be made. The caffeine content of RED + A was not reported. (We note that Wikipedia reports caffeine content of Monster energy drinks to be 160 mg/16 oz. http://en.wikipedia.org/wiki/Monster_Energy.) It is also important to note that in this study consumers ingested a commercially available pre-mixed caffeinated alcoholic beverage (malt beverage, *Orange Sparks*), representative of the products which FDA is concerned about.

Martin FH, and Garfield J. Combined effects of alcohol and caffeine on the late components of the event-related potential and on reaction time. Biol Psychol 71:63–73, 2006.

The objective of this study was to determine the effects of alcohol and caffeine alone and combined on event-related potential (ERP) components and reaction time (RT) in simple and choice RT tasks.

Sixteen (16) female college students (mean age: 24 years-old, mean weight: 67 kg, mean alcohol intake: 3.2 drinks/week, mean caffeine intake: 153 mg/d) volunteered for the study. Participants were asked to abstain from food for 4 hours, caffeine for 12 hours, alcohol for 24 hours prior to testing time. Participants were dosed (blindly): 2 Equal sweetener tablets (placebo) or 2 No-Doz tablets (200 mg caffeine) or 1.89 mL/kg Cossack Vodka (37 percent ABV, to provide 0.7 g/kg bw alcohol) or a No-Doz + vodka beverage. Forty-five minutes after ingestion, BAC was measured, after which simple and choice RT tasks were performed. The parameters assessed included: behavioral (accuracy, decision time (DT) & movement time (MT)), and ERP data (latency and amplitude).

The following results were reported:

1. Alcohol alone slowed/lengthened the DT component of RT, and the latency of the P200 and P300 components in both simple and choice RT tasks, reduced N200 amplitude, and increased P300 amplitude.
2. Caffeine plus alcohol significantly reduced certain sites of the N500 area (related to working memory process) when compared to alcohol alone
3. Caffeine plus alcohol reduced mean N200 latency in the choice RT task when compared to alcohol alone (287 milliseconds (ms) versus 276 ms).

The authors concluded that alcohol slows allocation of attention to task-relevant stimuli and impairs working memory processes, while caffeine accelerated response-related decisions and enhanced cortical arousal. The combination of alcohol and caffeine appear to impair working memory.

CFSAN notes that this study did not test either pure caffeine or energy drink. Also, the very different tastes of sweetener tablets and No-Doz tablets will significantly interfere with the blinding of these two treatments groups. Additionally, the sample size may be a limiting factor on the application of the results. This study brings to light some of the complexities that may exist in the interpretation of the data on human behavioral outcome associated with the co-ingestion of alcohol with caffeine as acknowledged.

Grattan-Miscio KE, Vogel-Sprott M. Alcohol, intentional control, and inappropriate behavior: Regulation by caffeine or an incentive. Exp Clin Psychopharmacol 13:48–55, 2005.

The objective of this study was to test the effects of caffeine or incentive treatments on automatic (displayed without awareness) and controlled (require effort and conscious intent) responses while under the influence of alcohol using a process dissociation paradigm.

Forty-four (44) healthy male undergraduate students, age: 19–25 years-old, mean drinking frequency: 1.3 drinks/week, mean drinking duration: 4.4 hr/occasion, alcohol intake 1.2 mL/kg/occasion (equivalent to 4.8 bottles of 5 percent alcohol beer for a 70 kg person), mean caffeine intake: 486.40 mg/week (approximately 4 cups of ground-roasted coffee)) participated in the study. They fasted for 4 hours and abstained from alcohol for at least 24 hours prior to study. Participants were randomly assigned to one of four groups (11/group): group A received 0.62 g/kg alcohol, group AC received 0.62 g/kg alcohol and 4.4 mg/kg caffeine in a beverage, group AR received alcohol and monetary reward (incentive) for correct responses, and participants in group P (placebo) were told they would receive alcohol but instead they received carbonated beverage containing a few drops of alcohol on the surface and also sprayed with alcohol mist. BAC was measured 30, 45, 70, and 90 minutes after drinking commenced, followed by these tasks: word list, word stem completion, beverage rating scale, and completion of a three-item questionnaire that asked about self-control during drinking occasions.

The following results were reported:

1. Controlled processes were significantly weakened by alcohol in group A compared to group P, while the alcohol and caffeine (AC) and incentive (AR) strengthened controlled processes to levels comparable to the sober state i.e., did not differ statistically from group P, with the AR group showing stronger influence than AC.
2. Participants in group A made the most mistakes (action slips) significantly higher (i.e., significantly lower correct responses) compared to group P, followed by group AC. The probability of relative likelihood of an action slip on a given trial was highest for group A (0.5), followed by group AC (0.34), with group AR making the least mistakes (0.2).

3. Automatic processes showed no significant group differences compared to group P, though group A was higher than P and AC and AR were lower than P.

The authors concluded that the results show that the depressive effect of alcohol on controlled processes can be counteracted by a stimulant drug, caffeine, and by incentive treatment as well. The authors suggest further research is needed to determine the processes underlying the reported effects.

CFSAN notes that this study does not include a caffeine-only group, thereby limiting the interpretation of the results of the AC group.

Fillmore MT, Vogel-Sprott M. Behavioral effects of combining alcohol and caffeine: Contribution of drug-related expectancies. Exp Clin Psychopharmacol 3:33–38, 1995.

The aim of this experiment was to test the hypothesis that drinkers' expectations about the behavioral effect of combining alcohol and caffeine predicted their psychomotor performance when they expected to receive both. Administration of alcohol was kept constant, while administration and expectation of caffeine was independently manipulated.

Fifty (50) healthy male volunteers (age: 19–27 years-old), fasted for 4 hours, abstained from alcohol for 24 hours, and from caffeine for 8 hours prior to the experiment. Their mean drinking frequency was 1.2 times/week, average alcohol dose was 1.14 mg/kg/occasion (about 4.7 beers containing 5 percent alcohol for a 70 kg person), average caffeine intake was 2.94 mg/kg (about 2 cups of brewed coffee for a 70 kg person)). Participants were randomly assigned to the following 5 groups (10/group):

- ECRC: Received alcohol (0.56 g/kg), expected to receive caffeine, received caffeine (4.4 mg/kg)
- ECRN: Received alcohol (0.56 g/kg), expected to receive caffeine, but did not receive caffeine
- ENRC: Received alcohol (0.56 g/kg), did not expect to receive caffeine, but received caffeine (4.4 mg/kg)
- ENRN: Received alcohol (0.56 g/kg), did not expect to receive caffeine, and did not receive caffeine
- NT: Received neither alcohol nor caffeine (control).

Participants rated the expected effect of combining alcohol and caffeine and then received alcohol then caffeine, both within 6 minutes. Twenty-three minutes after drinking began, BACs were measured before and after participants performed 12 trials on a pursuit rotor (PR).

The following results were reported:

1. Peak BACs for all groups administered alcohol (the ECRN, ENRN, ECRC, and ENRC groups) were similar.
2. Alcohol (ECRN and ENRN groups), significantly impaired performance compared to the NT group.
3. Performance was significantly improved when caffeine was co-administered (ECRC, ENRC) regardless of whether caffeine was expected. The mean change in performance for the ECRC group did not differ significantly from NT group.
4. Simply expecting to receive caffeine produced no overall effect. However, individual differences in expected effects influenced participants' performance when they expected to receive caffeine with alcohol.

5. Those who expected the most impairment from the combined ingestion of caffeine and alcohol did suffer the most interference in their responses regardless of whether caffeine was actually received or not.

The authors concluded that their research results have implications for understanding factors that contribute to individual differences in behavioral responses to drugs.

CFSAN concludes that the results show that administration of a moderate dose of caffeine (4.4 mg/kg or 308 mg/70 kg person), whether or not it was expected, diminished the impairment on a psychomotor task due to alcohol, but did not affect the blood alcohol concentration. The study results also show how individual differences in expectations influenced the amount of variance in behavior when alcohol is co-administered with caffeine. Finally, there is no description of whether or not any effort was made to blind the taste or odor characteristics of the specific treatment formulations administered.

Kerr JS, Sherwood N, Hindmarch I. Separate and combined effects of the social drugs on psychomotor performance. Psychopharmacol 104:113–119, 1991.

The objective of this study was to assess the separate and combined effects of alcohol with social drugs, i.e., caffeine and nicotine, on information processing and psychomotor performance. [Note: The alcohol alone, caffeine alone, and combination of caffeine and alcohol with the appropriate control groups are reviewed here.]

Ten (10) female volunteers (5 smokers (≥ 15 cigarettes/day for at least 5 years) and 5 nonsmokers) aged between 21 and 50 years-old (mean 32 years-old) participated in the study, each session was separated by 24-hour washout period. The treatments were as follows:

- Placebo: Orange juice plus sucrose capsule
- Alcohol alone: 30 g of 80 percent proof vodka (equivalent to 3 glasses of wine, will produce peak BAC of 60 mg/100 mL within 1 hour for a 60 kg subject)
- Caffeine alone: 300 mg caffeine in capsule (approximately 3 cups of strong coffee)
- Alcohol + caffeine: 300 mg caffeine + 30 g vodka.

Choice reaction time (CRT) and critical flicker fusion (CFF) were measured after 0.5 hour, while short-term memory and compensatory tracking task (CTT) were measured at 1, 2, 3, and 4 hours after treatment.

The following results were reported:

1. Alcohol impaired (increased) mean motor reaction time (MRT) while caffeine improved (decreased) MRT in comparison to placebo, alcohol plus caffeine slightly improved the MRT however it was not significantly different from the alcohol-only group.
2. Alcohol significantly impaired accuracy in CTT, caffeine alone improved CTT in comparison to placebo, alcohol plus caffeine improved CTT in comparison to alcohol only group, but not to a statistically significant extent.
3. Mean memory reaction time significantly improved in the caffeine alone group compared with placebo, while alcohol plus caffeine, and alcohol groups were both impaired and but no statistically significant difference was found between these two treatment groups.

The authors concluded that alcohol disrupted performance, and the caffeine plus alcohol combination antagonized the effects due to alcohol.

CFSAN notes that the sample size in this study (10) is very small and limits the interpretation and strength of the results. Additional factors that should be considered in interpreting the data include the fact that all the participants were female, gender-dependent differences in alcohol metabolism have been reported; five of the participants were smokers, cigarette smoking is reported to accelerate caffeine metabolism. Both of these influences on the rate of alcohol metabolism could have affected the intensity and duration of effects measured.

Price SR, Hilchey CA, Darredeau C, Fulton HG, Barrett SP. Energy drink co-administration is associated with increased reported alcohol ingestion. Drug Alcohol Rev 29:331-333, 2010.

The aim of the research was to characterize patterns of EDs and alcohol co-administration, using standardized, structured face to face interviews.

Seventy-two volunteers (31 males) age 17-29 years-old, from the Halifax University (Canada) student community who had used ED in the past month, participated in the study. Participants provided the following information during standardized, structured face to face interviews: life time ED and other substance use; instances of ED and alcohol use during the past week; and average number of alcoholic drinks/drinking sessions (alcohol alone and combined with ED). The analysis of co-administration was restricted to instances when alcohol was consumed within one hour of ED consumption.

Analysis of the data yielded the following results:

1. 76 percent (55/72) of participants have mixed EDs with alcohol in their life time
2. During their most recent use of EDs, 22 percent (16/72) also used alcohol, and 14 percent (10/72) reported trying ED for the first time while under the influence of alcohol.
3. 78 percent (56/72) of participants used alcohol during the previous week, 65 percent (47/72) used EDs, and 53 percent (38/72) used both alcohol and EDs.
4. Of the 38 reporting past-week use of both alcohol and EDs, 26 percent (10/38) used alcohol with and without ED co-administration.
5. Individuals drank significantly more alcohol when alcohol was combined with ED. Average number of alcoholic drinks per drinking session = 4.7 during alcohol only (non-ED) drinking session, and 8.6 during alcohol + ED drinking session.

The authors concluded that combined consumption of alcohol and ED is relatively common and appears to be associated with increased reported alcohol ingestion during drinking sessions. The authors, though uncertain about the reason for the association, suggest that it is possibly due to interactions involving caffeine and/or taurine present in the ED.

CFSAN notes that care should be taken in interpreting the increased alcohol consumption per drinking session (item #5) reported as this applies only to 10/72 (14 percent) volunteers.

Oborne DJ, and Rogers Y. Interactions of alcohol and caffeine on human reaction time. Aviat Space Environ Med 54:528-534, 1983.

The objective of this study was to investigate the direction of the interactive effects of alcohol and caffeine on reaction time, and to determine if using the Sternberg's Additive factor method for investigating human information processing (using reaction time) could provide analytic measures that may indicate which processing stages were affected by the interaction.

Eight (4 males (bw = 56.4–73 kg), four females (bw = 48–55 kg)) undergraduate students aged 19–25 years-old participated in the study conducted over a four-week period. Each subject served as his own control. The treatments groups were as follows:

- Group A - Alcohol + caffeine: subjects drank 2.2 mL/kg of 65.5 proof vodka in orange juice then 150 mg caffeine (equivalent to 1-2 cups of coffee) tablets mixed in 1 cup decaffeinated coffee
- Group B - Alcohol alone: 2.2 mL/kg vodka in orange juice which produced BAC = 80 mg/100 mL
- Group C - Caffeine alone: 150 mg caffeine tablets mixed in 1 cup decaffeinated coffee
- Group D - Placebo: Orange juice followed by decaffeinated coffee.

Measurements include breath alcohol concentrations (BAC), taken at 10 minute intervals, reaction times (RT), beginning after 40 minutes during the four-part memory set tasks.

The following results were reported:

1. Mean peak BAC for groups A, alcohol + caffeine (80.6 mg/100 mL) and B, alcohol alone (78.8 mg/100 mL) occurred at 40 minutes after ingestion. Non-significant but higher mean peak BAC in group A.
2. Reaction times were consistently highest for group A compared to other groups (B, C, D), suggesting that caffeine potentiates the alcohol-induced increase in reaction time.

The authors conclude that, under the conditions of their study, the results demonstrated that caffeine has a synergistic interaction with alcohol. Furthermore, it was shown, using the Sternberg's Additive factor method that the effects of alcohol, and alcohol + caffeine occur mainly at the peripheral stages of information processing (i.e., at the stimulus input and response output) rather than centrally.

CFSAN notes that these results further show the conflicting outcomes observed when individuals co-ingest alcohol with caffeine. It is not yet clear why some studies show antagonistic interaction while others (including this study) show a synergistic/potentiative interaction between alcohol and caffeine.

Fillmore MT. Alcohol tolerance in humans is enhanced by prior caffeine antagonism of alcohol-induced impairment. Exp Clin Psychopharmacol 11:9–17, 2003.

The objective of this study was to test the hypothesis that a history of drug-induced antagonism of alcohol impairment would increase alcohol tolerance in social drinkers.

Twenty-one adult volunteers (13 males) aged 21–31 years-old, mean body weight = 76.1, mean caffeine consumption 3.8 mg/kg/d (equivalent to one and a half 8 oz cups of coffee for a 75 kg person), mean drinking frequency of 1.7 times/week with a mean dose of 0.9 mL/kg (amounts to 4 bottles of beer with 5 percent ABV for a 75 kg person) participated in the study. Participants fasted for 4 hr, abstained from alcohol for 24 hr, and caffeine for 8 hr prior to each test day. Participants (n = 7/group) were randomly assigned to each of the following groups:

- Group A - Alcohol: subjects consumed 2 drinks containing total of 0.65 g/kg absolute alcohol (produces peak BAC of 75 mg/100 mL about 60 min after ingestion) mixed into lemon-flavored carbonated drink
- Group C - Caffeine: subjects consumed 4 mg/kg anhydrous caffeine powder mixed into lemon-flavored drink.
- Group AC - Alcohol + caffeine: subjects consumed 0.65 g/kg alcohol + 4 mg/kg caffeine.

Subjects participated in 5 trial blocks of the pursuit rotor (PR) tasks after drinking: block 1(pre-treatment alcohol challenge session at 20 min), blocks 2-4 (tolerance acquisition sessions at 40, 60, and 120 min respectively), block 5 (post-treatment challenge at 180 min). Sessions were separated by

a minimum of 24 hr. BACs measured after each block; biphasic alcohol effects scale (BAES) was performed after 65 min to measure subjective ratings of level of stimulation and sedation.

The results show that caffeine did not affect the peak BAC during the tolerance acquisition sessions, mean peak BAC = 81.1mg/100 mL, occurred during the first 60 minutes. Group AC showed reduced impairment during all three tolerance acquisition sessions compared to group A on the PR tasks. Sedation ratings was highest for group A, lowest for group C, group AC reported less sedation than group A.

The author concluded that the results showed that a history of combined alcohol and caffeine ingestion increased alcohol tolerance compared with an exposure history to either alcohol or caffeine alone. The author further stated that his findings may contribute to the understanding of the complexities of how alcohol tolerance may be affected by history of polydrug use.

CFSAN notes that the repeated combined consumption of alcohol and caffeine at the levels in this study appeared to have increased alcohol tolerance when compared to alcohol or caffeine alone.

Fillmore MT, Roach EL, and Rice JT. Does caffeine counteract alcohol-induced impairment? The ironic effects of expectancy. J Stud Alcohol 63:745–754, 2002.

This objective of this study was to test the hypothesis that drinkers who expected an antagonist effect of caffeine would be less likely to compensate for any alcohol-induced impairment and consequently would display greater impairment from alcohol than would those who did not expect an antagonist effect.

Participants were 42 social drinkers (23 males), mean age 23.3 years-old, with mean drinking frequency of 2.1 times/week and a mean dose/occasion of 1.1 mL/kg bw (equivalent to 4.8 bottles of beer containing 5 percent ABV for a 75 kg person), and daily caffeine consumption of 2.5 mg/kg (equivalent to 8 oz mug of brewed coffee). Participants fasted for 4 hours, abstained from alcohol for 24 hours, and caffeine for 8 hours prior to study. The study involved 4 expectancy testing groups (C+, C-, PC+, PC-) and two controls (A, PA). Participants (n = 7/group) were randomly assigned to each of the following 6 groups:

- Group A, alcohol only group: subjects consumed 2 drinks containing total of 0.65 g/kg absolute alcohol (produces peak BAC of 75 mg/100 mL about 60 min after ingestion) mixed into lemon-flavored soda.
- Group C+, alcohol + caffeine with positive/positive expectations: subjects consumed 0.65 g/kg alcohol + 4 mg/kg caffeine; they expected to receive caffeine and were led to expect that caffeine would counteract the impairing effect of alcohol.
- Group C-, alcohol + caffeine with positive/negative expectations: subjects consumed 0.65 g/kg alcohol + 4 mg/kg caffeine; they expected to receive caffeine and were led to expect no counteracting effect.
- Group PC+, alcohol only with positive/positive expectations: subjects consumed 0.65 g/kg alcohol + decaffeinated coffee; they were led to expect that caffeine would counteract the impairing effect of alcohol.
- Group PC-, alcohol only: subjects consumed 0.65 g/kg alcohol + decaffeinated coffee; they were led to expect no counteracting effect.
- Group PA, placebo: subjects consumed no caffeine and no alcohol.

Beverages were consumed within 8 minutes. Subjects participated in the pursuit rotor (PR) task in 5 blocks at 20, 40, 60, 120, 180 minutes after drinking, BACs were measured at the end of each block. Subjects completed the intoxication and expectancy scales after the PR tasks were completed.

The results of this study showed:

1. Compared to the placebo group (PA), alcohol significantly impaired PR performance as shown by group A. Impairment increased as BACs were ascending and diminished by the last block as BACs were declining.
2. Subjects led to expect that caffeine would counteract the impairing effect of alcohol (C+, PC+) displayed impaired performance similar in intensity and profile to the alcohol control group (A).
3. Subjects led to expect that caffeine would not counteract the effect of alcohol (C-, PC-) displayed little or no impairment with performance near or above baseline levels.
4. Results from the expectancy ratings showed that those led to expect a counteracting effect reported expecting no impairment at post-treatment whereas those led to expect no counteracting effect reported little change in their expectancy from pre- to post-treatment.

CFSAN agrees with the authors' conclusion that the findings appear to suggest that compensation for alcohol impairment occurs when drinkers hold clear expectations that the drug will disrupt performance, and that when no such clear expectation exists, no compensatory response occurs and the impairing effects of alcohol are observed.

Keuchel I, Kohnen R, Lienert GA. The effects of alcohol and caffeine on concentration test performance. Arzneim-Forsch / Drug Research 29:973–975, 1979.

The objective of this study was to use a 2 x 2 x 2 factorial design to determine the effects of alcohol or caffeine or their combination on concentration test performance.

Fifty-six (56) students (28 /sex, aged 19-29 years-old) volunteered for the study, and were randomly assigned to subgroups (n = 7). Subjects received a cup of 200 mL bitter lemon juice containing either alcohol (30 mL of a 70 percent solution) or caffeine (300 mg) or both. Twenty minutes after dosing subjects were given the Pauli-test (concentration test performance measured by an arithmetic test) 6 times at intervals of 6 to 40 minutes.

The results showed an interaction between alcohol, caffeine, and gender. In males all three treatments decreased test performance compared to the placebo group, with the alcohol and caffeine alone groups being the lowest, the combined treatment group performed better than those of caffeine or alcohol alone groups. For females, alcohol as well as caffeine increased concentration while the combined treatment had an antagonistic effect i.e., decreased test performance to levels similar to the female placebo group.

The authors concluded that caffeine partially compensates the inhibitory effect of alcohol only in males, not females. There are gender-specific differences in that alcohol and caffeine act synergistically in males and antagonistically in females.

CFSAN agrees with the authors that the interaction between alcohol and caffeine, at the doses tested, resulted in different effects in the performance of males and females on the arithmetic test.

Fudin R, and Nicastro R. Can caffeine antagonize alcohol-induced performance decrements in humans? Percept Mot Skills 67:375–391, 1988.

This publication reviewed the design and findings in several studies published between 1935 and 1983, which were conducted to investigate the effects of caffeine on alcohol-induced performance decrements in humans. [Note: The individual studies reviewed by Fudin et al. will be summarized

here, however studies by Oborne et al. (1983), Nuotto et al. (1982), Keuchel et al. (1979) and Franks et al. (1975) which have already been reviewed separately in this memorandum will not be discussed here.]

Strongin et al. (1935) measured parotid secretion, arm steadiness and motor coordination after dosing alcohol and caffeine. The exact dosages of caffeine and alcohol were not reported for this study, however caffeine was provided at several unspecified times before and after alcohol ingestion.

The following study results were reported:

1. Alcohol inhibited parotid secretion.
2. Caffeine ingested immediately after alcohol offset the alcohol-induced inhibition and disturbances of arm steadiness and eye-hand coordination for 1 hour for most subjects, after which the effects wore off and subjects again experienced alcohol's negative effects.
3. Caffeine ingested 45 minutes after alcohol was only partially effective in offsetting the alcohol-induced inhibition of parotid secretion.
4. Caffeine given several times before and after alcohol consumption offset the alcohol-induced inhibition of parotid secretion for 60 to 70 minutes.

CFSAN notes that Strongin et al. did not present any statistical analysis for their results.

Newman and Newman (1956) dosed 4 participants (gender unspecified) who were moderate social drinkers with 3.55 oz/68.04 kg bw absolute alcohol which was consumed over 2 hours and 300 mg caffeine (order of dosing not reported). They measured balance on one foot with eyes closed, hand steadiness, EEG, and flicker fusion. Compared to alcohol alone, alcohol + caffeine improved performance (balance on one foot with eyes closed) by 10 percent for all subjects.

Moskowitz and Burns (1981) conducted two experiments to test the possible antagonistic effects of caffeine on alcohol-induced impairments in driving-related skills. In both experiments alcohol was consumed over 30 minutes and caffeine capsules were ingested 10 minutes after alcohol. In experiment 1, 12 male subjects were dosed 0.58 g/kg absolute alcohol and 4.4 mg/kg caffeine, while in experiment 2 subjects (36 males) were dosed 0.50 or 0.99 g/kg alcohol and 2.93 or 5.87 mg/kg bw caffeine. They measured compensatory tracking, divided attention, reaction time (RT), information processing rate, and critical tracking.

The following study results were reported:

1. Experiment 1: Alcohol + caffeine lowered error rates to baseline values on compensatory tracking and visual search RT under divided attention.
2. Experiment 2: Compared to alcohol alone, 0.50 g/kg alcohol + 2.93 mg/kg caffeine improved performance in all measures, 0.50 g alcohol + 5.87 mg/kg caffeine improved performance on all measures except information processing rate.
3. Results for alcohol (0.5 g/kg) + caffeine (both doses) were superior to baseline values for compensatory tracking, RT, divided attention task, and critical tracking.
4. Alcohol (0.99 g) + caffeine improved performance compared to alcohol only group but the performances were inferior to baseline values.

The authors concluded that only certain alcohol-induced performances were influenced by caffeine, and the ability of caffeine to offset some alcohol-induced impairments was limited to alcohol dosages resulting in mean peak BACs of 0.047 percent and 0.065 percent (i.e., 0.5 and 0.58 g/kg alcohol). 200-400 mg caffeine antagonized some alcohol-induced driving-related decrements when BACs were below 0.10 percent. At mean peak BAC of 0.112 percent (produced by 0.99g/kg alcohol) caffeine did not offset any alcohol-induced impairments.

Forney and Hughes (1965) dosed 4 males and 4 females 1.52 oz of absolute alcohol (45 mL/150 pound body weight) and 500 mg of caffeine simultaneously. They measured verbal output, reverse reading, reverse counting, progressive counting, addition, subtraction, addition plus seven, subtraction plus seven, color word discrimination.

Forney and Hughes did not find significant differences between alcohol + caffeine and alcohol alone groups in all nine measures. However, in a footnote, the review authors stated that Forney and Hughes stated that orthogonal contrasts showed significant alcohol caffeine interaction in progressive counting and addition tests, with caffeine antagonizing the alcohol-induced decrements.

Carpenter (1959) dosed 9 males (moderate drinkers) 0.4 mL/kg (0.92 oz) or 0.8 mL/kg (1.84 oz) of absolute alcohol and 1.47 or 2.94 mg/kg caffeine (order of dosing not reported) and measured simple visual reaction time.

Carpenter reported that alcohol induced increases in simple visual RT were not decreased significantly by either of the two caffeine levels.

Fudin and Nicastro (authors of the review article) concluded that the results indicate that legally intoxicated individuals cannot antagonize alcohol-induced, driving-related decrements with caffeine prior to driving an automobile. They suggested further research into factors that could affect the interaction for example, areas of habitual use or nonuse of caffeine with typical alcohol consumption levels, interval between ingestion of alcohol and caffeine, and statistical analysis to allow for differentiation of results in which caffeine partially offsets an alcohol-induced decrement from more positive results in which caffeine returns functioning to its normal level.

CFSAN notes that none of the data in the above studies were statistically analyzed to support the authors' conclusions. However, most of the more recent studies on the interaction of alcohol with caffeine have made appropriate changes to the experimental designs to address the deficiencies in many of the studies reviewed by Fudin and Nicastro (1988).

Ferreira SE, de Mello MT, Formigoni ML. [Can energy drinks affect the effects of alcoholic beverages? A study with users]. Rev Assoc Med Bras 50:48–51, 2004 (article in Portuguese, abstract reviewed)

The objective of this study was to determine the pattern of use of EDs alone or combined with alcoholic beverages using a questionnaire. One hundred and thirty-six (136) volunteers, mean age 24±6 years-old, responded to the questionnaire and reported using EDs. The data show that average ED ingested per drinking occasion is 1.5 cans. Other results are tabulated below:

Categories reported on	Subjects consuming ED alone (percent)	ED + alcohol (whisky or vodka or beer) (percent)
Use pattern	79	76
Reporting no effect	61	14
Increased happiness	10	38
Euphoria	9	30
Insomnia	9	11
Uninhibited behavior	7	27
Increased physical vigor	61	26

The authors concluded that the effects of energy drinks are variable depending on the dose and individual sensitivity.

2. ***Studies on Physiological Effects Related to Co-consumption of Caffeine and Alcohol:***

Ferreira SE, de Mello MT, Pompeia S, and de Souza-Formigoni ML. Effects of energy drink ingestion on alcohol intoxication. Alcohol Clin Exp Res 30: 598–605, 2006.

The study authors explored the effects in male volunteers of simultaneous consumption of alcohol (vodka 37.5 percent by volume) and ED) (Red Bul®l) compared with those of male volunteers consuming energy drink or alcohol alone.

Participants were 26 healthy male volunteers (age: 23 years-old, bw: 69 kg, height: 1.74 m, years of education: 13). Subjects were randomly assigned to two groups: Group 1 received 0.6 g/kg alcohol (n=12), and Group 2 received 1.0 g/kg alcohol (n=14). Each group completed three drinking sessions in double-blind random order, 7 days apart, as follows: alcohol alone, ED alone, or alcohol plus ED. The volume of Red Bull® consumed was 3.57 mL/kg, which is equivalent to 1 can per person and contains 1.14 mg/kg bw (79.8 mg/70 kg person) caffeine. The following parameters were measured: BAC at 15, 30, 60, 90, 120, and 150 minutes after treatment; subjective effects of intoxication (i.e., headache, dizziness, tremor, sense of well-being, alteration in speech, sight, and hearing) at 30 and 120 minutes after treatment; visual reaction time at 30 and 120 minutes after treatment; and, motor coordination at 30 and 120 minutes after treatment.

The following study results were reported:

1. Compared to the alcohol only group, the ingestion of alcohol and ED significantly reduced subjects' perception of headache, weakness, dry mouth, and impairment of motor coordination at the 120 minutes evaluation; it prevented the sensation of headache due to alcohol.
2. Ingestion of alcohol plus ED did not significantly reduce the deficits caused by alcohol on objective motor coordination and visual reaction time.
3. Ingestion of alcohol plus ED did not alter the BAC in either the 0.6 or the 1.0g/kg alcohol groups.

The authors concluded that ED reduced the intensity of some subjective symptoms of alcohol intoxication, but did not significantly reduce deficits due to alcohol ingestion detected in objective measures. The authors explained that the reduction in intoxication symptoms by ED may be due to a possible reduction in the depressant effects of alcohol as well as due to an increase in the duration/intensity of alcohol's excitatory effects. The authors suggest that the effects observed when alcohol and ED are co-consumed seem to depend on the dose of each and individual sensitivity.

CFSAN concluded that these results demonstrated that consumption of a mixture of alcohol and ED reduced subjects' subjective perception of intoxication but did not affect the alcohol-induced decrements in motor coordination and visual reaction time assessed using objective measures. Additionally, the co-consumption of caffeine with alcohol did not affect the BAC.

Hasenfratz M, Bunge A, Dal Pra G, Battig K. Antagonistic effects of caffeine and alcohol on mental performance parameters. Pharmacol Biochem Behav 46:463–465, 1993.

This study was designed to study the antagonistic interaction of caffeine and alcohol on mental performance when caffeine treatment preceded the alcohol treatment.

Participants were 9 healthy undergraduate male students (average age of 24.7 years-old, average body weight of 78.3 kg), who consumed moderate amounts of coffee (average 1.5 cups/day) and alcohol (1

beer or a glass of wine on average of 3.6 times/week) some of them were occasional smokers (<5 cigarettes/day). They were requested to abstain from smoking, drinking caffeinated beverages and alcohol for at least 12 hours prior to eating breakfast on test mornings. On treatment days subjects ingested: 1 cup of decaffeinated coffee (Decaff), or Decaff plus 3.3 mg/kg caffeine alone or alcohol alone (0.7 g/kg alcohol) or both (3.3 mg/kg caffeine followed by 0.7 g/kg alcohol). Measurements were taken 30 and 80 minutes after the beginning of drinking, and included: BAC, and rapid information processing parameters (i.e., reaction time and processing rate).

The study results indicate that drinking coffee (3.3 mg/kg caffeine) prior to alcohol (0.7 g/kg):

1. Significantly decreased the BAC (after 30 mins/80 mins: BAC = 0.038 percent / 0.046 percent (alcohol only) versus 0.026 percent / 0.031 percent (alcohol plus caffeine).
2. Alcohol: increased reaction time, caffeine: decreased reaction time, caffeine plus alcohol increased reaction time compared to the caffeine only group, reaction time decreased compared to the alcohol only group.
3. Alcohol: decreased processing rate, caffeine: increased processing rate, caffeine plus alcohol increased processing rate compared with alcohol alone, however the increase was less than that observed for caffeine alone.

The authors conclude that under the test conditions, caffeine was able to offset the debilitating effects of alcohol. The order of the treatments might play an important role, if caffeine is ingested before the absorption of the alcohol is completed it can offset the debilitating effects of alcohol. Administering alcohol and caffeine simultaneously or caffeine after alcohol ingestion may lead to equivocal results.

CFSAN notes that the study sample size is very small (9), and the order of ingestion in this study (caffeine followed by alcohol) does not accurately reflect the co-consumption of caffeine and alcohol that are marketed together in caffeinated alcoholic beverages. However, the results suggest that ingestion of caffeine prior to absorption of alcohol antagonized the effects of alcohol alone, in part, probably by reducing the rate of absorption of alcohol.

Maczinski CA, and Fillmore MT. Clubgoers and their trendy cocktails: Implications of mixing caffeine into alcohol on information processing and subjective reports of intoxication. Exp Clin Psychopharmacol, 14: 450–58. 2006.

This study was designed to investigate the acute effects of caffeine and alcohol, alone and in combination, on cognitive performance and subjective intoxication in social drinkers.

Twelve adults (6 men, 6 women, average age = 23.5 years-old, average body weight = 69.6 kg) participated in the 7-session study over 18.8 days. Their mean drinking frequency was 1.6 times/week, with a mean dose of 1.3 g/kg (equivalent to 5 bottles of beer with 5 percent alcohol content for a 70 kg person), drinking duration = 4.3 hours, mean caffeine use = 6.8 mg/kg/day (equivalent to two 16-oz cups of Starbucks blend coffee or 9 cans of 355-mL cans of cola beverage for a 70 kg person). The subjects were instructed to abstain from alcohol for 24 hours, abstain from caffeine for 8 hours, and to fast 4 hours prior to each test session. Caffeine was given at doses of 0, 2.0, and 4.0 mg/kg; alcohol was given at a dose of 0.65 g/kg (produces average peak BAC of 80 mg/100 mL approx 60 min after drinking), and, caffeine and alcohol were co-administered.

Measurements included: BAC (from 30, 45, 60, and 90 minutes after start of drinking session); psychological refractory period (PRP) interference scores, reaction time, and beverage ratings (to assess participants' estimate of the amount of alcohol consumed/session).

The respective treatments mediated the following results:

1. Alcohol and caffeine, alone or combined, had no effect on reaction time and simple auditory discrimination performance.
2. Caffeine (both dose levels) plus alcohol significantly decreased the PRP interference scores compared with alcohol alone.
3. Caffeine (both dose levels) plus alcohol significantly reduced the participants' estimate of the amount of alcohol consumed compared with alcohol alone.

The authors conclude that the results of this study suggest that the new alcoholic drink preferences for caffeinated alcohol warrant further investigation, and that the findings raise important questions about co-administration of caffeine with alcohol, as caffeine's ability to counteract the effects of alcohol might contribute to binge drinking, alcohol abuse, or other harmful patterns of alcohol consumption.

CFSAN comments that caffeine co-administered with alcohol appears to counteract some aspects of performance impairment due to alcohol (i.e., response speed), but not others (i.e., response accuracy) in subjects who are regular consumers of alcohol and caffeine. The brain mechanisms responsible for the lack of uniform counteracting effects of caffeine on impairments of speed and accuracy due to alcohol are largely unknown. CFSAN further comments that these findings raise safety questions about co-administration of caffeine and alcohol.

Mackay M, Tiplady B, Scholey AB. Interactions between alcohol and caffeine in relation to psychomotor speed and accuracy. Hum Psychopharmacol 17:151–156, 2002.

This study attempted to examine alcohol and caffeine interactions and their effect on performance using the four choice reaction-time task in a randomized, double-blind, placebo-controlled study.

Sixty-four (42 females, 22 males) healthy undergraduate students (mean age: 21.3 years-old, body weight range 47–99 kg), who were social alcohol drinkers and habitual caffeine drinkers participated in the study. Participants were randomly assigned to 1 of 4 treatment groups as follows:

- Group 1 - alcohol (0.66 g/kg) plus coffee (110–120 mg/person caffeine)
- Group 2 - Alcohol alone
- Group 3 - Caffeine alone
- Group 4 - Placebo (no alcohol, no caffeine).

Participants abstained from coffee for 12 hours prior to the experiment. Alcohol was administered prior to the coffee beverage. Tests began 20 minutes after the completion of coffee, and 50 minutes following the alcohol. The students were asked to perform the four choice reaction-time (FCRT) and the digit symbol substitution (DSST) tasks.

The authors concluded that the results support the idea that caffeine selectively antagonizes the effects of alcohol on aspects of performance. These results do not indicate that the deleterious effect of alcohol on driving can be reversed by caffeine because 1) the antagonism is limited and is not found for the outcome measure that may have relevance for driving, and 2) the tests are short and the effects have been assessed at only a single time-point after administration of alcohol and caffeine.

CFSAN agrees that the results of this study show evidence that caffeine selectively antagonizes the effects of alcohol on certain aspects of test performance. CFSAN notes that the DSST is sensitive to changes in the single dimension of speed, while driving involves multiple performance parameters not examined in this study, and that the outcome in this study cannot be interpreted as indicating that the deleterious effects of alcohol on driving can be effectively or completely reversed by caffeine.

Liguori A, and Robinson JH. Caffeine antagonism of alcohol-induced driving impairment. Drug Alcohol Depend 63:123–129, 2001.

This study was designed to determine the extent to which caffeine antagonizes alcohol-induced impairment of simulated automobile driving using a double-blind randomized procedure.

Fifteen healthy non-smoking adults (9 females) (mean age: 32 years-old, average body weight of 74 kg) who usually consumed an average of 5 drinks/week and 337 mg caffeine/day (mostly from coffee) participated in this study. Subjects abstained from caffeine and alcohol for 12 hours prior to each session. Subjects swallowed caffeine (0, 200, or 400 mg/d) capsules first, after 2 minutes alcohol (0.6 g/kg, 50 percent vodka) was ingested, and 45–105 minutes later the subjects completed the tests. The tests or measurements that were conducted included dynamic posturography, critical flicker fusion, choice reaction time (CRT), divided attention (stroop test), driving simulator, subjective effects scales, heart rate, blood pressure, and breath alcohol concentration (BrAC).

The following results were reported:

1. Caffeine alone increased alertness and jitteriness.
2. Alcohol alone increased ratings of dizzy, drug and high effects, body sway, slowed CRT and braking latency.
3. Caffeine (400 mg) plus alcohol resulted in significantly fewer ratings of drowsy feeling compared to alcohol alone.
4. Caffeine (at both doses) plus alcohol counteracted the alcohol impairment of braking latency but not CRT or body sway.

CFSAN agrees with the authors' conclusion that these results suggest caffeine may increase alertness but will not completely counteract a driver's alcohol impairment. Any improvements in driving produced by caffeine plus alcohol relative to alcohol alone would not mitigate the potentially dangerous increases in reaction time relative to placebo.

Ferreira SE, de Mello MT, Rossi MV, Souza-Formigoni ML. Does an energy drink modify the effects of alcohol in a maximal effort test? Alcohol Clin Exp Res 28:1408–1412, 2004.

The main objective of this study was to verify the effects of alcohol, and alcohol combined with energy drink, on performance in a maximal effort test (ET) and also on physiological indicators and biochemical variables.

Fourteen male volunteers (mean age: 24 years-old, BMI of 23, education:13 years, moderate consumers of alcohol and energy drinks) participated in the double-blind protocol made up of 4 sessions: control (water), alcohol (1.0g/kg vodka Smirnoff®), energy drink (ED) (3.57 mL/kg Red Bull® equivalent to one 250 mL can for a 70 kg person, Red Bull® contains 32 mg caffeine/100 mL), and alcohol plus energy drink, each one week apart. Test substance was administered 60 minutes after a meal. Blood samples were collected 30 minutes after ingesting test substance, immediately after ET (cycle ergometer), 30, and 60 minutes after ET for the following: glucose, lactate, insulin, adrenocorticotropic hormone (ACTH), cortisol and catecholamines, and BAC. Physiological indicators measured include: heart rate, oxygen uptake (VO_2), ventilatory threshold and blood pressure (BP).

The results of the study show that:

1. No significant differences among all trials in BAC, BP, glucose, insulin, dopamine, adrenaline, ACTH, and cortisol levels, and VO_2.

2. Heart rate at the ventilatory threshold was significantly higher in the alcohol alone and alcohol plus ED trials than in the control and ED trials.
3. Alcohol plus ED ingestion significantly increased blood lactate levels immediately after the ET compared with the control, alcohol only and ED alone trials.
4. Alcohol alone and alcohol plus ED ingestion significantly increased blood noradrenaline levels 30 minutes after ET compared with the control, and ED alone trials.

The authors concluded that the results do not confirm the reports on the efficacy of ED in antagonizing the harmful effects due to alcohol consumption. However, due to increasing popularity of the combination of ED with alcohol, the authors suggest that other studies are needed.

CFSAN notes that there were no significant differences between alcohol and alcohol plus ED groups in the physiological and biochemical parameters measured. The results suggest that combined ingestion of ED (containing 32 mg caffeine) and alcohol did not antagonize the effects due to alcohol. This study tested only one dose of ED plus alcohol, it is not clear if higher doses of ED could have antagonized the effects due to alcohol.

Franks HM, Hagedorn H, Hensley VR, Starmer GA. The effect of caffeine on human performance, alone and in combination with ethanol. Psychopharmacologia 45:177–181, 1975.

The aim of this study was to determine the effect of caffeine alone or in combination with alcohol on human performance during a series of cognitive, perceptual, and motor function tests.

Sixty-eight (68) healthy university students (31 males and 37 females, ages 20–28 years-old) having mild to moderate drinking habits participated in the study conducted over an 8-week period. Subjects abstained from caffeinated beverages before arrival. Subjects were assigned to one of 4 groups and administered (blindly), placebo (decaffeinated coffee or orange squash (a fruit-based beverage)), or caffeine (300 mg/70 kg bw), or alcohol (0.75 g/kg), or caffeine plus alcohol (caffeine was ingested immediately after the alcohol). Twenty minutes after ingestion of the respective beverages, the following tests were performed: plasma alcohol and lactate concentration, and a battery of tests (stand steadiness, simple and complex reaction time, manual dexterity, numerical reasoning, perceptual speed and verbal fluency).

The results of the study show that:

1. Caffeine prolonged peak plasma alcohol concentration. Plasma alcohol concentration (mg/100 mL) peaked after 40 minutes for the alcohol and alcohol plus caffeine groups respectively (92 versus 91), declined at 100 minutes for alcohol group only but stayed at peak level for the caffeine plus alcohol group (83 versus 91), and was higher at 160 minutes after ingestion (72 versus 78).
2. Alcohol and alcohol plus caffeine decreased the standing steadiness time at 40 and 100 minutes after ingestion, standing steadiness time began to increase after 120 to 160 minutes, but was still below time for caffeine only and placebo groups. Caffeine alone increased standing steadiness time at 40 minutes.
3. Alcohol alone increased complex reaction time, while caffeine alone decreased it compared to placebo; alcohol plus caffeine decreased complex reaction time compared with the alcohol alone group, but reaction time was still higher than the placebo and caffeine only groups.
4. Alcohol significantly increased the visual reaction time and auditory reaction time, caffeine plus alcohol reduced the visual and auditory reaction times compared to the alcohol only group at 160 minutes.

5. Alcohol alone and alcohol plus caffeine groups both showed significant increase in number of errors in numerical reasoning compared with placebo and caffeine only groups at 160 minutes.

The authors concluded that caffeine did not antagonize the alcohol-induced decrement in performance except in the reaction time tests, and that caffeine alone increased body sway significantly at 40 minutes.

CFSAN notes that caffeine decreased some effects associated with alcohol consumption but had no effect on blood alcohol concentration. The data show that in the presence of caffeine, plasma alcohol concentration remained at the peak level for a longer period of time. The results are consistent with other study results in showing the danger in the combined ingestion of alcohol with caffeine, the drinker may feel more alert and less drunk and may remain unaware of continuing impairment of motor coordination and engage in risky behaviors such as driving while legally intoxicated.

Azcona O, Barbanoj MJ, Torrent J, Jane F. Evaluation of the central effects of alcohol and caffeine interaction. Br J Clin Pharmacol 40:393–400, 1995.

The objective of this study was to evaluate the effects of alcohol as a depressant and caffeine as a stimulant when administered alone or combined, to healthy volunteers, using psychomotor performance and electrophysiological tests, and tools to assess subjective feelings.

Participants (8 healthy males, mean age: 24.5 years-old, body weight: 71.6 kg, mean height: 176 centimeters) in the double-blind, placebo-controlled, cross-over trial, abstained from alcohol, coffee, tea and cola beverages for 24 hours prior to and throughout the study. Treatments were administered to subjects in 4 sessions, with a one week wash-out period between each session, as follows: 1) placebo (orange juice and lactose capsule), 2) alcohol (0.8 g/kg), 3) caffeine (400 mg capsule), and 4) alcohol (0.8 g/kg) plus+ caffeine (400 mg). The following parameters were measured: 1) objective measures include psychomotor performance (critical flicker fusion frequency (CFF), simple reaction time (SRT), and tapping test), visual evoked potentials (VEP); 2) subjective measures include visual analogue scales (VAS), and profile of mood states (POMS); 3) plasma alcohol and caffeine concentrations; 4) clinical evaluations include electrocardiogram (ECG), blood pressure, heart rate, and 28 effects experienced symptoms (EES) e.g., diuresis, lightheadedness, euphoria, blurred vision, headache, palpitations. Evaluations were done after 0.5, 1.5, 2.5, 4, and 6 hours after ingestion of the test substance.

The study results show that:

1. Alcohol (0.8 g/kg) significantly impaired (increased) SRT, while caffeine (400 mg) significantly decreased SRT compared to alcohol alone and placebo groups. Alcohol (0.8 g/kg) plus caffeine (400 mg) decreased SRT (ameliorated alcohol impairment) compared to the alcohol group, with the effect significant after 0.5, 2.5 and 4 hours after consumption, but not after 6 hours.
2. Alcohol significantly decreased central inter-peak amplitudes of the VEP and caffeine increased amplitude of the VEP, while central inter-peak amplitudes for alcohol plus caffeine group were in between.
3. Alcohol alone and alcohol plus caffeine produced a significant feeling of drunkenness as measured by POMS and VAS, the feeing of drunkenness due to alcohol and the combination was statistically different from caffeine at 0.5, 1.5, and 2.5 hours after ingestion.
4. Clinical symptoms most frequently reported were: alcohol alone: light-headedness (8.9 percent), increased diuresis (8.9 percent), feeling tired (8.2 percent); caffeine alone: euphoria

(8.3 percent), increased diuresis (7.8 percent); alcohol plus caffeine: light-headedness and euphoria (8 percent), increased diuresis and feeling tired (9.4 percent).

The authors concluded that at the doses tested, both caffeine and alcohol administered alone displayed their known behavioral CNS effects as a stimulant and depressant, respectively. Combined ingestion of caffeine plus alcohol counteracted some of the effects due to alcohol. Only those objective tests that demonstrated significant effect with caffeine (i.e., SRT, VEP and CFF) were able to detect the counteracting effects of caffeine over alcohol.

CFSAN notes that there were no differences in plasma alcohol concentrations between the alcohol alone and caffeine plus alcohol groups. Alcohol (at the dose tested) appears to prolong/inhibit the metabolism of caffeine as indicated by kinetic results in this study. Plasma caffeine concentration peaked at 90 minutes (caffeine only group) versus 120 minutes (caffeine plus alcohol group), and plasma caffeine concentration remained higher for the caffeine plus alcohol group at 6 hours.

Nuotto E, Mattila MJ, Seppala T, Konno K. Coffee and caffeine and alcohol effects on psychomotor function. Clin Pharmacol Ther 31:68–76, 1982.

This study was designed to assess the interactions of alcohol and caffeine in a double-blind crossover trial using either a fixed dose of alcohol with variable doses of caffeine (study I), or a fixed dose of caffeine with two doses of alcohol (study II).

Participants were 20 healthy male volunteers (10/study) with average age 21.3 years-old, body weight 67.6 kg, and height 176.4 cm for study I; average age 21.1 years-old, body weight 67.4 kg, height 175.6 cm for study II. They were requested to fast for 4 hours, abstain from alcohol, coffee, tea, and cola beverages for 24 hours prior to test sessions.

In study I (4 sessions), caffeine was administered 60 minutes after ingestion of alcohol. The four study sessions were as follows:

1. H1 A1.0 (alcohol only): 1 g/kg alcohol (in 300 mL juice) + 1 cup (250 mL) decaffeinated coffee (Hag)
2. H3 A1.0 (alcohol only): 1 g/kg alcohol + 3 doses Hag
3. C2 A1.0 (alcohol plus caffeine): 1 g/kg alcohol + 200 mg caffeine in 1 cup Hag
4. C5 A1.0 (alcohol plus caffeine): 1 g/kg alcohol + 500 mg caffeine in 1 cup Hag

In study II (6 sessions), caffeine/decaffeinated coffee (Hag) was administered at 60 and 105 minutes. The six study sessions were as follows:

1. H1 P (placebo group): Juice + 1 cup Hag
2. C5 P (caffeine): Juice + 250 mg caffeine + 250 mg caffeine
3. H1 A0.7 (alcohol): 0.7 g/kg alcohol + 1 cup Hag
4. C5 A0.7 (alcohol plus caffeine): 0.7 g/kg alcohol + 250 mg caffeine + 250 mg caffeine
5. H1 A1.5 (alcohol): 1.5 g/kg alcohol + 1 cup Hag
6. C5 A1.5 (alcohol plus caffeine): 1.5 g/kg alcohol + 250 mg caffeine + 250 mg caffeine

Parameters measured (at 45, 90, 120 and 180 minutes) include: BACs, serum caffeine, body sway/balance, hand-eye coordination, hand steadiness, choice reaction test, central visual processes, esophoria, and horizontal nystagmus.

The following results were observed:

1. Peak BACs (mg/mL)/time (minutes) were 0.94/45 after dosing 1.0 g/kg in study I, and 0.55/90 after dosing 0.7 mg/kg alcohol and 1.2/90 after dosing 1.5 g/kg in study II. Caffeine had no effect on BAC.
2. Alcohol dose-dependently increased body sway with eyes open, and impaired coordination skills, effect was greatest at 90 and 120 minutes in study I & II respectively. Combined intake of 1.5 g/kg alcohol plus 500 mg caffeine lowered body sway for measurements taken at 120 and 180 minutes compared to the alcohol only group.
3. In study II, alcohol significantly elevated serum caffeine concentration in a dose-dependent manner when 500 mg caffeine was dosed (12.9 (C5 P), 14.8 (C5 A0.7), 17.2 (C5 A1.5) µg/mL).

CFSAN agrees with the authors' comments and conclusions that the study design allowed absorption of most of the alcohol prior to consumption of caffeine. The elevated serum caffeine concentrations after alcohol plus caffeine ingestion may be due to a nonspecific alcohol load to the metabolic capacity of the liver or that alcohol, by increasing hepatic blood flow, reduces the first-pass metabolism of caffeine during its absorption phase. The authors concluded that there was no clear caffeine-alcohol interaction in objective or subjective parameters measured, and that results of interaction studies may depend on the tests or doses used, or the trial design.

C. Summary of Animal data

1***. Studies on Physiological Effects Measured with Caffeine and Alcohol:***

Jain AC, Mehta MC, Billie M. Combined effects of caffeine and alcohol on hemodynamics and coronary artery blood flow in dogs. J Cardiovascular Pharmacol 33: 49–55, January 1999.

This study was designed to assess the combined effects of caffeine and alcohol on cardiovascular hemodynamics. Fifteen dogs were lightly anesthetized and prepared to measure heart rate (HR), coronary artery blood-flow reserve (CFR), pulmonary artery and left ventricular (LV) pressure measurements, and cardiac output (CO) in response to four treatments: 1) caffeine; 2) alcohol; 3) caffeine plus alcohol; and 4) alcohol plus caffeine administered by intracoronary bolus.

In Phase I intravenous (i.v.) doses of 5 mg/kg caffeine and 400 mg of alcohol were injected and blood caffeine and alcohol levels (66 +/- 10 mg/100 mL) were determined. Caffeine showed mild, non-significant increase in HR, systolic (S) and diastolic pressure (D) and mild, non-significant decreases in CO, stroke volume (SV). Alcohol doses of 400 mg/kg showed mild, non-significant increases in HR, D, MAP and a mild, non-significant decrease in SV and systemic vascular resistance (SVR).

In Phase II caffeine was injected followed by alcohol and multiple recordings were made for up to 30 minutes. Results were: significant synergistic increase in HR, S, D, MAP, SV, and SVR; however, CO and CFR did not change significantly.

Phase III- alcohol then caffeine were injected with multiple recordings up to 30 minutes. Results were: mostly non-significant changes, but alcohol's actions were antagonized by caffeine and no changes in HR, MAP, CO, SV, SVR.

CFSAN notes that caffeine mediates complex and occasionally antagonistic cardiovascular responses depending on dose, order of dosing and conditions prevailing at the time of their administrations. The responses appear to be the result of the complex activity from the overall balance between caffeine's numerous physiological effects and interactions: phosphodiesterase inhibition, adenosine receptor blocker, release of catecholamines, increased rennin activity in plasma, effects on intracellular

calcium, adenylcyclase activity and changes to cyclic adenosine monophosphate (AMP) levels. In sum, both the authors and CFSAN conclude that these results suggest that caffeine reverses some of the hemodynamic changes mediated by alcohol.

Case TS, Saltzman MJ, Cheuk J, Yazdani M, Sadeghpour A, Albrecht D, Rossowska MJ, Nakamoto T. Combined effects of caffeine and alcohol during pregnancy on bones in newborn rats. Res Exp Med 196: 179–185, 1996.

Pregnant rats were assigned to four groups: 1) control; 2) caffeine; 3) alcohol; and 4) caffeine plus alcohol. Alcohol was given by intubation two times daily (1 g/kg bw) starting on day 9 of gestation. Caffeine was given as a dietary supplement (2 mg/100 grams body weight (mg/g bw)). At birth, randomly selected pups were killed and the mandible and femur were taken and dried. Measurements of calcium (Ca), phosphorus (P), magnesium (Mg), zinc (Zn) and hydroxyproline were conducted.

There were no changes in the weight of the femur and mandible but calcium content of bones in the caffeine group, in contrast to the alcohol group, decreased 20–30 percent compared to controls. There were no calcium-related changes found to the calcium in the alcohol group; however, this effect may depend on dosage as chronic alcohol consumption leads to skeletal changes in both animals (Lee et al., 1968) and man (Clarren S.K. et al., 1978).

The content of calcium in the mandible and femur in the caffeine plus alcohol group decreased by 27 percent and 38 percent, respectively. Intake of both compounds appears to increase the calcium demineralization effect when compared to caffeine or alcohol given alone. In the same group, phosphorous was affected less; thus, 14 percent and 25 percent decreases in the mandible and femur, respectively. The decreased calcium content in the bones also leads to a decreased calcium/phosphorus ratio. A significant increase in magnesium (18 percent) and hydroxyproline was found in the alcohol group. In response to the caffeine plus alcohol group a loss of magnesium and hydroxyproline content occurred. The content of zinc was decreased more by the combined exposure to caffeine and alcohol than to caffeine alone.

Study authors stated that the adverse effects on bone mineralization were greater with the combination administration of caffeine and alcohol compared to the effects of the individual agents.

CFSAN agrees with the authors' conclusions and indicates that these potential demineralization effects, taken as a whole, indicate the need for women to exercise caution in the combined consumption of caffeine and alcohol when pregnant or attempting to become pregnant.

Hannigan, JH. Effects of prenatal exposure to alcohol plus caffeine in rats: pregnancy outcome and early offspring development. Alcohol Clin Exp Res 19: 238–246, 1995.

Rats were exposed to about 15 g/kg bw/day of alcohol with or without caffeine (84 mg/kg bw/d) from gestation days 6–20 by liquid diet. Prenatal exposure to both alcohol and caffeine resulted in decreased weight gain by the dams and decreased birth weight of the pups while increasing the pup mortality. Prenatal alcohol exposure had a significant negative effect on several developmental measures, including grip strength, and negative geotaxis. Prenatal caffeine exposure only produced a reduction of the concentration of the enzyme, alkaline phosphatase. This study showed that caffeine can worsen some of alcohol's prenatal adverse effects, i.e., reduced birth weight, litter size and postnatal survival. Moreover, the authors note that one of the main diagnostic criteria for Fetal Alcohol Syndrome is decreased birth weight.

CFSAN notes the very large doses of alcohol used in this study, but concludes that at these doses the results suggest that high levels of maternal caffeine intake in humans could increase the probability that a child exposed prenatally to alcohol could be born with a significantly lowered birth weight or other alcohol-related birth defects.

Kunin D, Gaskin S, Rogan F, Smith BR, Amit Z. Augmentation of corticosterone release by means of a caffeine-ethanol interaction in rats. Alcohol 22:53–56, 2000.

Alcohol and caffeine when given intraperitoneally (i.p.) as single agents mediated no change in corticosterone (CORT) serum levels in rats. When caffeine was administered 30 minutes prior to the alcohol dosing, there was a statistically significant rise in CORT compared to single agent dosing. Another study (Fahlke et al., 1994) showed that removal of the adrenal gland resulted in reduced alcohol intake. When CORT was added to the drinking water before alcohol ingestion, alcohol intake returned. Caffeine facilitates the intake of alcohol in a dose-responsive manner and at the same dose augments the intake of alcohol in rats with a pre-established alcohol drinking habit (Kunin, et al., 2000). It is hypothesized that CORT increases alcohol consumption by enhancing the positive reinforcing properties of alcohol.

The authors argue that this caffeine-mediated rise in CORT serum levels seen in this study may affect the caffeine-induced elevations in alcohol intake observed in other studies. CFSAN concludes that this is a plausible, but as yet unproven, explanation of the results observed in this study.

2. *Studies on* ***Behavioral Effects Related to Co-administration of Caffeine and Alcohol:***

Hilakivi LA, Durcan MJ, Lister RG. Effects of caffeine on social behavior, exploration and locomotor activity: interaction with ethanol. Life Sci 44:543–553, 1989.

The interactions of caffeine with alcohol were examined in a test of social behavior and a test of exploration and locomotion using a "holeboard." This apparatus consists of a walled space with 1.25 inch holes drilled in the floor on 3 inch centers. Alcohol doses of either 0 or 2.0 g/kg bw were given 30 minutes before the test. Caffeine doses of 0, 15, 30 or 60 mg/kg bw were injected i.p. 30 minutes before the test. The final test phase used the same doses of alcohol and caffeine that were co-administered 20 minutes before the test began. Animals were placed in the test apparatus either in pairs or alone on the holeboard. Social interaction and motor activity were measured. Only the 60 mg/kg bw dose of caffeine had a significant effect on these two measures, it reduced both of them. The duration and frequency of avoidance-irritability behavior was increased in a dose-dependent manner. The caffeine also mediated a dose-dependent increase in locomotor activity as measured on the holeboard. The 30 mg/kg bw dose of caffeine reversed the alcohol-induced reduction of time spent in social interaction. The 60 mg/kg bw dose of caffeine antagonized the alcohol-induced increase in locomotor activity in both the social behavior and the holeboard tests. These caffeine-mediated interferences with alcohol's activities appears to result from a pharmacodynamic rather than pharmacokinetic mechanism as the blood levels of alcohol were comparable in both conditions, either alcohol alone or caffeine administered with alcohol. The authors conclude that the mechanism whereby caffeine affects alcohol's effects is not known at this time. CFSAN agrees with that conclusion and also notes that in this study as well as others discussed in this section of animal behavioral test responses, the presence of caffeine alters the animal's responses to alcohol in an unpredictable manner.

Elsner J, Alder S, Zbinden G. Interaction between ethanol and caffeine in operant behavior of rats. Psychopharmacology 96: 194-205, 1988.

The interaction between alcohol and caffeine on operant behavior was assessed in 24 water-deprived male rats trained in a discrete trial spatial alternation design with water as the reinforcer. One single drug dose-response experiment or one dose combination of alcohol and caffeine and the appropriate control treatments were run on 4 successive days in one week. The four treatments of one week were applied in a predetermined order until all 24 possible treatment combinations were completed. Single drug doses for alcohol were 0.25, 0.50, 0.75, and 1.0 g/kg bw administered i.p. and for caffeine they were 5, 10, 20, and 40 mg/kg bw given orally (p.o.). All combinations of alcohol at 0.5 and 1.0 g/kg bw i.p. and caffeine at 25 and 50 mg/kg bw p.o. were administered to all rats.

The two substances when given alone mediated characteristic, and, in many ways, similar effects on the operant behavior in spatial alternation, the combination of alcohol with caffeine resulted in a complex response pattern. Caffeine generally increased the deleterious effects of alcohol on performance variables such as accuracy, latency and attention (pause length and response spans), but it partially normalized the depression-type variables such as pause length, intertrial interval response rate and response duration. While potentiating the deterioration of accuracy, caffeine in high doses reduced the effect of high-dose alcohol on error persistence, therefore exhibiting a particular influence on alcohol-induced performance decrements.

The authors hypothesize that one might compare and extrapolate these animal results to experiments run on human subjects under similar co-exposure scenarios. These human subjects judge that their alcohol-induced behavioral deficits are compensated by caffeine. One might suggest that caffeine containing beverages can improve a subjective depression caused by alcohol, but at the same time potentiate behavioral inabilities to perform critical tasks. Consequently, an individual feels more able to perform, but the actual behavioral accuracy is impaired even more with the combination than with alcohol alone.

CFSAN agrees that the effects on these substances on behaviors manifested in these experiments are akin to those behaviors that have been observed and described in human literature (e.g., O'Brien et al., 2008).

Kuribara H, Tadokoro S. Caffeine does not effectively ameliorate, but rather may worsen the alcohol intoxication when assessed by discrete avoidance in mice. Jpn J Pharmacol 59: 393–398, 1992.

Male mice of the ddY strain were acclimated to apparatus used in avoidance tests for lever-press avoidance and shuttle avoidance. The foot shock was administered following a 5 second warning followed by an intertrial interval of 25 seconds. Outputs measured were the response rate (frequency of lever-presses or shuttles) and the percentage of avoidances (number of avoidance responses/number of avoidance trials). The drugs used in this study were: caffeine (0, 1, 3, 10, 30, and 100 mg/kg bw orally), alcohol (0, 0.8, 1.6, 2.4, 3.2 gm/kg bw given orally), diazepam (2 mg/kg bw), and pentobarbital (10 mg/kg bw) both given subcutaneously.

Alcohol disrupted the lever-press and the shuttle avoidances in mice in doses over 1.6 and 2.4 g/kg with a dose-dependent decrease in the percentage avoidance with little change in the lever-press response rate. Caffeine increased the response rate of both avoidances at doses of 1–30 mg/kg bw, but disrupted both avoidances at 100 mg/kg bw. Caffeine (10 mg/kg bw) reduced the decreased percentage of shuttle avoidance responses by alcohol with a significant elevation in lever-press response. On the other hand, the percentage of shuttle avoidance was significantly lessened after the combined administration of alcohol with caffeine than after alcohol alone.

Diazepam and pentobarbital significantly decreased both the lever-press response rate and the percentage shuttle avoidance. Caffeine ameliorated the decreased lever-press response rate and the percentage of avoidance mediated by diazepam and pentobarbital. The authors note that the influence of caffeine on alcohol's responses is different than the effects of caffeine on diazepam and pentobarbital responses.

These results indicated to CFSAN that there was a differential effect of caffeine on alcohol compared to its effects on other depressant-type substances, e.g., diazepam and pentobarbital and that caffeine does not effectively attenuate, but may result in a worsening of the alcohol-mediated toxicity.

Kuribara, H. Enhancement of the behavioral toxicity induced by combined administration of ethanol with methylxanthines: Evaluation by discrete avoidance in mice. J Toxicol Sci 18:95–101, 1993.

The author of this paper studied the effect of alcohol (1.6 and 3.2 g/kg bw) and methylxanthines, caffeine (3–30 mg/kg bw), theophylline (3–100 mg/kg bw) and theobromine (3–100 mg/kg bw) with all agents and doses administered orally. Mice were tested in a lever press and shuttle avoidance operant design. After a signal (stimulus) or warning, the mice either pressed a lever or shuttled to other side of the enclosure. Either response would allow the mouse to avoid the electric shock. Successfully pre-trained mice were used to measure the effect of alcohol and the methylxanthines on shock avoidance. Alcohol given alone in two doses disrupted the decrete lever-press and shuttle avoidance, producing a decrease in avoidance rate. The 3.2 mg/kg dose of alcohol mediated an increase in the response rate. Each of the methylxanthines across all doses produced no significant change in either the response rate or the avoidance rate when administered singly. Lower doses of these agents increased the number of shuttle avoidances, but produced no change in rate of avoiding shocks. Intermediate doses of the methylxanthines resulted in an inhibition of the decrease in shuttle avoidances by a non-specific increase in the response rate. In shuttle avoidance the response rate for combined alcohol and methylxanthines was sometimes increased.

The authors and CFSAN interpret these results to suggest that, although alcohol and methylxanthines have CNS depressant and stimulant activities, respectively, methylxanthines, including caffeine, do not specifically improve, but instead may worsen, the alcohol-induced avoidance disruption, indicating an augmentation of alcohol's behavioral toxicity.

Kuribara H, Asahi T, Tadokoro S. Ethanol enhances, but diazepam and pentobarbital reduce the ambulation-increasing effect of caffeine in mice. Jpn J Alcohol Drug Depend 27:528–539, 1992 [Arukoru Kenkyuto Yakubutsu Ison. 1992 Oct;27(5):528-39].

The objective of this study was to assess the combined administration of alcohol and caffeine on the ambulatory activity of mice. Diazepam and pentobarbital were also studied with combined administration with alcohol. The rate of ambulatory activities were elevated in response to the concurrent administration of caffeine (10 mg/kg bw orally) and alcohol (1.6, 2.4, 3.2 gm/kg bw orally) compared to the ambulatory rates induced by individual administration of these agents. Alcohol at 1.6 g/kg bw was chosen as the test dose to be given with caffeine. Doses of diazepam (0.25, 0.5, and 2 mg/kg bw subcutaneously) and pentobarbital (1, 3, and 10 mg/kg bw subcutaneously) were concurrently given with alcohol as well. Alcohol at lower doses, i.e., 0.4-1.6 gm/kg bw increased ambulatory responses only slightly, but doses of 2.4 and 3.2 g/kg bw produced greater responses, but with ataxia as well. Caffeine alone caused a larger increase in ambulation than any of the alcohol doses alone. When caffeine was co-administered with alcohol the level of ambulation was increased further yet. Diazepam and pentobarbital given as individual agents did not change the ambulatory rate, but when they were combined with caffeine, they significantly reduced

the enhanced rate of ambulation manifested by caffeine. CFSAN finds that these results suggest that mice manifest a dose-related increase in locomotor activity that is elevated further by the co-administration of caffeine and in addition interferes with balance and gait. Diazepam and pentobarbital have a different effect.

Ferreira SE, Hartmann Quadros IM, Trindade AA, Takahashi S, Koyama RG, Souza-Formigoni ML. Can energy drinks reduce the depressor effect of ethanol? An experimental study in mice. Physiol Behav 82: 841–842, 2004.

Albino Swiss male mice at 75 days were orally administered energy drink (Red Bull®) in doses equivalent to 1, 3, 5, and 10 cans. Alcohol was diluted in energy drink or water in concentrations from 0.5g/kg bw to 2.5 g/kg bw and given orally.

Procedures included screening for pharmacologic activity, locomotor activity effects and measurement of blood alcohol levels. There were no indications of pharmacological effects following alcohol or energy drinks. Total locomotor activity at 45 minutes in response to energy drink was increased in all doses.

The interaction of alcohol and energy drink was complex with high-dose alcohol not affecting the dose-related increase in locomotor activity induced by energy drink. Lower doses, however, significantly reduced this stimulant effect on this parameter at 15–30 minutes and tended to reduce it at 30–45 minutes. The intermediate dose of alcohol reduced the stimulant effect at all time periods. The high dose of alcohol (2.5 g/kg bw) significantly decreased locomotor activity compared to controls at 30–45 minutes; however, this depressant effect could be attenuated by concurrently giving energy drink. No differences were found in the rate of metabolism of alcohol when co-administered with energy drink.

CFSAN agrees with the authors who concluded that while the data support the conclusion that the dose of 10.7 mL/kg bw of energy drink antagonized some of the depressant effects of alcohol on the locomotor activity of mice, this reversal of effect was only to control levels and there was not a complete reversal of the acute effects of alcohol on locomotor activity by the energy drink.

Waldeck, B. Ethanol and caffeine: a complex interaction with respect to locomotor activity and central catecholamines. Psychopharmacologia 36: 209–220, 1974.

The response to alcohol and caffeine on the locomotor activity (motility) of mice was studied. Caffeine, 25 mg/kg bw, which alone stimulated motility enhanced the motility elicited by alcohol (1–2 g/kg). When 3 g/kg bw alcohol was given, caffeine, 25 and 50 mg/kg bw, did not change the level of activity while 100 mg/kg bw abolished the increase in activity caused by alcohol alone. A mixture of ET495 and clonidine, which stimulate central dopamine and noradrenaline receptors respectively, causes reversal of the reserpine-induced suppression of motility. Caffeine, 25 mg/kg bw, but not alcohol, 1 g/kg bw, potentiated this reversal. Two methods of neurochemically measuring the accumulation of tritiated-dopamine and tritiated-noradrenaline after injection of tritiated-tyrosine, the biochemical starting point for synthesis of the two former neurochemical substances, were employed. Both methods showed a marked increased synthesis of brain catecholamines after combined treatment with caffeine and alcohol as compared with the result obtained after either drug alone or after saline injections. These responses are evidence of the involvement of central catecholamine mechanisms in the interaction between caffeine and alcohol. FDA notes that the doses of alcohol and caffeine used to produce these effects are quite elevated.

Gulick D, Gould TJ. Effects of ethanol and caffeine on behavior in C57BL/6 mice in the plus-maze discriminative avoidance task. Behav Neurosci 123:1271–1278, 2009.

This study examined whether caffeine interacts to modify alcohol-induced changes in anxiety, locomotion, and learning in the plus-maze discriminative avoidance task (PMDAT). The testing used an elevated maze in the form of a "+". Two of the arms are open and two of them are closed. One of the closed arms is an aversive arm and to signal this when the test subject enters the aversive arm, a strong light and white noise (conditioning stimuli only used during training) are emitted until the animal withdraws from the aversive arm. Time spent in the open arms, compared with time in all arms, is used as a measure of anxiety. Time in the aversive enclosed arm compared with time in the non-aversive enclosed arm is used as a measure of learning. Total entries into all arms are used as a measure of locomotion. Alcohol (1.0–1.4 g/kg bw) decreased anxiety and learning in a dose-dependent manner and increased locomotion. When caffeine was given (5.0–40.0 mg/kg bw), it increased anxiety in a dose-dependent manner and decreased locomotion and learning. When both agents were administered at the same time, caffeine failed to reverse alcohol-induced learning deficits and 1.4 g/kg bw alcohol blocked the anxiogenic effect of caffeine. CFSAN interprets these results to be partially analogous to results in clinical studies where caffeine given with alcohol reversed some facets of CNS depression mediated by alcohol. The present study's authors suggest that alcohol-induced reduction of anxiety may contribute to continuing ingestion of alcohol, while alcohol's blockade of caffeine-induced anxiety may encourage concurrent ingestion of these substances. Thus, CFSAN concludes that these data indicate that these mice consumed more alcohol when they are also consuming caffeine, producing greater intoxication and leading to greater decreases in learning.

Kunin D, Gaskin S, Rogan F, Smith BR, Amit Z. Caffeine promotes ethanol drinking in rats. Examination using a limited-access free choice paradigm. Alcohol 21:271–277, 2000.

Male Wistar rats were presented a one-hour session in which they chose between water and increasing levels of alcohol (2–10 percent). Each alcohol level was available for 5 days for a total duration of exposure of 20 days. Intraperitoneal (i.p.) injections of either alcohol (5-10 mg/kg) or saline were given to the rats 30 minutes before each choice session. The lower dose of caffeine caused an increase in alcohol drinking. A second study involved the effect of caffeine on the continuation of previously established alcohol consumption. The rats were allowed an additional 18 (10 percent level) alcohol doses, consisting of an additional 6-day baseline period, followed by 6-day treatment period in which rats received 2.5, 5, 10 mg/kg caffeine or saline before being placed in the water-alcohol choice chamber. There was a final 6-day period without any alcohol or caffeine being given. The low and high doses produced no effect on the alcohol consumption, but the middle dose enhanced alcohol drinking which continued throughout the post-treatment phase. A third experiment demonstrated that caffeine did not change levels of blood alcohol within the confines of the alcohol choice presentation.

The authors postulate that one hypothesis to account for these results is that caffeine may have sensitized the rats to the reinforcing properties of alcohol, thereby leading to enhancement of alcohol intake. The authors provide a second hypothesis to explain this behavior, which is that the rat is simply over-stimulated and increases the intake of alcohol to reduce that effect. The authors of the study and CFSAN conclude that whatever the final explanation proves to be for this effect, the fact that caffeine may increase the tendency of the animals to increase alcohol intake may prove to be of significance and concern to those individuals who concurrently consume both alcohol and caffeine because of the well-known effects of alcohol to interfere with neurally-mediated and neuromuscular responses.

Kunin D, Bloch RT, Terada Y, Rogan F, Smith BR, Amit Z. Caffeine promotes an ethanol-induced conditioned taste aversion: A dose-dependent interaction. Exp Clin Psychopharmacol 9:326–333, 2001.

The methods and materials of this study are very similar to the study described immediately above. The same strain of rats and doses of caffeine and alcohol were used. The design and objectives of this study were, however, different. The present study was designed to use the same dose-range that enhanced voluntary alcohol intake and determine whether it would modify an alcohol-mediated conditioned taste aversion (CTA).

The results demonstrate that the interactive effect of caffeine on an alcohol-induced CTA was complex and dose-dependent. Thus, the lower dose of alcohol which did not induce a CTA when combined with caffeine pretreatment at 2.5 and 10 mg/kg bw, did then facilitate the CTA. Interestingly, the CTA mediated by the high dose of alcohol (1.5 g/kg bw) was not affected by caffeine pretreatment at any caffeine dose.

The authors postulate and the FDA concurs that caffeine enhanced or encouraged the alcohol-induced CTA and suggests that instead of promoting alcohol drinking by neutralizing alcohol's aversive effects, caffeine may encourage alcohol drinking by increasing the reinforcing efficacy of alcohol. Other animal studies using somewhat different experimental approaches have found similar effects of caffeine on alcohol and these results raise the possibility that caffeine may not neutralize alcohol's reinforcing effects but extend and enhance them.

Spinetta M J, Woodlee MT, Feinberg LM, Stroud C, Schallert K, Cormack LK, and Shallert T. Alcohol-induced retrograde memory impairment in rats: prevention by caffeine. Psychopharmacology 201:361–371, 2008.

The authors of this study allowed rats to explore a wood bead taken from another rat's cage then habituated the rat to its odor by three exposure trials. Immediately following the habituation the rats received saline, 25 mg/kg bw pentylenetetrazole (causes seizures which produce retrograde amnesia) as a positive control, 1 g/kg bw or 3 g/kg bw alcohol. The next day the rat was presented the N1 and the bead (N2) from a second rat's cage. Rats given saline or the lower dose of alcohol showed memory for the N1 bead by preferentially examining the N2 bead. In contrast rats receiving either pentylenetetrazole or the higher dose of alcohol manifested equal exploration of beads N1 and N2, indicating amnesia for the previous day's experiences with bead N1. If 5 mg/kg bw was administered either 1 hour after the 3 g/kg bw dose of alcohol or 20 min. prior to habituation to N1, the alcohol-mediated amnestic response to memory decline was blocked or compensated. Administration of a combination of two agents that mimic the two main mechanisms of caffeine's actions; phosphodiesterase-5 inhibition and adenosine receptor antagonism also compensated for or blocked the amnestic response as well. These two agents given singly, however, did not produce this same effect. The authors of this paper and CFSAN interpret the results of this study as providing evidence that caffeine, in the proper dose, is capable of reversing alcohol's disruption of odor memory storage and recall. Comparably controlled clinical studies would be necessary to assess whether caffeine is capable of blocking alcohol's amnestic response that is observed in humans.

3. ***Studies on the Neurochemical and Receptor Effects of Co-Administration of Caffeine and Alcohol.***

Dar MS and Wooles WR. Effect of chronically administered methylxanthines on ethanol-induced motor incoordination in mice. Life Sci 39: 1429-1437, 1986.

The effect of 10-day administration of methylxanthines, caffeine, IBMX (a methylxanthine mimetic) and theophylline on acute alcohol-induced motor incoordination was studied in mice. In mice that received caffeine, at 45 and 90 mg/kg bw per 24 hours, alcohol at 1.5 g/kg bw, produced motor incoordination significantly greater than controls. Significantly greater alcohol-induced motor incoordination was observed in animals fed IBMX at 30 and 60 mg/kg bw per 24 hours compared to controls. The alcohol-induced increase in motor incoordination in these four treatment groups was also associated with significantly increased binding of a centrally-acting adenosine analog, 3H-R-PIA compared to water controls. Theophylline (75 and 159 mg/kg bw per 24 hours) administration (a non-centrally acting methylxanthine), was not associated with increased incoordination or elevated binding of the adenosine receptor ligand, 3H-R-PIA. These experimental results support the hypothesis that CNS activity of adenosine plays some role in the centrally-mediated effects of alcohol.

FDA agrees these experimental results suggest that the motor incoordination produced by alcohol is at least partially induced by its activity at adenosine receptors in the CNS.

Prediger RD, Batista LC, Takahashi RN. Adenosine A_1 receptors modulate the anxiolytic-like effect of ethanol in the elevated plus-maze in mice. Eur J Pharmacol 499:147–154, 2004.

The anxiolytic (stress-reducing) property of alcohol is generally accepted to be an important factor motivating its ingestion and underlying the development of alcohol dependence (Ferreira et al., 2000). Published studies support the hypothesis that adenosine receptors are the basis for mediating some of the important activities of alcohol, including motor incoordination and hypnotic effects (Franks et al., 1975; Fillmore and Bogel-Sprott, 1995; Liguouri and Robinson, 2001). This more recent study was designed to evaluate the role of adenosine receptors in the anxiolytic-like effect of alcohol in mice. Four adenosine receptor ligands: caffeine (non-selective antagonist); DPCPX (A_1 receptor antagonist); ZM241385 (A_{2A} receptor antagonist) and CCPA (A_1 receptor agonist) were tested for their effects on performance in a elevated A+ maze.

Highest doses of caffeine (30 mg/kg bw, i.p.) and DPCPX (6 mg/kg bw, i.p.), the A_1 receptor antagonist, produced an anxiogenic-like response, while CCPA dosing (0.25 mg/kg bw, i.p.), A_1 receptor agonist, demonstrated an anxiolytic-like effect. If "non-anxiogenic" doses of caffeine (10 mg/kg bw, i.p.) and DPCPX (3 mg/kg bw, i.p.) were given first; then alcohol (1.2 mg/kg bw, i.p.) was given, the usual anxiogenic effect was attenuated (anxiolytic effect). The A_{2A} receptor antagonist, ZM241385 (1 mg/kg bw, i.p.) did not produce the same anxiolytic effect if given before the 1.2 g/kg bw, i.p. dose of alcohol. Furthermore, an anxiolytic-like response was observed when "non-anxiolytic" doses of CCPA (0.125 mg/kg bw, i.p.) and alcohol (0.6 g/kg bw, i.p.) were administered. All of these results support the involvement of adenosine in anxiety and that the activation of adenosine A_1 receptors, but not adenosine A_{2A} receptors, induce the anxiolytic-like effect induced by alcohol in mice.

D. Summary, Interpretation, and Conclusions Derived from Clinical and Animal Studies

SUMMARY OF CLINICAL AND ANIMAL STUDY RESULTS

In this summary section, the main effects from numerous physiological and behavioral studies designed to observe and measure the responses to caffeine and alcohol administered both alone and together will be reviewed and discussed. These studies have been designed and conducted both by clinical and animal experimentalists. The results, effects or responses will be presented in categories designed to emphasize effects from both clinical and animal sources that appear to replicate or reinforce the findings of the other. In the discussion below, italicized references are to animal studies.

Effect Category I: Survey, Observational, and Behavioral Studies

Item A. Results of a large, multi-campus survey found that **25 percent** of current college student drinkers consume caffeine mixed with alcohol (O'Brien, et al., 2008). This behavior places them at increased risk of alcohol-related consequences (Thombs, et al., 2010).

Item B. Consumption of the caffeine-alcohol mixture is dangerous because it prevents the drinker from feeling (i.e., the mixture masks) certain adverse effects of alcohol intoxication. Subjects may end up consuming more alcohol, which may, in turn, increase the chance of alcohol dependence and car accidents (Oteri, et al., 2007).

Item C. Repeated combined consumption of alcohol and caffeine at the levels in this study appeared to have increased alcohol tolerance more than when compared to alcohol's or caffeine's effects alone (Fillmore, 2003).

Item D. Based on a study of discriminative avoidance in mice, the authors suggest that the alcohol-induced reduction of anxiety may contribute to continuing ingestion of alcohol, while alcohol's blockade of caffeine-induced anxiety may encourage concurrent ingestion of both of these substances. As a result these mice consumed more alcohol when they were also consuming caffeine, producing greater intoxication and leading to greater decreases in learning (*Gulick and Gould, 2009; Kunin et al., 2000; Kunin et al., 2001).* The results of these studies raise the possibility that caffeine may not neutralize alcohol's reinforcing effects but extend and enhance them (*Kunin et al., 2001).*

Discussion: These studies collectively show that a large minority of college students consume caffeinated alcoholic beverages. This behavior results in greater consumption of alcohol, a behavior that masks sensations of drunkenness and impairs judgment so that more risky or dangerous behaviors are manifested. The studies also suggest that there is increased probability of engaging in chronic, excessive consumption, which may result in an increase in the probability of alcohol dependence and other risks, such as automobile accidents. The study results reported in Items C and D demonstrate in both animals and man that the ingestion of the caffeine-alcohol combination encourages more alcohol consumption and tolerance (thus, dependence) than the consumption of alcohol alone.

Effect Category II: Principal Effects of Clinical and Animal Studies

Item E. A very strongly and consistently manifested result of these studies was that co-exposure to caffeine and alcohol induced more intense response impairment than that measured from exposure to either substance given alone. Some alcohol-impaired responses (e.g., increased reaction time) are somewhat counteracted by the co-administration of caffeine; however, other more complex responses (e.g., when appropriate to withhold a response) become even more impaired with co-ingestion (Marczinski & Fillmore, 2003; Kerr et al., 1991; Moskowitz and Burns, 1981; Carpenter, 1959; Ferreira et al., 2006; Marczinski and Fillmore, 2006; Mackay et al., 2002; Liguori and Robinson, 2001; Azcona, et al., 1995; *Elsner et al., 1988; Kuribara et al., 1992; Kuribara, 1993; Kuribara et al., 1992*).

Item F. In three studies, caffeine improved alcohol-diminished performance on reaction time. (Osborne, 1983; Forney and Hughes, 1965; Hasenfratz et al., 1993). Alcohol-weakened controlled processes; this effect was counteracted by caffeine, and by a performance incentive. There was no caffeine-only treatment group (a weakness of the study design). (Grattan-Miscio and Vogel-Sprott, 2005).

Discussion: This effect category presents the core findings of most of these studies (Item E.), whether they are clinical or animal. One outcome that is observed very clearly and consistently is that co-ingestion of the combination of caffeine and alcohol resulted in more severe response impairment (by several different types of tests and observational measures) than ingestion of either substance alone. Co-administration of caffeine with alcohol results in a lessening of the alcohol impairment of some of the simple behaviors and/or tests, but not with more complex tests or behaviors. The last three studies (Item F) report an ability of caffeine co-administration to reverse or compensate for alcohol-induced impairment of responses. These latter results may indicate real differences in response or they may be due to the use of simple tests in a different test environment. None of the last three studies (Item F) tested more complex behaviors to assess caffeine's effect on performance in the presence of alcohol.

Effect Category III: Unexpected or Unexplained Effects from Clinical and Animal Studies

Item G. Expectancies of the drinker can affect his/her ability to compensate for alcohol-induced decrements of performance. When told there is no way for them to compensate, subjects do worse in compensating for alcohol-mediated impairment even if also ingesting caffeine. When told they can compensate, they do better with caffeine and even with no concurrent ingestion of caffeine than the other test group. (Fillmore & Vogel-Sprott, 1995; Fillmore et al., 2002).

Item H. In a test of concentration performance, gender-specific response differences were observed in that co-ingested alcohol and caffeine acted synergistically in males, but antagonistically in females (Keuchel, et al., 1979).

Item I. Various studies have demonstrated complex, variable, dose-dependent, dosage-order dependent, time-of-study effects on the comparative responses of caffeine and alcohol given together versus each substance administered alone (*Jain, et al., 1999; Ferreira et al., 2004; Waldeck, 1974).*

Discussion: This effect category deals with behavior and responses that were unexpected or unexplained. As Item I suggests, the outcomes of these studies are controlled by several to many variables, some of which we are aware and some of which we do not recognize as being influential. Thus, based on our present state of knowledge, we have unpredictable outcomes. Our current and deficient knowledge base underlies the need for more extensive and systematic investigations of the effects of the combined use of caffeine and alcohol in order to detect and determine the influences exerted by less recognized and more subtle variables.

Through the insights this proposed additional research will provide, we may be able to ascertain the reasons for our present ignorance and enable the development of more advanced hypotheses to test. These hypotheses may allow us ultimately to unravel and counteract some of the more destructive outcomes resulting from the combined use of caffeine and alcohol.

Effect Category IV: Physiological Effects from Clinical and Animal Studies

Item J. During co-ingestion of caffeine and alcohol, the half-life of caffeine is increased up to 72 percent and the clearance through the kidneys is decreased up to 36 percent. Alcohol maintains the plasma concentration and effects of caffeine at their peak for a longer time than during the administration of caffeine alone (George et al., 1986; Franks, et al., 1975; Azcona et al., 1995).

Item K. The combined effect of caffeine and alcohol on 1) apparent bone demineralization, 2) adverse pregnancy and offspring development, and 3) increased corticosterone levels were greater

than either substance elicits when given alone (*Case et al., 1996; Hannigan, et al., 1995; Kunin et al., 2000*).

Discussion: In addition to the observational, behavioral and operant testing designs, a few studies were reported that provided information on the metabolism of caffeine in the presence of alcohol. Alcohol has a very significant, decreasing influence on caffeine's rate of metabolism and excretion. This quite effective inhibition of caffeine metabolism by alcohol may provide a partial explanation for the strong stimulatory influence caffeine has on the neural depression normally produced by alcohol.

The effects of alcohol on the metabolism of caffeine are desirable for those individuals wishing to stay awake longer and drink more alcohol. One of the studies found increases in corticosterone plasma levels by alcohol as well. This somewhat unexpected response is the augmentation of all of the adverse effects by the caffeine-alcohol combination compared to either of these substances given alone. The authors of this study postulate that corticosterone's effect is to support or elicit the positive reinforcing properties of alcohol, and this would encourage continued if not expanded consumption of alcohol.

Two of the effects listed in Item K have been known about caffeine for decades i.e., the tendency to demineralize bone and to produce adverse effects on reproduction of animals at high doses. Reproductive effects have been reported in humans, but their true significance remains the subject of active debate.

CONCLUSIONS FROM THESE STUDY RESULTS:

The results of the foregoing studies show that consumption of the combination of caffeine and alcohol augments several adverse behavioral outcomes that are known to occur when alcohol is consumed alone. Examples of such adverse behavioral outcomes that may be increased include physical and sexual assault; tendency to drive while significantly impaired thereby risking injuries or death due to automobile accidents; alcohol consumption (both acute and long-term); number of drinking episodes per week; and risk of eliciting alcohol tolerance and alcohol dependence.

Some investigators have observed that in certain studies of the caffeine-alcohol combination, there are inconsistencies in the observed responses; such inconsistencies underscore the need for additional testing and further study to provide a better understanding of the basis of these inconsistent outcomes. Indeed, a common theme in the discussion section of the reviewed articles is that the authors advocate for further testing on the effects of the caffeine-alcohol combination. Some of the study results (see Effect Category III) were unexpected or produced results that are not easily explained and consequently, they provide an additional impetus to continue to advance the basic science (metabolism and organ system functioning effects) as well as observational, behavioral, and operant testing of the caffeine-alcohol combination. The experimental results observed in one of the physiological studies (Jain et al., 1999) demonstrate how difficult it is to predict responses when the complicated actions of caffeine-alcohol are imposed on an inherently complex and homeostatically self-correcting cardiovascular system.

Based on the effects of the caffeine-alcohol combination in both clinical and animal studies that are reported in the scientific literature, it is clear that not enough is known about the possible responses to this combination of psycho-active substances to form the basis of a consensus among qualified experts that caffeine in the presence of alcohol is generally recognized as safe. The state of the relevant scientific knowledge is clear when authors in this research area consistently encourage additional research to evaluate and understand the effects of the caffeine-alcohol combination. In essence, the relevant literature shows that consumption of this mixture is associated with some

behaviors that are unpredictable and risky and other behaviors that leave certain risk questions unsatisfactorily answered. This literature also provides no information on the nature and intensity of effects associated with chronic consumption of this mixture. Given this incomplete state of the publicly available scientific literature, it is clear that there is no basis to conclude that the use of caffeine in alcoholic beverages is generally recognized as safe.

References

Azcona O, Barbanoj MJ, Torrent J, Jane F. Evaluation of the central effects of alcohol and caffeine interaction. Br J Clin Pharmacol 40:393–400, 1995.

Benet LZ, Kroetz DL, and Sheiner LB. (1996). Pharmacokinetics: The dynamics of drug absorption, distribution, and elimination. In: Molinoff, P.B., & Ruddon, R.W., eds. Goodman and Gillman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw-Hill: 3–27.

Bonnie R, O'Connel M., Editors. Reducing underage drinking: A collective responsibility, Washington, DC., The National Academies Press.

Benowitz, N.L. Clinical pharmacology of caffeine. Annu Rev Med 41:277–288, 1990.

Cardoso RA, Brozowski SJ, Chavez-Noriega LE, Harpold M, Valenzuela CF, Harris RA. Effects of ethanol on recombinant human neuronal nicotinic acetylcholine receptors expressed in *Xenopus* oocytes. J Pharmacol Exp Ther 289: 774–80, 1999.

Case TS, Saltzman MJ, Cheuk J, Yazdani M, Sadeghpour A, Albrecht D, Rossowska MJ, Nakamoto T. Combined effects of caffeine and alcohol during pregnancy on bones in newborn rats. Res Exp Med 196: 179–185, 1996.

Cargiulo T. Understanding the health impact of alcohol dependence. Am J Health Syst Pharm. 64(5 Suppl 3): S5–S11, 2007

Centers for Disease Control and Prevention. Caffeinated alcoholic beverages fact sheet. Available at: http://www.cdc.gov/alcohol/fact-sheets/cab.htm, accessed 10/18/10.

Chawla, J., Suleman, A. Neurologic effects of caffeine, 2008. http://emedicine.medscape.com/article/1182710-overview

Cheng WS, Murphy TL, Smith MT, Cooksley WG, Halliday JW, Powell LW. Dose-dependent pharmacokinetics of caffeine in humans: Relevance as a test of quantitative liver function. Clin Pharmacol Ther 47:516–524, 1990.

Clarren SK, Smith DW., The fetal alcohol syndrome. N Engl J Med 298:1063-1067, 1978

Cornelius MC, El-Sohemy A, Kabagambe EK, Campos H., Coffee, CYP1A2 genotype, and risk of myocardial infarction. JAMA 295:1135–1141, 2006.

Curry K, Stasio MJ. The effects of energy drinks alone and with alcohol on neuropsychological functioning. Hum Psychopharmacol Clin Exp 24:473–481, 2009.

Davies M. The role of GABAA receptors in mediating the effects of alcohol in the central nervous system. J Psychiatry Neurosci. 28:263–274, 2003.

Dunn N, Cook CC. Psychiatric aspects of alcohol misuse. Hosp Med. 60 (3): 169–72, 1999.

Dar MS and Wooles WR Effect of chronically administered methylxanthines on ethanol-induced motor incoordination in mice. Life Sciences 39: 1429-1437, 1986.

Eckardt MJ, File SE, Gessa GL, Grant KA, Guerri C, Hoffman PL, Kalant H, Koob GF, Li TK, Tabakoff B. Alcohol Clin Exp Res: 22: 998–1040, 1998.

Elsner J, Alder S, Zbinden G. Interaction between ethanol and caffeine in operant behavior of rats. Psychopharmacology 96: 194-205, 1988.

European Centre for Monitoring Alcohol Marketing (EUCAM) report, Drinks with a boost: Alcoholic energy drinks trends in alcohol marketing, 2008. http://www.eucam.info/content/bestanden/alcohol-with-a-boost_final.pdf

Ferreira MP, and Willoughby D. Alcohol consumption: the good, the bad, and the indifferent. Appl Physiol Nutr Metab. 33:12–20, 2008.

Ferreira SE, de Mello MT, Pompeia S, and de Souza-Formigoni ML. Effects of energy drink ingestion on alcohol intoxication. Alcohol Clin Exp Res 30, 598–605, 2006.

Ferreira SE, de Mello MT, Rossi MV, Souza-Formigoni ML. Does an energy drink modify the effects of alcohol in a maximal effort test? Alcohol Clin Exp Res 28:1408–1412, 2004.

Ferreira SE, de Mello MT, Formigoni ML. [Can energy drinks affect the effects of alcoholic beverages? A study with users]. Rev Assoc Med Bras 50:48-51, 2004 (article in Portuguese).

Ferreira SE, Hartmann Quadros IM, Trindade AA, Takahashi S, Koyama RG, Souza-Formigoni ML. Can energy drinks reduce the depressor effect of ethanol? An experimental study in mice. Physiol Behav 82:841–847, 2004.

Fillmore MT, Vogel-Sprott M. Behavioral effects of combining alcohol and caffeine: Contribution of dru-related expectancies. Exp Clin Psychopharmacol 3:33–38, 1995.

Fillmore MT, Roach EL, and Rice JT. Does caffeine counteract alcohol-induced impairment? The ironic effects of expectancy. J Stud Alcohol 63:745-754, 2002.

Fillmore MT. Alcohol tolerance in humans is enhanced by prior caffeine antagonism of alcohol-induced impairment. Exp Clin Psychopharmacol 11:9–17, 2003.

Fisone G, Borgkvist A, Usiello A. Caffeine as a psychomotor stimulant: mechanism of action, Cell Mol Life Sci 61:857–872, 2004.

Food Standards Agency (FSA), http://www.food.gov.uk/news/pressreleases/2008/nov/caffeineadvice

Franks HM, Hagedorn H; Hensley VR, Starmer GA. The effect of caffeine on human performance, alone and in combination with ethanol. Psychopharmacologia 45:177–181, 1975.

Fudin R, and Nicastro R. Can caffeine antagonize alcohol-induced performance decrements in humans? Percept Mot Skills 67:375–391, 1988.

George J, Murphy T, Roberts R, Cooksley WG, Halliday JW, Powell LW, Influence of alcohol and caffeine consumption on caffeine elimination, Clin Exp Pharmacol Physiol 13:731–736, 1986.

Grattan-Miscio KE, Vogel-Sprott M. Alcohol, intentional control, and inappropriate behavior: Regulation by caffeine or an incentive. Exp Clin Psychopharmacol 13:48–55, 2005.

Griffiths RR, Chausmer AL., Caffeine as a model drug dependence: Recent developments in understanding caffeine withdrawal, the caffeine dependence syndrome, and caffeine negative reinforcement, Jpn J neuropsychopharmacol 20:223–231, 2000.

Grilly DM. (2002). Drugs and human behavior. 4th ed. Toronto: Allyn and Bacon.

Grosso LM, Bracken M.B. Caffeine metabolism, genetics, and perinatal outcomes: A review of exposure assessment considerations during pregnancy. Ann Epidemiol 15:460–466, 2005.

Gulick D, Gould T.J. Effects of ethanol and caffeine on behavior in C57BL/6 mice in the plus-maze discriminative avoidance task. Behav Neurosci 123:1271–1278, 2009.

Hannigan, JH. Effects of prenatal exposure to alcohol plus caffeine in rats: pregnancy outcome and early offspring development. Alcohol Clin Exp Res 19: 238–246, 1995.

Hasenfratz M, Bunge A, Dal Pra G, Battig K. Antagonistic effects of caffeine and alcohol on mental performance parameters. Pharmacol Biochem Behav 46:463–465, 1993.

Health Canada, http://www.hc-sc.gc.ca/hl-vs/alt_formats/pdf/iyh-vsv/food-aliment/caffeine-eng.pdf

Hilakivi LA, Durcan MJ, Lister RG. Effects of caffeine on social behavior, exploration and locomotor activity: interaction with ethanol. Life Sci 44:543–553, 1989.

Huang ZL, Qu WM, Eguchi N, Chen JF, Schwarzschild MA, Fredholm BB, Urade Y, Hayaishi O. Adenosine A2A, but not A1, receptors mediate the arousal effect of caffeine, Nat Neurosci 8:858-859, 2005

Humayun MU, Rader RS, Pieramici DJ, Awh CC, de Juan E. Quantitative measurement of the effects of caffeine and propranolol on surgeon hand tremor, Arch Ophthalmol 115:371–374, 1997.

Jain AC, Mehta MC and Billie M. Combined effects of caffeine and alcohol on hemodynamics and coronary artery blood flow in dogs. J Cardiovascular Pharmacol 33: 49–55, January 1999.

Katzung B.G. (2001). Basic and clinical pharmacology. 8th ed. Toronto: Lange Medical Books/McGraw-Hill.

Kerr JS, Sherwood N, Hindmarch I. Separate and combined effects of the social drugs on psychomotor performance. Psychopharmacol 104:113–119, 1991.

Keuchel I, Kohnen R, Lienert GA. The effects of alcohol and caffeine on concentration test performance. Arzneim-Forsch / Drug Research 29:973-975, 1979.

Kunin D, Gaskin S, Rogan F, Smith BR, Amit Z. Caffeine promotes ethanol drinking in rats. Examination using a limited-access free choice paradigm. Alcohol 21:271–277, 2000.

Kunin D, Gaskin S, Rogan F, Smith BR, Amit Z. Augmentation of corticosterone release by means of a caffeine-ethanol interaction in rats. Alcohol 22:53–56, 2000.

Kunin D, Bloch RT, Terada Y, Rogan F, Smith BR, Amit Z. Caffeine promotes an ethanol-induced conditioned taste aversion: A dose-dependent interaction. Exp Clin Psychopharmacol 9:326–333, 2001.

Kuribara H, Tadokoro S. Caffeine does not effectively ameliorate, but rather may worsen the ethanol intoxication when assessed by discrete avoidance in mice. Jpn J Pharmacol 59: 393–398, 1992.

Kuribara H, Asahi T, Tadokoro S. Ethanol enhances, but diazepam and pentobarbital reduce the ambulation-increasing effect of caffeine in mice. Jpn J Alcohol Drug Depend 27:528–539, 1992 [Arukoru Kenkyuto Yakubutsu Ison. 1992 Oct;27(5):528-39].

Kuribara, H. Enhancement of the behavioral toxicity induced by combined administration of ethanol with methylxanthines: Evaluation by discrete avoidance in mice. J Toxicol Sci 18:95–101, 1993.

Jain AC, Mehta MC, and Billie M. Combined Effects of Caffeine and Alcohol on Hemodynamics and Coronary Artery Blood Flow in Dogs J. Cardiovascular Pharmacol. 33: 49–55, 1999.

Lee M, Leichter J. Skeletal development in fetuses of rats consuming alcohol during gestation. Growth 47:254-262, 1968.

Lieberman HR, Wurtman RJ, Emde GG, Roberts C, Coviella IL, The effects of low doses of caffeine on human performance and mood, Psychopharmacology 92:308–312, 1987.

Liguori A, Robinson JH. Caffeine antagonism of alcohol-induced driving impairment. Drug Alcohol Depend 63:123–129, 2001.

Lovinger DM. 5-HT3 receptors and the neural actions of alcohols: an increasingly exciting topic. Neurochem Int 35: 125–30, 1999.

Mackay M, Tiplady B, Scholey AB. Interactions between alcohol and caffeine in relation to psychomotor speed and accuracy. Hum Psychopharmacol 17:151–156, 2002.

Maczinski CA, and Fillmore MT. Clubgoers and their trendy cocktails: implications of mixing caffeine into alcohol on information processing and subjective reports of intoxication. Exp Clin Psychopharmacol, 14: 450–458. 2006.

Marczinski CA, and Fillmore MT. Dissociative antagonistic effects of caffeine on alcohol-induced impairment of behavioral control. Exp Clin Psychopharmacol 11:228–236, 2003.

Martin CS, Earleywine M, Musty RE, Perrine MW, Swift RM (1993) Development and validation of the biphasic alcohol effects scale. Alcohol Clin Exp Res 17:140–146.

Martin FH, and Garfield J. Combined effects of alcohol and caffeine on the late components of the event-related potential and on reaction time. Biol Psychol 71:63–73, 2006.

Meister K.A., Whelan E.M., and Kava R. (2000). The health effects of moderate alcohol intake in humans: an epidemiologic review. Crit Rev Clin Lab Sci 37: 261–296.

Miller, KE. Wired: energy drinks, jock identity, masculine norms, and risk taking. J Am College Health, 56, 481–489, 2008.

Motl RW, Dishman R K. Effects of acute exercise on the soleus H-reflex and self-reported anxiety after caffeine ingestion, Physiol Behav 80:577–585, 2004.

Nawrot P, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, Feeley M. Effects of caffeine on human health. Food Addit Contam 20:1–30, 2003.

Nuotto E, Mattila MJ, Seppala T, Konno K. Coffee and caffeine and alcohol effects on psychomotor function. Clin Pharmacol Ther 31:68–76, 1982.

Oborne DJ, and Rogers Y. Interactions of alcohol and caffeine on human reaction time, Aviat Space Environ Med 54:528-534, 1983

O'Brien MC, McCoy T, Rhodes SD, Wagoner A, and Wolfson M. Caffeinated cocktails: Energy drink consumption, high-risk drinking and alcohol-related consequences among college students. Acad Emerg Med 15, 453–460, 2008.

Oteri A, Salvo F, Caputi AP, and Calapai G. Intake of energy drinks in association with alcoholic beverages in a cohort of students of the School of Medicine of the University of Messina. Alcohol Clin Exp Res 31:1677–1680, 2007.

Palatini P, Ceolotto G, Ragazzo F, Dorigatti F, Saladini F, Papparella I., Mos L, Zanata G, Santonastaso M. CYP1A2 genotype modifies the association between coffee intake and the risk of hypertension. J Hypertens 27:1594–1601, 2009.

Prediger RD, Batista LC, Takahashi RN. Adenosine A_1 receptors modulate the anxiolytic-like effect of ethanol in the elevated plus-maze in mice. Eur J Pharmacol 499:147-154, 2004**.**

Price SR, Hilchey CA, Darredeau C, Fulton HG, Barrett SP. Energy drink co-administration is associated with increased reported alcohol ingestion, Drug Alcohol Rev 29:331-333, 2010.

Quinlan PT, Lane J, Moore KL, Aspen J, Rycroft JA, O'Brien DC. The acute physiological and mood effects of tea and coffee: the role of caffeine level. Pharmacol Biochem Behav 66:19–28, 2000.

Ramchandani VA, Kwo PY, and Li TK. 2001. Effect of food and food composition on alcohol elimination rates in healthy men and women. J. Clin. Pharmacol. 41: 1345–1350.

Rush CR, Higgins ST, Hughes JR, Bickel WK, Wiegner MS, Acute behavioral and cardiac effects of alcohol and caffeine, alone and in combination, in humans, Behav Pharmacol 4:562–572, 1993.

Satel S. Is caffeine addictive: - A review of the literature, Am J Drug Alcohol Abuse 32:493–502, 2006

Simon M, Mosher J. Alcohol, energy drinks, and youth: A dangerous mix. Marine Institute, San Rafael, CA.

Smith A. Effects of caffeine on human behavior, Food Chem Toxicol 40:1243–1255, 2002.

Spinetta MJ, Woodlee MT, Feinberg LM, Stroud C, Schallert K, Cormack LK, Shallert T. Alcohol-induced retrograde memory impairment in rats: prevention by caffeine. Psychopharmacology 201:361–371, 2008.

Strain JJ, Stimulant Drinks Committee Report (SDCR) (Republic of Ireland). Review of the health effects of stimulant drinks, March 19, 2002. http://www.safefood.eu/Global/Publications/Research%20reports/FSPB%20Stimulant%20drinks%20.pdf?epslanguage=en

Swampillai J, Rakebrandt F, Morris K, Jones CJ, Fraser AG. Acute effects of caffeine and tobacco on arterial function and wave travel. Eur J Clin Invest 36:844–849, 2006.

Thombs DL, O'Mara RJ, Tsukamoto M, Rossheim ME, Weiler RM, Merves ML, and Goldberger BA. Event-level analysis of energy drink consumption and alcohol intoxication in bar patrons. Addictive Behaviors 35, 325–330, 2010.

Valenzuela CF, Cardoso RA, Wick MJ, Weiner JL, Dunwiddie TV, Harris RA. Effects of ethanol on recombinant glycine receptors expressed in mammalian cell lines. Alcohol Clin Exp Res 22: 1132–1136, 1998.

Waldeck, B. Ethanol and caffeine: a complex interaction with respect to locomotor activity and central catecholamines. Psychopharmacologia 36: 209-220, 1974.

Wang X, Wang G, Lemos JR, Treistman S.N. Ethanol directly modulates gating of a dihydropyridine-sensitive Ca2+ channel in neurohypophysial terminals. J Neurosci 14: 5453–5460, 1994.

Wiberg GS, Samson JM, Maxwell WB, Coldwell BB, and Trenholm HL. Further Studies on the acute toxicity of ethanol in young and old rats: relative importance of pulmonary excretion and total body water. Toxicol. Appl. Pharmacol. 20: 22–29, 1971.

Widmer H, Lemos JR, Treistman SN. Ethanol reduces the duration of single evoked spikes by a selective inhibition of voltage-gated calcium currents in acutely dissociated supraoptic neurons of the rat. J Neuroendocrinol 10: 399–406, 1998.

Winston A, Hardwick E, Jaberi.N. Neuropsychiatric effects of caffeine. Adv Psychiatr Treatment, 11: 432–439, 2005.