Executive summary of NIH workshop on the Use and Biology of Energy Drinks: Current Knowledge and Critical Gaps

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Sales of energy drinks in the United States reached \$12.5 billion in 2012. Emergency department visits related to consumption of these products have increased sharply, and while these numbers remain small relative to product sales, they raise important questions regarding biological and behavioral effects. Although some common ingredients of energy drinks have been extensively studied (e.g., caffeine, B vitamins, sugars, inositol), data on other ingredients (e.g., taurine) are limited. Summarized here are data presented elsewhere in this issue on the prevalence and patterns of caffeine-containing energy drink use, the effects of these products on alertness, fatigue, cognitive functions, sleep, mood, homeostasis, as well as on exercise physiology and metabolism, and the biological mechanisms mediating the observed effects. There are substantial data on the effects of some energy drink ingredients, such as caffeine and sugars, on many of these outcomes; however, even for these ingredients many controversies and gaps remain, and data on other ingredients in caffeine-containing energy drinks, and on ingredient interactions, are sparse. This summary concludes with a discussion of critical gaps in the data and potential next steps.

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INTRODUCTION

While there is a long history of human caffeine consumption via traditional beverages such as cocoa, coffee, guarana (*Paullinia cupana*), tea, and yerba maté (*Ilex paraguariensis*), caffeine-containing energy drinks are relatively new in the marketplace. Availability of these products in the United States dates back less than 20 years,¹ yet sales reached \$12.5 billion by 2012.² Emergency department visits related to caffeine-containing energy drink consumption increased nearly 14-fold between 2005 and 2011.³ The majority of these were reported as adverse events involving only a caffeine-containing energy drink, without evidence of involve-

ment of alcohol, legal or illegal drugs, or dietary supplements. While the United States does not currently have a regulatory definition of energy drinks, the definition used by the US Substance Abuse and Mental Health Services Agency for these analyses is “flavored beverages containing high amounts of caffeine and typically other additives, such as vitamins, taurine, glucuronolactone, herbal supplements, creatine, sugars, and guarana . . .”³; see Table 1^{4–6} for examples. Although the Substance Abuse and Mental Health Services Agency report³ does not describe the specifics of the adverse events, in other data on caffeine-containing energy drinks, the most commonly reported adverse events are seizures and arrhythmias or dysrhythmias.^{7,8} The increase in the number of

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Table 1 Calorie, sugar, and caffeine content of the top-selling caffeine-containing energy drinks in the United States versus brewed coffee.

Product ^a	Amount per 8 fluid ounces ^b			Available container size(s)(oz)
	Calories	Sugars (g)	Caffeine (mg)	
1. Red Bull	110	27	83	8.4 and 16
2. Monster Energy	100	27	92	8 and 16
3. Rockstar Energy Drink Double	140	31	80	8.4, 16, and 24
4. NOS Energy Drink	110	26	130	16
5. Amp Energy	110	29	71	8, 16, and 24
6. Full Throttle	220	58	210	8 and 16
7. Xylence Xenergy	0	0	94	8
8. Coffee (brewed) ^c	0	0	85–100	Variable

^a The seven top-selling caffeine-containing energy drinks in the United States as of March 25, 2013, according to Sauter and Weigley (2013).⁴

^b Data from Consumer Reports (2012)⁵ and Torpy (2012).⁶

^c Data from Torpy (2012).⁶

reported emergency department visits associated with use of caffeine-containing energy drinks raises important questions about the biological and behavioral effects, prevalence and patterns of use of these products by different population subgroups, and the contribution of ingredients other than caffeine to their effects (including the potential to modulate caffeine's biological activities). Despite substantial research, many biological and behavioral activities of caffeine are still incompletely understood, and the contribution of noncaffeine components of cocoa, coffee, and tea to their biological activities are even less well understood. Peer-reviewed data on the potential for interactions between ingredients in the relatively novel combinations found in caffeine-containing energy drinks are also limited.

To assess research status and needs, a workshop entitled "The Use and Biology of Energy Drinks: Current Knowledge and Critical Gaps" was held at the National Institutes of Health (NIH) on August 15 and 16, 2013. This workshop focused on caffeinated beverages other than cocoa, coffee, tea and colas that are marketed as promoting alertness, concentration, energy, weight loss, athletic performance and/or stamina, and contain additional ingredients such as amino acids, vitamins, herbals, and sugar or other sweeteners. Specific areas of focus for the NIH workshop included contributions of noncaffeine ingredients to biological and/or behavioral effects; epidemiology, use by youth, minorities and the military; mechanisms of effects on cognition, mood, sleep, behavior, homeostasis and metabolism; and effects of chronic use.

The workshop did not focus on cardiovascular or pregnancy-related effects of energy drinks, or on adverse event reports, as these were areas of focus of an earlier workshop.⁹ The major findings and most critical needs discussed at the workshop held at the NIH are summarized below.

Setting the stage: who, when, how much, how often

To provide context both for understanding the existing research on caffeine-containing energy drinks and to guide future research, seven speakers focused on the prevalence and patterns of, and reasons for use. These presentations revealed that different pictures of the prevalence of use emerge when different methods are used to collect the data.

The annual Monitoring the Future (MTF) survey, which is the national survey of secondary school students in the United States, reported that in 2011, 35% of 8th graders and 29% of 10th and 12th graders consumed caffeine-containing energy drinks, with almost 20% of 8th grade students reporting daily use.¹⁰ In the 2011 MTF survey, the strongest predictors of frequent use were age, and smoking and alcohol use. In another study published in 2007, Malinauskas et al.¹¹ reported that 51% of 496 randomly selected eastern US college students said they had consumed more than one energy drink per month during the current semester. In that study, the reason most commonly given for energy drink use (67%) was to compensate for insufficient sleep,¹¹ whereas in the MTF survey of 2011, 54% of respondents reported mixing the beverages with alcohol.¹⁰ These consumers indicated that they often drank three or more caffeine-containing energy drinks while "partying."

In contrast to the youth-focused MTF survey, population-wide surveys generally report lower prevalence of use. The 2007–2010 National Health and Nutrition Examination Survey (NHANES; see Bailey et al.¹² in the present issue) and data presented by the International Life Sciences Institute showed prevalence of caffeine-containing energy drink consumption of less than 10%, even in the subpopulations with the highest prevalence of use, i.e., 19–30-year-old non-Hispanic whites. A 2011

paper¹³ also reported relatively low prevalence of use; 3.4% of high school girls and 6.6% of high school boys reported consuming caffeine-containing energy drinks at least daily during the last week. NHANES data from 1999–2010 do show that coffee and caffeine-containing energy drinks provide an increasing proportion of the caffeine consumed by US children.¹⁴

The reported prevalence of caffeine-containing energy drink use in the military during deployment in Afghanistan was substantially higher than that reported for the civilian population. A 2010 survey of 1,249 military personnel serving in Afghanistan¹⁵ found that 44.8% consumed energy drinks daily. Those who reported drinking three or more energy drinks per day were significantly more likely to report sleep disruption because of stress or illness, and to report sometimes or often falling asleep while on duty (see also Stephens, et al.¹⁶ and Wesensten¹⁷ in this issue).

Data on the prevalence of caffeine-containing energy drink use by minorities vary depending on the population studied. While the NHANES found the highest prevalence of use among non-Hispanic whites (as discussed in the present issue by Bailey et al.¹²), locally focused studies reported higher use overall, particularly among racial minorities compared to whites. One study performed in Milwaukee¹⁸ found the highest prevalence of use among male, nonblack minorities (likely Hispanic/Latino groups given the population studied), and a survey of nightclub-going young adults in New York City¹⁹ reported the highest prevalence of energy drink use among Hispanic/Latino participants (42.4%), followed by African Americans (35.4%; see also Grandner et al.²⁰ in this issue).

Regulatory landscape for caffeine-containing energy drinks

Caffeine-containing energy drinks are marketed and labeled, at their manufacturers' discretion, as either beverages or dietary supplements. The category matters from a regulatory point of view, as the two differ with respect to ingredient regulation, labeling requirements, and good manufacturing practices. In beverages, added caffeine is afforded "generally recognized as safe" status when used in cola-type beverages at levels not in excess of 0.02% (weight per volume) of the beverage. Food labels are required to list ingredients present in excess of 2% by weight in decreasing order of the amounts present, and to list the amounts of nutrients. Thus, in a beverage, of the ingredients commonly found in caffeine-containing energy drinks, statement of the amount of each B-vitamin (per serving) would be required, but statement of the amount per serving of caffeine or herbal ingredients might not be required (if they account for less than 2% by

weight). The requirements for labeling of dietary supplements differ from those for foods and beverages (see Rosenfeld et al.²¹ in the present issue for an in-depth history and analysis of regulation of caffeine and caffeine-containing energy drinks). A dietary supplement label would be required to indicate the amount of caffeine added as a dietary ingredient, but if caffeine were present in a proprietary blend, the label would only have to indicate the total amount of the blend – and not the amounts of each ingredient in the blend. In April 2013, two industry organizations updated their approaches for the labeling of caffeine-containing products.²² The American Herbal Products Association announced an amendment of its trade requirement on the labeling of caffeine-containing products, effective for member organizations on September 6, 2013, and the Council for Responsible Nutrition also issued new recommended guidelines for caffeine-containing dietary supplements in 2013. Under these changes, the presence of caffeine would be disclosed on products that contain more than 5 mg of caffeine per serving either from added caffeine, or as a naturally occurring constituent of one or more herbal ingredients. Products containing more than 25 mg of caffeine per serving would state the amount or range of amounts of caffeine in mg per serving and/or in equivalent cups of coffee. If these changes penetrate the caffeine-containing energy drink market, the ability of consumers and researchers to assess total caffeine intake will be enhanced.

Neuropsychopharmacological mechanisms of caffeine-containing energy drinks

Caffeine is, by far, the best-studied ingredient in energy drinks, especially with respect to neuropsychopharmacology. It is absorbed from the digestive tract within about 45 min, and acts primarily by antagonizing adenosine receptors in the central nervous system; perhaps its most significant effect is counteracting the sensation of tiredness. There is ongoing controversy as to whether caffeine increases alertness or more complex cognitive performance independent of the effects of reversing caffeine withdrawal in habituated consumers (see Owens, et al.²³ in this issue). As newly reported elsewhere in this issue (Spaeth et al.²⁴), caffeine can counteract some of the effects of sleep deprivation, such as slowed reaction time and decreased attentiveness, but other decrements in performance, such as impairments in more complex cognitive functions and working memory, are improved only by sleep and not by caffeine.

Research on the effects of caffeine, and perhaps other energy drink ingredients, in humans is likely to be complicated by inter-individual variation in responses to both sleep deprivation and caffeine. Polymorphisms in the

genes for both a cytochrome P450 critical for caffeine metabolism, and an adenosine receptor (among others) have been reported to be associated with differential responses or sensitivities to caffeine (see Spaeth et al.²⁴ in this issue).

Data on the effects of other caffeine-containing energy drink ingredients on cognition and mood are generally quite sparse (see Childs²⁵ in this issue). There appears to be some agreement that combining sugar with caffeine can prolong alertness. L-theanine has been reported to decrease caffeine withdrawal headaches. Guarana, another traditionally used plant rich in caffeine, can add to the caffeine content of energy drinks. Data on the effects of taurine, *Ginkgo biloba*, and ginseng are inconsistent as well as sparse.

Interactions between caffeine-containing energy drinks and circadian rhythm

The circadian clocks of mammals coordinate behavioral and physiological rhythms, including periodic variation in levels of alertness/fatigue and in metabolic rates, with environmental cues. Clock genes in individual cells throughout the body, are able to maintain a circadian period of approximately 24 h under constant conditions. Among the regulated genes are those in tissues such as liver and pancreas that are responsible for metabolic activities, including metabolism of caffeine-containing energy drinks. Cues such as light or food synchronize the endogenous rhythm with the environment. Two major ingredients in caffeine-containing energy drinks, caffeine and simple sugars, interact with circadian rhythm. Chronic caffeine consumption has been reported to lengthen the endogenous circadian period,²⁶ including the circadian variation in glucose metabolism and insulin response. Glucose tolerance, insulin production, and insulin sensitivity are all decreased in the evening (as compared to the morning), suggesting that those who consume sugar-sweetened, caffeine-containing energy drinks to maintain alertness or energy late in the day, or to work through the night, may be less tolerant of the sugar.

Drivers and behavioral correlates of caffeine-containing energy drink use

Some of the molecular mechanisms underpinning the interactions between circadian rhythms and caffeine-containing energy drinks are just beginning to be elucidated. For example, decreases in peak melatonin production during puberty shift the preferred sleep and wake times of adolescents to later times (see Carskadon and Tarokh²⁷ in this issue). When these biological changes conflict with early school start times, they may result in

insufficient sleep, daytime fatigue, and increased caffeine use. This pattern may lead to a vicious cycle in which increased caffeine use impairs sleep, leading to greater fatigue, and further caffeine consumption.

In an interesting parallel to data for the military, the 2006 National Sleep Foundation Sleep in America survey reported that although 8% of students who consumed little or no caffeine reported falling asleep in school, 15% of those who regularly consumed two or more servings of caffeine a day reported nodding off in classes.²⁸ Others have also reported an association between caffeine use by youth and poorer academic performance.^{28,29} Caffeine-consuming students were also somewhat more likely to report anxiety and depression.²⁸

Use of caffeine-containing energy drinks has been reported to be significantly associated with additional risky behaviors,³⁰ including involvement in interpersonal violence and seatbelt omission while driving. In whites only, caffeine-containing energy drink use was associated with nonmedical use of prescription drugs, and with use of cigarettes and alcohol, as well as with “alcohol problems.”³⁰

Caffeine-containing energy drinks and alcohol

Soon after the 2005 introduction in the United States of beverages that combined alcohol and a caffeine-containing energy drink in a single bottle,³¹ concerns were raised regarding the potential impact of this combination on public health. Although production and marketing of premixed caffeinated alcoholic beverages has since been reduced by state and federal actions, consumption of alcohol mixed with energy drinks remains high among young people, including both college and high school students. For example, among secondary school students, the prevalence of consuming alcohol mixed with caffeine-containing energy drinks in 2011 was approximately 12% for 8th graders, 23% for 10th graders, and 26% for 12th graders.³²

Research on alcohol mixed with caffeine-containing energy drinks has focused on questions about the effects of the mixtures on performance (e.g., do the caffeine-containing energy drinks counteract the effects of alcohol?), on perception of intoxication, and on risk-taking behaviors, including the likelihood of increased alcohol consumption. The data available so far are largely correlational and inconsistent across laboratories and methodologies^{33,34} (see Arria et al.,³⁵ and Marcinski et al.³⁶ in this issue). There is evidence that caffeine-containing energy drinks may antagonize some aspects of alcohol's effects on performance, while other aspects are unchanged or worsened. Elucidation of the mechanisms underlying the effects of caffeine-containing energy drinks on alcohol consumption, and replication of the

existing data, preferably using a variety of methods, as well as assessment of the contributions of ingredients other than caffeine to the effects of energy drinks, are all needed.

Caffeine-containing energy drink effects on metabolism: tissue-specificity and ingredient interactions

In light of the limited research on energy drinks as a whole, the following discussion of how they affect metabolism focuses primarily on the effects of caffeine and carbohydrates.

The importance of the interactions between the ingredients in caffeine-containing energy drinks is highlighted by differences in the effects of isolated caffeine and coffee (containing an equivalent amount of caffeine) on insulin sensitivity. In a study of 11 healthy males, 4.45 mg/kg of purified caffeine significantly increased whole-body insulin resistance, but the effect was blunted when the same caffeine dose was administered as a naturally occurring component of coffee.³⁷ Decaffeinated coffee slightly increased whole-body insulin sensitivity, raising the possibility that noncaffeine components of coffee counteract the effects of caffeine on insulin sensitivity. Caffeine and caffeine-containing energy drinks have been reported to increase serum levels of free fatty acids, which suggests a possible mechanism for the observed effect of caffeine on insulin sensitivity, as increases in serum free fatty acid levels are independently associated with decreased insulin sensitivity.³⁸

The form in which caffeine is presented to the body may also alter caffeine absorption; absorption of caffeine from chewing gum is faster than from a capsule, which in turn is faster than from coffee.³⁷ There also appear to be important differences in response to acute, as opposed to chronic, exposure to caffeine. Despite the increase in insulin resistance following acute caffeine intake, epidemiological data show an association between chronic coffee consumption and decreased risk of type 2 diabetes.³⁹

The effects of caffeine on glucose uptake differ between liver and skeletal muscle (see Shearer and Graham⁴⁰ in this issue); these differences highlight both the importance of tissue-specific effects, and of interactions between energy drink ingredients. Caffeine causes a net increase in glucose uptake in the liver, but impairs glucose uptake by skeletal muscle.

Caffeine-containing energy drinks and athletic performance: fluid balance

Caffeine-containing energy drinks, with their low salt concentrations (compared to sports drinks), may not be

the optimal beverage to maintain hydration during prolonged vigorous exercise, or exercise in a warm environment. Caffeine acts as a diuretic, and also decreases sodium reabsorption in the kidneys through adenosine receptor antagonism, which would increase sodium loss. Failure to replace sodium and chloride lost in perspiration would be expected to have deleterious effects on hydration, skeletal muscle performance, and cardiac stability, and perhaps result in an increase in core temperature.⁴¹

Caffeine-containing energy drinks and athletic performance: effects on strength and endurance

Although caffeine-containing energy drinks may not be the optimal choice for maintaining hydration during prolonged exertion in a warm environment, they may provide performance benefits for both endurance exercise and maximal output in short bursts of exercise. Beverages providing at least 2 mg/kg of caffeine appear to improve endurance during prolonged exercise (approximately one hour). Mora-Rodriguez and Pallarés⁴² suggest in this issue that the amount of caffeine required to increase muscle power output is dependent on the resistance the musculature must overcome, with 3 mg/kg sufficient for relatively low loads, but 9 mg/kg required before an effect above 90% of maximal exertion is achieved. Side effects may increase at these high caffeine levels; 400 mg per day is the “amount not generally associated with dangerous, negative effects” in healthy adults, according to the FDA.⁴³ The generally lower levels of caffeine supplied by most caffeine-containing energy drinks, as well as variation in the time elapsed between caffeine-containing energy drink consumption and outcome measurement, and inter-individual variation in rate of caffeine metabolism may explain the variation in activities reported in the literature. The mechanism(s) responsible for caffeine’s effects on athletic performance remain to be elucidated.

FUTURE RESEARCH NEEDS

In addition to summarizing the available data on the effects of caffeine-containing energy drinks, speakers at the workshop discussed types of data or experiments that would advance understanding of the biological and/or behavioral effects of these products.

Epidemiological data

To provide context for assessing the significance of adverse events reported in association with caffeine-containing energy drink consumption, better data on the

prevalence of use are needed. Questions to guide this research include the following: Do the strikingly different levels of use reported in national surveys such as NHANES, and in focused surveys of young adults and military personnel simply reflect the difference in populations studied (US as a whole, as opposed to very specific subgroups), or do different methodological approaches to querying caffeine-containing energy drink use in different surveys differ in their ability to detect actual use?

A closer look at the available data may address these questions, at least in part, and a careful consideration of survey approaches (e.g., separate collection of data on sports drink and energy drink use, with caffeine-containing energy drinks as a separate category) may provide clearer information in the future.

Research needs and research reporting

More data on product ingredients other than caffeine and sugars as well as on ingredient interactions are needed. In many cases, available data on the activities and effects of individual ingredients of energy drinks are inconsistent. More detailed and consistent reporting are required for items such as product compositions (e.g., the content of proprietary blends, and total caffeine content, where the product contains both caffeine and caffeine-containing herbs), serving size/dose, (mg/kg) of each product ingredient, time of consumption relative to outcome assessment, prior caffeine exposure, and the extent to which participants in studies were able to distinguish caffeine-containing energy drinks from control beverages; many other critical details should also be identified and reported in all research on these products. Attention to these critical details should contribute to a better understanding of the effects of caffeine-containing energy drinks.

Circadian timing should be controlled for and reported on in research involving caffeine-containing energy drinks; blood pressure, alertness, and muscle strength and power output (among other characteristics) all vary with time of day. For example, the effect of caffeine for at least some performance outcomes is significant in the morning due to sleep inertia, but the improvement observed merely restores performance to the level seen in the afternoon without caffeine.⁴⁴

Acute and long-term effects of caffeine-containing energy drinks

Caffeine and caffeine-containing energy drinks clearly have the potential to improve alertness and some aspects of cognitive and physical performance in fatigued individuals, which raises a variety of important questions about both the long-term effects of chronic use, and the

most effective way(s) for those who must sometimes stay alert when fatigued to use them (e.g., “in theater” military personnel and shift workers).

Questions of interest with respect to the optimal use of caffeine-containing energy drinks to maintain alertness in fatigued individuals include the following: Can individualized models be developed that account for differences in the known, relevant genotypes, and predict the optimal caffeine dose for a given individual and desired outcome? For a given individual, what is the optimal intervention (dose, timing) for each formulation (e.g., caffeine-containing energy drink, capsule, coffee) and desired outcome (e.g., alertness or endurance exercise)?

The following critical, unanswered questions regarding the effects of caffeine-containing energy drink use on sleep should also be addressed: What effect do caffeine-containing energy drinks have on night-time sleep? Do they affect circadian rhythms? What is the effect of caffeine-containing energy drinks on alertness, performance, and attention, especially in the teenagers and young adults who are the most prevalent users? Do caffeine-containing energy drinks affect sleep-dependent learning?

Additional critical questions regarding the long-term consequences of chronic caffeine-containing energy drink or caffeine use include the following: Are there effects that are independent of the effects of chronic sleep insufficiency? Does chronic consumption of caffeine-containing energy drinks or caffeine modulate the effects of chronic sleep insufficiency on body mass index? Is long-term, chronic consumption of caffeine-containing energy drinks associated with higher or lower body mass index, or with pre-diabetes or diabetes?

Caffeine-containing energy drink use, alcohol use, and risk behaviors

A better understanding of the interaction of caffeine or caffeine-containing energy drinks with alcohol consumption, and perceived intoxication will require the following: 1) consistent and confirmatory results obtained through the application of a variety of methods, including use of animal models to assess neural mechanisms through which caffeine-containing energy drinks may modulate the effects of alcohol; 2) studies that control for personality traits such as propensity for risk-taking, use of prospective or within-subject designs, and the use of verifiably matched and inactive placebos; 3) data that may be used for rigorous assessment of the potential of caffeine-containing energy drinks and their individual ingredients to modulate the addictive potential of alcohol; and 4) more data to support assessment of the relationship between consumption of caffeine-containing energy drinks mixed with alcohol and high-risk behaviors.

Drivers of caffeine-containing energy drink use

If the use of caffeine-containing energy drinks is found to be definitively and causally associated with alcohol addiction, driving while intoxicated, or other risky behaviors, or with other adverse effects, it will become important to understand the motivations for their use. Among the important, unanswered questions are the following: How do attitudes toward healthy sleep influence the propensity to use caffeine-containing energy drinks? What are the effects of both caffeine and noncaffeine energy drink ingredients, both alone and in combination, on mood in rested and fatigued individuals of various ages? How do advertising patterns (especially as they reflect marketing to specific population subgroups) affect use of energy drinks? Is fatigue an initial driver of caffeine-containing energy drink use, or are there other critical drivers, with fatigue (as part of a vicious cycle) playing a more important role in chronic use than initial use?

CONCLUSION

Some of the research needs described above may be addressed by future prospective studies or further analysis of existing data. Approaches to address these needs are under discussion. One outcome of these discussions is the recent publication by the National Institutes of Health of PA 14-024, a funding opportunity that seeks to collect data on the use, mechanisms of action, and effects of dietary supplements, including caffeine-containing energy drinks, in conjunction with existing NIH awards. Other research questions reflect the general need for greater clarity and transparency in the reporting of both clinical and preclinical research.⁴⁵ Obtaining data to address these needs and gaps should provide a better understanding of the prevalence and patterns of use of caffeine-containing energy drinks, the effects of mixing them with alcohol, and the biological and behavioral effects of their acute and chronic use.

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