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Caffeine: Friend or Foe?

Candace Doepker,[1] Harris R. Lieberman,[2] Andrew Paul Smith,[3] Jennifer D. Peck,[4] Ahmed El-Sohemy,[5] and Brian T. Welsh[1]

[1]ToxStrategies, Inc., Austin, Texas 78759; email: cdoepker@toxstrategies.com

[2]US Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760; email: harris.r.lieberman.civ@mail.mil

[3]Centre for Occupational and Health Psychology, School of Psychology, Cardiff University, Cardiff CF10 3AS, United Kingdom; email: smithap@cardiff.ac.uk

[4]Department of Biostatistics & Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73104; email: jennifer-peck@ouhsc.edu

[5]Department of Nutritional Sciences, University of Toronto, Toronto, Ontario M5S 3E2, Canada; email: a.el.sohemy@utoronto.ca

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Abstract

The debate on the safety of and regulatory approaches for caffeine continues among various stakeholders and regulatory authorities. This decision-making process comes with significant challenges, particularly when considering the complexities of the available scientific data, making the formulation of clear science-based regulatory guidance more difficult. To allow for discussions of a number of key issues, the North American Branch of the International Life Sciences Institute (ILSI) convened a panel of subject matter experts for a caffeine-focused session entitled "Caffeine: Friend or Foe?," which was held during the 2015 ILSI Annual Meeting. The panelists' expertise covered topics ranging from the natural occurrence of caffeine in plants and interindividual metabolism of caffeine in humans to specific behavioral, reproductive, and cardiovascular effects related to caffeine consumption. Each presentation highlighted the potential risks, benefits, and challenges that inform whether caffeine exposure warrants concern. This paper aims to summarize the key topics discussed during the session.

INTRODUCTION

When considering the possible regulation of food ingredients, it is prudent to take an approach informed by scientific data. Although the sentiment behind terminology such as science-based regulation is reasonable, the path can make it difficult to accomplish. For example, the consideration of how or whether to regulate caffeine comes with significant challenges, particularly in interpreting the science, thus making it difficult to formulate clear science-based regulatory guidance. Caffeine, for reasons discussed below, has been a subject of controversy for more than 100 years. In recent years, various stakeholder groups across the globe have requested that government agencies provide evidence-based recommendations for the safe intake level of caffeine (Durbin 2012; Durbin & Blumenthal 2012; Eur. Food Saf. Auth. 2015; Inst. Med. 2013; U.S. Food Drug Admin. 2012a,b). This likely arose because of the apparent increase in the diversity of caffeine-containing foods, beverages, and consumer products as well as their accessibility to populations of interest, namely adolescents and children. Caffeine has been studied for many years, and some of the originally identified issues remain unresolved today. Furthermore, publications on intake suggest that 80% of the population is ingesting caffeine nearly every day with no adverse effects likely to occur (Fredholm et al. 1999). Along with this, PubMed search results show that more than 8,400 scientific papers were published on caffeine in the past 10 years. Incorporating such breadth and depth into the regulatory process is indeed challenging for decision-makers.

The North American Branch of the International Life Sciences Institute (ILSI) convened a panel of subject matter experts for open discussion with a diverse audience at a caffeine-focused session entitled "Caffeine: Friend or Foe?" held on January 20, 2015, during the 2015 ILSI Annual Meeting. This paper aims to summarize the key topics discussed therein. The panelists' expertise covered many areas of knowledge and research, including why caffeine occurs naturally in plants, interindividual metabolism of caffeine in humans, and behavioral, reproductive, and cardiovascular benefits and concerns related to caffeine consumption. Throughout the presentations, panelists highlighted potential risks and benefits as well as some of the challenges (e.g., genetic predisposition, methodological issues, etc.) that affect the determination of whether exposure to caffeine warrants concern. Many of the difficulties in evaluating caffeine's safety stem from the great variability in the human population (e.g., consumption practices, metabolism differences, sensitivity in pharmacokinetic responses, etc.), methodological issues in the design of caffeine-focused epidemiological studies, and the fact that caffeine intake has been associated with beneficial effects in humans. All of these are important considerations when trying to discern whether caffeine is a friend or foe.

BACKGROUND

Caffeine (1,3,7-trimethylxanthine) is the most commonly consumed stimulant worldwide (Fredholm et al. 1999). Caffeine is unique in that it is a nutritive food constituent sold in a variety of products, including foods, dietary supplements, and drugs. In North America, approximately 75% of dietary caffeine comes from coffee (Spiller 1998). The remaining dietary sources of caffeine include tea, cocoa products, cola beverages, and energy drinks (EDs) (Fredholm et al. 1999, Harland 2000, Mandel 2002, McCusker et al. 2006, Spiller 1998). At the doses present in these sources, caffeine affects brain function and behavior. As such, it is consumed primarily for its psychoactive and stimulating properties, with individuals usually adjusting their consumption to attain the desired effects while avoiding potential adverse effects (Fredholm et al. 1999, Smith 2002). Consumer demand has likely driven manufacturer control of the caffeine level in products, resulting in offerings that either contain caffeine or are decaffeinated (e.g., soft drinks and coffee).

Most people recognize that caffeine occurs naturally in coffee, tea, and cocoa. Its natural presence in certain plants provides an extraordinary example of convergent evolution, because a variety of very different species took unique evolutionary paths to synthesize caffeine (Denoeud et al. 2014). Because caffeine's synthesis evolved naturally in plants, it likely provides some evolutionary advantage. In fact, there are a number of reported functions; for example, caffeine acts as an herbicide when the leaves of caffeine-containing plants inhibit the growth of other plants nearby, as an insect repellent owing to its bitterness, or as a toxicant at high doses (Lee et al. 2009). However, some plants that contain very low doses of caffeine in their nectar appear to attract insects and modify their behavior as a strategy to increase pollination. For example, low levels of caffeine are found in citrus plants such as grapefruit, pomelo, and orange, and recent research suggests that honeybees are much more likely to remember the scent of that plant for up to 24 hours when rewarded with low doses of caffeine in simulated nectar versus placebo nectar. It is believed the plant is consequently more likely to be pollinated and to reproduce (Wright et al. 2013). Because coffee, tea, and cocoa all serve as natural sources of caffeine, an interesting parallel can be drawn between the benefit concept in nature and the psychostimulatory benefit that humans seek.

Despite its general safe history and widespread use, caffeine presents a particularly complex challenge for regulatory and public health authorities because it both occurs naturally and can be added synthetically in the manufacturing process. Caffeine-containing products thus have a range of doses per serving, from 1 mg in milk chocolate up to >300 mg in dietary supplements (Carvey et al. 2012). Additionally, caffeine's effects are dose dependent, and there is a very large, sometimes contradictory body of literature on the behavioral, physiological, and health-related effects of caffeine. A recent US Food and Drug Administration (FDA) statement brings to light the additional challenges. According to Rosenfeld et al. (2014), "While patterns of use of caffeine-containing products appear to be changing, the implications of these changes for public health are not well understood." They also note that "While it is commonly stated that different types of caffeinated products are substituted for each other (e.g., caffeine-containing EDs for coffee and vice versa), however, there are few data documenting this assertion." A recent study by Mitchell et al. (2014) helps in better understanding such changes in caffeine consumption practices. Combining these findings with previous intake work, data suggest that caffeine consumption practices have not changed drastically over time as the number of caffeine-containing products has increased; thus, consumers are substituting sources of caffeine to achieve the same levels of intake.

PREVALENCE AND USE

Caffeine is consumed in moderate doses by most of the US adult population, with a current estimated mean intake of approximately 180 mg/day (Fulgoni et al. 2015, Mitchell et al. 2014). Caffeine consumption depends on many factors, such as age, sex, social environment, nutritional status, personality, culture, and level of habituation (Brice & Smith 2002). It is likely that the combined interaction of these environmental factors partly explains the considerable variation in the amount of caffeine consumed worldwide (Fredholm et al. 1999). Interestingly, twin studies have also revealed a strong heritability (30%–77%) for caffeine consumption behaviors, indicating that genetic variation may play a role in both the experience of caffeine's effects and the motivation for its consumption (Yang et al. 2010).

Despite differences in consumption behaviors, there is good evidence for the stability of caffeine consumption over multiple decades. Average adult caffeine intakes in the United States were 185 mg/day, 168 mg/day, and 176 mg/day in 1975, 1989, and 2009–2010, respectively (Barone & Roberts 1996, Fulgoni et al. 2015). These estimates are consistent with data by Mitchell et al. (2014), which were based on the Kantar Worldpanel Beverage Consumption Panel survey

conducted in 2010–2011. The adult intake data suggest no new major trends in consumption despite the extraordinary changes that have occurred in the availability of caffeine-containing foods and beverages over the past few decades. Although the reasons for caffeine's widespread, consistent popularity over time and across numerous cultures are not known, its popularity is likely due in part to its effects on mood. A recent survey of 1,248 students conducted at five geographically dispersed US colleges found that feeling awake (77%), taste (66%), social aspects (38%), improved concentration (30%), physical energy (26%), improved mood (18%), and alleviation of stress (9%) were the most often cited reasons for consuming caffeine (Lieberman et al. 2015).

Adolescents also regularly consume caffeine-containing drinks (Mitchell et al. 2014). Knowledge of the effects of caffeine on children is very limited, and further research is needed to determine whether they may be more sensitive to its negative effects compared with adults (Temple 2009). A growing body of literature suggests that caffeine use in adolescents and young adults can be associated with impulsivity, risk taking, and sensation seeking (Azagba et al. 2014). Unfortunately, owing to the correlational nature of these studies, it is not possible to determine the direction of causality. Other researchers suggest that caffeine is associated with behavioral problems in children through a link with daytime sleepiness (James et al. 2011). Regardless of the population, self-titration of caffeine (i.e., individuals limiting their intake because of the perceived pharmacologic effects) is often discussed, although its effectiveness is questioned. Understanding if, when, and how self-titration occurs in any population would be valuable. Current assumptions around self-titration are mainly based on observance of societal behaviors and not on well-designed and/or controlled studies. Although solid scientific data may not exist on the pharmacologic basis for self-titration, there is a good understanding of the metabolism of caffeine and its subsequent metabolic effects.

PHARMACOLOGY

In humans, the principal metabolic pathway for caffeine is catalyzed by the cytochrome P450 (CYP) enzyme CYP1A2 in the liver and accounts for approximately 95% of its initial breakdown. The process begins with removal of a methyl group to form the primary metabolite paraxanthine; however, theobromine and theophylline are also formed in smaller concentrations.

The half-life of caffeine in healthy adults is approximately 4–5 hours (Carvey et al. 2012). Habitual heavy users of caffeine are faster metabolizers, as are cigarette smokers, who typically consume more caffeine than nonsmokers. Children aged $\leq$12 years metabolize caffeine more rapidly than adults (Arnaud 1993, Knight et al. 2004), and pregnant women are slower metabolizers, especially in the later stages of pregnancy.

In amounts typically consumed from dietary sources, caffeine mediates many of its physiological actions through the antagonism of central adenosine receptors (ARs) (Daly et al. 1981, Fredholm 1980, Snyder 1981). Adenosine is an inhibitory neuromodulator in the central nervous system, with sedative-like properties. Four subtypes (A_1, A_{2a}, A_{2b}, and A_3) of G protein–coupled ARs have been identified. Although the contribution of each is uncertain, A_1 and A_{2a} ARs in the brain are responsible for the behavioral effects of caffeine.

Because variations in the genes encoding the ARs exist, individuals with these variants serve as good candidates to study the differing physiological effects of caffeine. It was recently suggested that even consumption habits have been linked to the genetic constitution of the ARs. For example, a C > T substitution at position 1976 in the A_{2a} AR (*ADORA2A*) gene has been associated with habitual caffeine consumption (Cornelis et al. 2007). Subjects consuming >200 mg/day of caffeine (equivalent to about two small cups of coffee) were significantly less likely to have the variant TT genotype compared with subjects consuming <100 mg/day. Subjects consuming >400 mg/day of caffeine were even less likely to have the TT genotype. These results

are supported by double-blind placebo-controlled studies showing that subjects with the TT genotype report greater anxiety after administration of caffeine (Alsene et al. 2003, Childs et al. 2008, Rogers et al. 2010). Taken together, these studies indicate that genetic variation in ARs may explain some variability in the acute effects of caffeine and consumption behaviors.

All of the above factors (consumption habits, underlying genetics, and demographics) can influence the variation experienced in the many physiological effects of caffeine. Although research suggests that caffeine can impact nearly every system in the body, this discussion focuses mainly on three endpoints of interest: cardiovascular effects, pregnancy outcomes, and neurobehavioral effects, with respect to the challenges that underlie conclusions on the risks and benefits of caffeine.

CARDIOVASCULAR EFFECTS

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide, and it encompasses a range of serious conditions, including hypertension and coronary heart disease (CHD). Myocardial infarction (MI), the most severe form of CHD, occurs when an occlusion of the coronary artery interrupts the oxygen supply to the heart, resulting in myocardial cell death (Marmot & Elliott 2005). Several risk factors for MI are well established and include elevated blood pressure and heart rate (Gillum et al. 1991, Yusuf et al. 2004). Diet is also a recognized risk factor for CVD and its related conditions (Srinath Reddy & Katan 2004) and has thus been an important focus in cardiovascular research. Caffeine is one dietary component that has been extensively investigated for its role in CVD; however, the findings remain equivocal (Cornelis & El-Sohemy 2007, Riksen et al. 2009).

Reports of adverse cardiovascular effects of caffeine have made this compound an obvious candidate underlying the association between coffee and CVD (Nawrot et al. 2003, Ranheim & Halvorsen 2005). Several epidemiological studies have examined the association between coffee consumption and risk of CVD, but the findings have been unclear (Andersen et al. 2006, Azevedo & Barros 2006, Cornelis et al. 2006, Greenland 1993, Hammar et al. 2003, Happonen et al. 2004, Kawachi et al. 1994, Kleemola et al. 2000, Lopez-Garcia et al. 2006, Myers & Basinski 1992, Nawrot et al. 2003, Nilsson et al. 2010, Panagiotakos et al. 2003, Rosner et al. 2007, Sofi et al. 2007, Woodward & Tunstall-Pedoe 1999, Wu et al. 2009). Previous reports have suggested that coffee either increases, has no effect, or decreases the risk of CVD. The protective effect of moderate intakes of coffee on CVD is evidenced by an inverse or U- or J-shaped association (Andersen et al. 2006, Azevedo & Barros 2006, de Koning Gans et al. 2010, Happonen et al. 2004, Kleemola et al. 2000, Panagiotakos et al. 2003, Woodward & Tunstall-Pedoe 1999). Inadequate adjustment for confounding variables is a major criticism of the epidemiological studies examining the effects of caffeine on CVD. However, caffeine consumption may be a marker of a lifestyle characterized by atherogenic factors and not a causal factor in itself (Jacobsen & Thelle 1987). For example, cigarette smoking is an obvious confounder because high intakes of caffeine are frequently associated with smoking (Schreiber et al. 1988). Despite the common criticism, an extensive range of potential confounders have also been identified and controlled for, including smoking, age, sex, alcohol consumption, diet factors, body mass index, medical history, physical activity, area of residence, and education level.

As suggested above regarding variation in ARs, genetic variability between the populations examined may partly account for the discrepancies between studies relating caffeine and CVD. It is well established that genetic factors play an important role in the development of CVD (Arnett et al. 2007, Mayer et al. 2007). Until recently, most studies of caffeine and CVD included family history as a measure of inherited susceptibility. However, much of the inherited predisposition to CVD is likely related to common polymorphic variants that do not give rise to CVD in most carriers

but can affect risk only after exposure to specific dietary or lifestyle factors (Corella & Ordovas 2014). If caffeine increases risk only in susceptible individuals, studying a mix of susceptible and nonsusceptible people attenuates the risk of CVD seen for caffeine. The use of genetic modifiers of exposure or biological effect in nutritional epidemiology is a promising new approach that can help address many of the limitations identified in previous studies (Smith & Ebrahim 2003).

In addition to defining susceptible subpopulations, the use of single nucleotide polymorphisms (SNPs) in candidate genes to study the association between caffeine and CVD could both address concerns of confounding and aid in identification of mechanisms underlying the association between caffeine and CVD. Some of these points have been managed by including a genetic marker of caffeine metabolism in studies of coffee and the risk of MI (Cornelis et al. 2006). Considering amounts of caffeine typically consumed from dietary sources, CYP1A2-mediated metabolism accounts for >95% of the overall caffeine clearance from the plasma, and large variability in this enzyme's activity is primarily responsible for the well-known interindividual variations in caffeine metabolism (Gu et al. 1992, Tantcheva-Poor et al. 1999). An A > C SNP at position −163 in the *CYP1A2* gene was associated with reduced enzyme inducibility, resulting in slower caffeine metabolism (Castorena-Torres et al. 2005, Han et al. 2001, Sachse et al. 1999). Therefore, because coffee is an inducer of the CYP1A2 enzyme (Djordjevic et al. 2008, Le Marchand et al. 1997), subjects with heavy coffee consumption and the *CYP1A2* −163 AA genotype have significantly higher CYP1A2 activity than heavy coffee consumers with the *CYP1A2* −163C allele (Djordjevic et al. 2010). Furthermore, an increased risk of MI was associated with coffee consumption only among individuals who were carriers of the −163C allele (Cornelis et al. 2006), which corresponds to the genotype associated with a slower rate of caffeine metabolism. It is unlikely that this association between coffee and MI is due to residual confounding because the *CYP1A2* genotype is not associated with (potentially) confounding lifestyle variables and, other than caffeine, no major compound in coffee is known to be detoxified by CYP1A2.

Many studies investigating caffeine utilize coffee drinkers as a good exposure population. For the CVD endpoint, it is worth noting that coffee is also a dietary source of flavonoids, plant-derived molecules that are proposed to have beneficial effects on the cardiovascular system (Cornelis & El-Sohemy 2007). Although in vitro studies suggest that CYP1A2 may play a role in flavonoid metabolism, it would not be to detoxify these compounds (Breinholt et al. 2002). Thus, these findings provide good evidence that caffeine is a major component of coffee that could lead to an increased risk of MI (Cornelis et al. 2006). Interestingly, Cornelis et al. (2006) also found that moderate consumption (1–3 cups/day) of coffee had a protective effect among fast metabolizers, which was more pronounced among subjects aged <59 years. This suggests an unmasking of the cardiovascular-protective effects of certain coffee compounds, such as flavonoids and polyphenols, in the subpopulation of fast caffeine metabolizers.

The finding that slow caffeine metabolizers are more vulnerable to its adverse cardiovascular effects than fast metabolizers was corroborated in a prospective study that followed a young cohort of 553 Italian subjects for incident physician-diagnosed hypertension (Palatini et al. 2009). Coffee drinkers with the slow *CYP1A2* −163C allele demonstrated a significantly increased risk of developing hypertension compared to abstainers, whereas coffee drinkers with the −163 AA genotype (fast metabolizers) were significantly protected. Together, these studies suggest the possibility that slow caffeine metabolizers who consume caffeinated coffee may have an increased risk of CVD, whereas fast caffeine metabolizers may be protected from this risk by the antioxidants and other beneficial compounds present.

Although the −163 A > C polymorphism in the *CYP1A2* gene has a significant impact on the rate of caffeine metabolism, other *CYP1A2* polymorphisms, as well as polymorphisms in other genes that influence CYP1A2 activity, can influence the rate of caffeine metabolism. The studies

by Cornelis et al. (2006) and Palatini et al. (2009) involving *CYP1A2* implicated caffeine in the development of CVD, but genetic modifiers of the targets of caffeine action on the cardiovascular system could help elucidate the mechanisms of action by which caffeine contributes to CVD and thus identify other subgroups. Although the main pharmacological effect of caffeine is to antagonize ARs, the physiological effects of caffeine depend on the intracellular mechanisms of action and secondary effects on many classes of neurotransmitters, including dopamine, norepinephrine, and 5-hydroxy-tryptamine (serotonin) (Bickford et al. 1985, Fernstrom & Fernstrom 1984, Shi et al. 1993). Genetic variations in the signaling pathways stimulated by caffeine may partly explain the inconsistencies among studies relating caffeine and CVD.

In summary, a variation in the *CYP1A2* gene (−163A > C), which influences the rate of caffeine metabolism, has been shown to modify the association between caffeinated coffee consumption and the risk of CVD (Cornelis et al. 2006) and hypertension (Palatini et al. 2009). These findings suggest that caffeine, as a component in coffee, may have adverse effects on cardiovascular health. More work is likely needed to better understand the impact of genotypic differences in the human population and the subsequent interaction of lifestyle factors such as exposure to caffeine.

REPRODUCTIVE EFFECTS

Caffeine exposure is prevalent among women of reproductive age and is similar to caffeine intake patterns for the general US population. Among US women aged 18–34 years, mean caffeine intake from beverages was 166 mg/day in 2011 based on 7-day diaries (Mitchell et al. 2014). Approximately 68% of women continue caffeine consumption after becoming pregnant, with mean intake reported at 125 mg/day during pregnancy (Frary et al. 2005, Knight et al. 2004).

Concerns have been, and continue to be, raised that pregnant women and their fetuses may be susceptible to the potentially harmful effects of caffeine. Although the actual mechanism by which caffeine could alter fetal development is not known, caffeine crosses the placental barrier and is poorly metabolized by the fetus (Arnaud 1993). The increased half-life of caffeine during pregnancy, attributed to reduced activity of CYP1A2, can lead to accumulation of circulating caffeine concentrations in the mother and fetus (Aldridge et al. 1981, Arnaud 1993). Proposed mechanisms for the effects on fetal development include increased catecholamines in the mother and fetus, blocked ARs, and phosphodiesterase inhibition, leading to uteroplacental vasoconstriction (Kirkinen et al. 1983), hypoxia, and interference with fetal growth and development (by increasing cAMP), respectively (Weathersbee & Lodge 1977).

To date, much of caffeine research has focused on reproductive and perinatal endpoints such as subfecundity, fetal loss, fetal growth restriction, preterm delivery, and congenital malformations; however, drawing conclusions with confidence from this body of evidence is difficult due to the uncertainty associated with inconsistent findings and methodological issues that complicate interpretation. These complicating issues are discussed below in the context of studies on fetal growth restriction and fetal loss, because both of these outcomes tend to be at the center of attention due to the frequency with which positive associations are reported. Among caffeine consumers, reports of increased preterm delivery (Sengpiel et al. 2013), subfecundity (Hatch et al. 2012, Jensen et al. 2010, Taylor et al. 2011), and specific congenital malformations (Benedum et al. 2013, Browne et al. 2011) have been less frequently reported.

Results from studies evaluating associations between caffeine intake and fetal growth are divided. Approximately half of the studies reported weak associations with small for gestational age (SGA) or reduced birth-weight endpoints, whereas others found no statistically significant associations (Leviton & Cowan 2002, Peck et al. 2010). Two large prospective cohort studies recently made notable efforts to improve upon the methodological limitations of previous

research. Studies by Sengpiel et al. (2013) and the CARE Study Group (2008) both incorporated comprehensive exposure assessments, attempted to adjust associations for confounding by nausea during pregnancy, and examined the use of customized growth curves to define SGA. The latter tool is considered useful for distinguishing constitutionally small but healthy babies from those who fail to obtain their inherent growth potential. In their study of >59,000 Norwegian women with uncomplicated pregnancies, Sengpiel et al. (2013) observed modest associations between caffeine intake and SGA, with odds ratios (ORs) of 1.11 per 100 mg/day [95% confidence interval (CI) = 1.08–1.15] and 1.62 (95% CI = 1.36–1.92) for >300 mg/day compared to 0–50 mg. The authors examined concerns about caffeine intake measurement error by incorporating a validation substudy of 119 participants, which compared caffeine intake collected from the food frequency questionnaire (retrospectively reported for weeks 5–12 of pregnancy) with intake recorded in a prospective 4-day food diary. Although the correlation was reasonably strong (Spearman $r = 0.70$), comparisons between the retrospective questionnaire and prospective diary demonstrated that caffeine intake could be misrepresented for some participants by as much as 150 mg/day in either direction (Brantsaeter et al. 2008). Thus, it is necessary to consider the impact of exposure measurement error on the modest associations observed in such studies.

Another large UK prospective study of fetal growth restriction reported modest associations between intrauterine growth restriction and average caffeine intake throughout pregnancy (OR = 1.4; 95% CI = 1.0–2.0 for ≥300 mg/day versus ≤100 mg/day). This study is an additional example of a design that evaluated the quality of retrospectively reported caffeine intake values. The validation substudy compared their retrospective questionnaire (recalled exposure for weeks 5–12 of pregnancy) with a 3-day diary (Boylan et al. 2008). Using a sample of 24 pregnant women, there was moderate agreement (κ coefficient = 0.50) between the two instruments when caffeine intake was dichotomized at the median. Agreement further increased when the comparison was restricted to those interviewed closer to the reference period, but there was still some indication of inaccurate classification for a proportion of the study population.

When attempting to interpret the evidence for a causal link between caffeine and fetal growth restriction (or other outcomes), it is necessary to consider other possible explanations for the observed association or lack thereof. Because of the difficulty in measuring caffeine consumption, exposure measurement error is a major limitation of caffeine studies. Retrospective self-reports can be prone to error and the caffeine content of foods and beverages can vary by source, serving size, product brand, and method of preparation (Bracken et al. 2002). Studies of perinatal exposure have the added difficulty of capturing intake patterns that change during pregnancy (Lawson et al. 2004). Interindividual variation in caffeine metabolism may also be an important component of exposure assessment if metabolism rate is a factor that could modify the effect of maternal caffeine consumption on perinatal outcomes; however, relatively few studies of reproductive and perinatal outcomes have incorporated measures of CYP1A2 activity (Grosso & Bracken 2005).

Although measurement error is well acknowledged as a limitation of caffeine intake assessment, the potential impact of exposure measurement error on study results is less appreciated (Jurek et al. 2006). When studies calculate measures of association (e.g., ORs, risk ratios) based on the observed data, the degree to which the point estimates approximate true values relies on several factors, such as the sensitivity and specificity of the measurement tool, differences in accuracy by outcome status, and the prevalence of exposure in the source population (Szklo & Nieto 2014).

The potential magnitude and direction of bias introduced by measurement error can be difficult to qualitatively assess; therefore, quantitative methods have been proposed as an improvement to describe such limitations. Bias (or sensitivity) analyses apply informed estimates of the sensitivity and specificity of the exposure measurement to quantitatively adjust measures of association for misclassification (Greenland & Lash 2008, Johnson et al. 2014). Despite measurement error being

one of the primary limitations of caffeine research, studies of caffeine and reproductive health have not incorporated these methods to date. Including bias analyses in future caffeine studies could strengthen their methodology and aid interpretation.

Fetal loss is another pregnancy outcome that is reported to have a high frequency of positive associations with caffeine intake. Two of the most recent studies on caffeine and spontaneous abortion were designed using prospective cohorts and were published in the same year (Savitz et al. 2008, Weng et al. 2008), and both serve as good examples to elucidate methodological limitations. In a study of 1,000 health plan members, consumption of ≥200 mg/day of caffeine was associated with increased miscarriage risk (hazard ratio = 2.2; 95% CI = 1.3–3.7) compared to <200 mg/day (Weng et al. 2008). However, because 59% of miscarriages occurred before participants reported caffeine intake, critics expressed concern for potential recall bias (i.e., a methodological limitation). Savitz et al. (2008) stratified the analysis of 2,400 pregnant women by the timing of exposure assessment. When cases were limited to the 29% of women who were interviewed after their loss, caffeine intake exceeding median levels (≥144.3 md/day) was positively associated with miscarriage (OR = 1.9; 95% CI = 1.1–3.5). When cases were interviewed before the miscarriage occurred, the association was no longer observed (OR = 1.1; 95% CI = 0.6–1.8). Thus, the results of the Savitz et al. (2008) study provided evidence for potential recall bias in studies with retrospective exposure assessment administered after the event had occurred.

There is also a concern that the positive associations reported for caffeine and spontaneous abortion could be due to reverse causality. Stein & Susser (1991) hypothesized that pregnancy symptoms such as nausea, vomiting, and increased aversions to certain tastes and smells (e.g., coffee) may be the result of a healthy and viable pregnancy. As behavior changes in response to such symptoms (e.g., avoidance of items with strong odors), caffeine consumption may coincidentally decrease. Women with what were deemed unhealthy pregnancies (destined to miscarry) would not experience the same symptoms (nausea/aversion to strong smells) or signals and therefore would not avoid certain food or beverage items, hence maintaining higher levels of caffeine consumption. This phenomenon is known as the pregnancy signal hypothesis. The hypothesis proposes that higher caffeine intake among those with higher risk of miscarriage may result from their poor condition rather than a causal factor. Studies have demonstrated patterns of decreasing caffeine intake with increasing nausea during pregnancy (Cnattingius et al. 2000, Lawson et al. 2004), but empirical evidence of confounding by pregnancy symptoms is somewhat limited. Some studies reported that associations were attenuated among those with the strongest signals (Weng et al. 2008). Others, however, failed to observe increased risk among those without symptoms (Wen et al. 2001) and adjustment for nausea did not eliminate associations with fetal loss in all prospective studies (Greenwood et al. 2010). Measures limited to nausea, however, may not accurately capture the complexities of the pregnancy signal.

It is also possible that the pregnancy signal hypothesis may impact associations with other outcomes; however, evaluation of pregnancy symptoms in studies of perinatal outcomes other than fetal loss is limited. For example, in the CARE study, nausea was not associated with fetal growth restriction and associations between caffeine (first- and second-trimester intake) and fetal growth restriction did not differ with the presence of nausea (Boylan et al. 2013). The previously reported findings of increased odds of fetal growth restriction among caffeine consumers were no longer observed among the subset of the study population with nonmissing data on nausea.

Smoking is a known risk factor for numerous adverse pregnancy outcomes. Because heavier smokers consume greater quantities of caffeine (Zavela et al. 1990), controlling for confounding by smoking is an important consideration in study design. The stigma of smoking during pregnancy can lead to inaccurate reporting, with nondisclosure among pregnant smokers reported to be as high as 22.9% (95% CI = 11.8–34.6) (Dietz et al. 2011). Furthermore, measurement is frequently

limited to self-reported current smoking status (yes/no); as such, residual confounding may remain an influential factor in many studies (Morrison 1984).

Although the results of individual studies have been inconsistent with respect to caffeine consumption and fetal growth restriction or spontaneous abortion, the conclusions presented by the growing collection of critical reviews and advisory reports are relatively consistent, showing that moderate caffeine consumption (200–300 mg/day) is unlikely to increase risk of adverse reproductive and perinatal outcomes (Am. Coll. Obstet. Gynecol. 2010, Brent et al. 2011, Bull et al. 2015, Higdon & Frei 2006, Int. Food Inf. Counc. Found. 2008, Leviton & Cowan 2002, Nawrot et al. 2003, Peck et al. 2010, Signorello & McLaughlin 2004).

Although systematic errors (e.g., biases) may explain many of the observed associations with caffeine, such reports cannot be dismissed without stronger evidence of their direction and magnitude. The incorporation of bias analyses, which quantitatively evaluate the impact of exposure misclassification (and other biases) on the risk ratio, would offer important methodological advancements to this research area and aid interpretation. Validation substudies that estimate the sensitivity and specificity of caffeine exposure measurement in the source populations would inform the assumptions required for bias analyses that address measurement error. Other considerations for improving the quality of the evidence include comprehensive exposure assessment across etiologically relevant time points and detailed measurement of important confounders such as smoking and the pregnancy signal.

CAFFEINE AND HUMAN BEHAVIOR

The effects of caffeine on behavior have been widely studied and reviews in this area discuss many different outcome measures (Glade 2010; Lieberman 1992; Smith 2002, 2005a, 2011, 2014). It appears that individuals seek caffeine-containing products mainly for their behavioral effects. Previous reviews suggest that these are often positive except when one considers very large doses of caffeine and the ranges of effects in individuals. Desirable effects attributed to low or moderate intake levels, such as changes in mood, energy, alertness, and vigor, may mildly reinforce consumption for some individuals (Fredholm et al. 1999, Garrett & Griffiths 1997, Lorist & Tops 2003, Nehlig 1999; Smith et al. 2005). High intake levels of caffeine are reported to produce negative effects, such as anxiety, jitters, and nervousness (Benowitz 1990, Fredholm et al. 1999, Garrett & Griffiths 1997, Lorist & Tops 2003), which may discourage further intake. Recent research has investigated these effects in a wide range of scenarios and real-life activities, as discussed below.

A review of the behavioral effects of caffeine concluded that they are often most beneficial when alertness is already reduced (e.g., after lunch or when working at night, when sleep deprived, or during a cold) (Smith 2011). The American Academy of Sleep Medicine (Bonnet et al. 2005) examined the efficacy and safety of caffeine use during sleep loss and concluded that caffeine can (*a*) increase alertness and improve performance after acute restriction of sleep (at doses of 75–150 mg) and (*b*) provide similar benefit after a night or more of total sleep loss (at doses of 200–600 mg). The major disruptive effects of caffeine on sleep are unlikely to occur more than 8 hours after administration, and prolonged administration of caffeine is not recommended because of the increasing likelihood of side effects (e.g., interference with sleep, increased anxiety and blood pressure) with high doses.

The potential benefits or concerns of caffeine consumption while working have been investigated in various settings, including military personnel, white-collar and factory workers, and individuals performing day-to-day lifestyle tasks. Lieberman et al. (2002) examined many studies investigating the effects of caffeine in sustained military operations and concluded that "When cognitive performance is critical and must be maintained during exposure to severe stress,

administration of caffeine may provide a significant advantage." Smith (2005b) also investigated associations between habitual caffeine consumption and performance and safety at work. The first study showed that those who consumed higher levels of caffeine (i.e., >220 mg/day) reported significantly greater increases in alertness and a significantly smaller slowing of reaction time over the course of the working day (defined as the difference between reaction time at the start and end of the day). Secondary analyses of associations between caffeine consumption and the frequency of cognitive failures were then examined in a sample of white-collar workers, and further analyses examined associations between caffeine consumption and accidents at work. After controlling for possible confounding factors, higher caffeine consumption was associated with approximately half the risk of frequent/very frequent cognitive failures and a similar reduction in risk for accidents at work. A recent review considered the effects of caffeine for preventing injuries, errors, and cognitive problems caused by impaired alertness in persons doing shift work, and Ker et al. (2010) concluded that "Based on the current evidence, there is no reason for healthy individuals who already use caffeine within recommended levels to improve their alertness to stop doing so." Finally, comparable findings during everyday tasks were obtained in analyses of human error and accidents in a nonworking sample (Smith 2009).

Research has shown that caffeine can improve other tasks, such as reducing the impaired driving performance observed in sleepy drivers given placebo. Smith (2014) described a study examining associations between caffeine consumption and traffic accidents in a representative community sample ($N = 6{,}648$). Logistic regressions, including demographic, lifestyle, and psychosocial characteristics, showed that caffeine consumption nearly halved the risk of being in a road accident (OR = 0.58; 95% CI = 0.35–0.98).

Caffeine's role in lowering the rate of cognitive decline and the risk of dementia is another promising area of research. A systematic review and meta-analysis (Santos et al. 2010) considered nine cohort studies and two case control studies, which examined associations between caffeine consumption and dementia/cognitive impairment in elderly individuals. The summary relative risk for the association between caffeine intake and the different cognitive measures was 0.84 (95% CI = 0.72–0.99), which suggests a trend toward a protective effect of caffeine. Although further research is needed, this should remain a topic of interest because Alzheimer's disease and dementia are prevalent in the aging population.

Although much research demonstrates the likely benefits of caffeine on behavior, some controversy remains regarding its potential for negative behavioral effects. Most individuals consider these to include jitteriness, anxiety, nervousness, and sleep disturbances. Regarding impairment of sleep, many consumers reduce their consumption later in the day to prevent such effects, which is another example of self-titration of caffeine ingestion. Indeed, research suggests that caffeine-induced sleep disruption is mainly observed when higher doses (>300 mg) are consumed immediately before bedtime (Smith et al. 1993).

Caffeinism is one of the more extreme examples of caffeine's adverse effects and has been discussed as a potential psychiatric disorder (Victor et al. 1981). Caffeinism is usually associated with daily intake of 1,000–1,500 mg caffeine. This term refers to a constellation of symptoms associated with very high caffeine intake that are virtually indistinguishable from severe chronic anxiety; however, caffeinism appears to be a specific condition, and there is little evidence for correlations between caffeine intake and anxiety in either nonclinical volunteers or psychiatric outpatients (Lara 2010). In the case of depression, moderate caffeine intake has been associated with fewer symptoms and a lower risk of suicide. This antidepressant effect of caffeine may have implications for other aspects of health due to the strong association of depression with immunosuppression. Smith (2011) describes secondary analyses of a large epidemiological database that aimed to examine associations between caffeine and both chronic and acute health outcomes. Many of the initial

associations between caffeine and health were no longer significant when potential confounders such as demographic and lifestyle factors were examined, although caffeine consumption was still significantly associated with reduced depression in the final regressions. The secondary analyses showed that caffeine consumption was also associated with fewer upper respiratory tract symptoms in a dose-response manner. This suggests that caffeine may influence the immune system, either directly or indirectly, by reducing depression.

Despite the potential behavioral benefits discussed above, it should be noted that some researchers have proposed that there are no direct benefits of caffeine on behavior. Rather, it is hypothesized that caffeine withdrawal impairs performance, and ingestion of subsequent caffeine simply removes the negative effects of withdrawal (James & Rogers 2005). However, this theory is unlikely [see Smith (2005a) for a detailed review] because effects of caffeine are observed in animals and nonconsumers (who by definition are not experiencing withdrawal; Smith et al. 2013) and after a seven-day washout period (when any effects of withdrawal have diminished). Effects of caffeine can also be observed after prior consumption (i.e., when the person is not deprived) (Smith et al. 2005).

Due to the growth of caffeine-containing EDs in the marketplace, studies of their acute effects on the behavior of young adults are being published, along with data regarding the health effects of ED consumption in general (Seifert et al. 2011). Although this area is likely to continue to warrant scrutiny and interest, the available studies confirm that following ED ingestion, young adults experience increases in alertness and attention (Alford et al. 2001, Scholey & Kennedy 2004, Smith 2013) and improvements in alertness under sleep-deprived simulated driving (Horne & Reyner 2001, Mets et al. 2011), and night shift workers experience reductions in sleepiness (Smith 2013). However, despite the potential benefits of EDs in young adults, studies suggest that their consumption may be associated with behavioral problems in children (Reissig et al. 2009, Schwartz et al. 2015). Further research is needed, as it is often unclear whether ingestion of EDs is causing behavioral problems or whether those with behavioral problems are choosing to consume EDs (Smith 2014).

It has been hypothesized that some individuals may intentionally seek some of the negative effects of caffeine. These adverse effects, which may be intentionally sought by high-dose bolus consumers, may be a manifestation of stimulation-seeking behavior (Terry-McElrath et al. 2014). This type of behavior is often seen in young males; however, most individuals (including young males) choose to use moderate doses of caffeine and have characteristic and regular patterns of consumption (Fulgoni et al. 2015, Mitchell et al. 2014).

Despite the potential for some thrill-seeking behavior with regard to intake, it appears that ad libitum caffeine consumption remains consistent over time, which might make one ponder why this is so, especially because there have been large changes in product choice, availability, and social norms, as previously described. A possible answer may be that humans are very good at sensing and regulating their own mood state. Caffeine's behavioral dose-response function is nonlinear, with maximum positive effects at moderate doses, and the optimal single dose is approximately equal to the dose found in one to two cups of coffee (Smith 2002, 2005a, 2011). If humans are using caffeine to optimize mood, then an optimal dose would likely produce the most desirable mood: increased vigor, less fatigue, and more mental energy. This may be a Goldilocks zone of AR antagonism.

In summary, extensive research exists that demonstrates beneficial behavioral effects of caffeine. Most neurobehavioral studies find that the desirable benefits of caffeine are common and can be achieved at dose levels that appear to warrant no concern. Negative effects are very rare and may largely be restricted to consumption of high doses by susceptible individuals. Further research is

required to address current topics of concern, such as caffeinism or the effects of consuming EDs on the behavior of school children.

CONCLUSIONS

One of the goals of the "Caffeine: Friend or Foe?" session was to present some of the risks and benefits of caffeine, while simultaneously elucidating some of the issues that challenge the interpretation of these studies. Understanding these nuances is particularly timely, as authoritative agencies continue to receive pressure to identify either a common health metric or a recommended safe level of caffeine intake. As these evaluations take place and subsequent decisions are made, it will be important to find the right balance between the benefits and risks that may be associated with caffeine exposure.

Although they are only briefly highlighted in this paper, there are a number of challenges in assessing the literature concerning the health benefits and risks of caffeine. Caffeine is a complicated chemical that is naturally occurring and can be synthetically manufactured and added to food, dietary supplements, cosmetics, and drugs. This contributes to some of the challenges regulators face as they consider potential guidance for regulating its intake. Additionally, caffeine has effects on nearly every health endpoint, including various cardiovascular, reproductive, and behavioral outcomes considered herein. Importantly, caffeine is generally ingested by choice and caffeine-containing products can be easily avoided if desired. Given that a large percentage of the population chooses to make caffeine a part of their daily lifestyle, the answer to whether caffeine is a "friend" or "foe" may vary from individual to individual, determined by underlying differences ranging from genetic variations to taste preferences.

Metabolism, although well understood biochemically, has a genetic component that creates differences in physiological responses between individuals, particularly in the ARs. These genetic polymorphisms may complicate or confound some of the existing scientific research on caffeine if not appropriately accounted for. Genetic makeup may even affect factors such as taste and self-titration, which can influence consumption practices.

Not only is the potential for exposure to caffeine broad, but the possible effects of caffeine are also diverse. The three main effect areas presented and discussed in this paper are related to cardiovascular health, reproductive health, and behavior. This review serves to highlight examples of challenges that exist in interpreting the risks and benefits of caffeine. Although caffeine has effects on many other endpoints, these three tend to be heavily studied; despite numerous publications and reviews, difficulties remain in drawing concrete conclusions. Defining some of the challenges should prove helpful to both regulators and consumers alike.

Caffeine has been extensively researched for its potential role in the development of CVD, yet the findings remain equivocal. Genetic variation, particularly in CYP1A2, may account for some of the discrepancies in the association between caffeine and risk of CVD. It appears that more investigation is needed to study whether caffeine, as a lifestyle factor in certain susceptible individuals, may increase the risk of CVD.

Caffeine and its relationship with reproductive health outcomes remain of much interest because many women of reproductive age, including pregnant women, elect to ingest caffeine-containing products. This review focuses on two aspects of female reproductive health that have frequently reported (positive) associations with caffeine: fetal growth restriction and fetal loss. A closer look at relevant studies uncovers methodological complications that must be taken into account when drawing conclusions. Exposure measurement error (under- or over-reporting consumption) can make interpretation of reproductive studies challenging, and the use of bias analysis

can be a valuable tool to reduce this type of error. Regarding reverse causality, the pregnancy signal hypothesis demonstrates the complexity of the pregnant female's physiology (e.g., influence of hormones), which must be factored into study design and interpretation. Despite such underlying methodological challenges, it appears that moderate caffeine intake in pregnant women is unlikely to increase the risk of adverse reproductive and perinatal outcomes.

Finally, similar methodological concerns are likely important to behavioral endpoints (e.g., understanding intake and appropriately controlling for confounding). The majority of the neurobehavioral work suggests that the desirable benefits of caffeine (e.g., increased alertness) are ubiquitous. Caffeine is typically consumed at 180–200 mg/day and can provide the desired benefit sought by the majority of users (i.e., mental alertness) with a low risk of negative side effects (e.g., jitters, anxiety, or sleep disturbance) (Fulgoni et al. 2015, Mitchell et al. 2014). To this end, caffeine has been shown to reduce the risk of workplace accidents. However, concern has been raised that caffeine may cause behavioral issues in children and adolescents. Caution is warranted in generalizing these conclusions until preexisting behavioral conditions of a given population are examined and the cause-effect relationship between caffeine consumption and behavioral problems is clearer.

In addressing some of the underlying challenges, a validated and systematic approach may provide valuable balance to understanding the risks and benefits of caffeine. The Benefit Risk Analysis for Foods (BRAFO) Executive Project model is one model that has successfully been used for other food ingredients. The BRAFO tiered approach begins with a preassessment of the issue and problem formulation, followed by an individual assessment of the risks and benefits. Later tiers then compare and qualitatively integrate these benefits and risks to derive a common health metric (Vidry et al. 2013). The goal of this model is to help decision-makers account for the full scope of benefits and risks when setting guidance. However, the BRAFO model may prove challenging for caffeine because BRAFO is designed to evaluate benefits such as lowering the risk of disease, as opposed to the neurobehavioral benefits that caffeine offers. Regardless, until the exercise is initiated, the challenges in application will remain unknown. Thus, one potential next step could be to determine whether BRAFO would be applicable to the study of caffeine and whether it would help authoritative agencies in determining an appropriate level of protection and whether one is even needed. Without a formal assessment, it remains apparent that the self-limiting aspects of caffeine ingestion suggest that despite a lack of current official guidance, most individuals seeking caffeine can consider it a friend and are capable of recognizing when it becomes a foe.

DISCLOSURE STATEMENT

C.D. and B.W. are both consultants for and at times provide technical advice to coffee companies and coffee-related trade groups. Both are currently collaborating with ILSI–North America on a systematic review of caffeine for publication in a peer-reviewed journal. A.E.S. holds shares of Nutrigenomix Inc, a genetic testing company. J.P. is scientific advisor and H.L. is government liaison to the ILSI–North America Caffeine Working Group, and both serve as advisors for the ongoing project on systematic review of caffeine.

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The opinions contained herein are the private views of the coauthors and are not to be construed as official or as reflecting the views of the US Army or the Department of Defense. Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations. This work is approved for public release; distribution is unlimited.

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