THE Society for Food Science & Technology

Journal of Food Science

A Publication of the Institute of Food Technologists

Caffeine (1, 3, 7-trimethylxanthine) in Foods: A Comprehensive Review on Consumption, Functionality, Safety, and Regulatory Matters

MELANIE A. HECKMAN, JORGE WEIL, AND ELVIRA GONZALEZ DE MEJIA

ABSTRACT: Caffeine ranks as one of the top most commonly consumed dietary ingredients throughout the world. It is naturally found in coffee beans, cacao beans, kola nuts, guarana berries, and tea leaves including yerba mate. The total daily intake, as well as the major source of caffeine varies globally; however, coffee and tea are the 2 most prominent sources. Soft drinks are also a common source of caffeine as well as energy drinks, a category of functional beverages. Moderate caffeine consumption is considered safe and its use as a food ingredient has been approved, within certain limits, by numerous regulatory agencies around the world. Performance benefits attributed to caffeine include physical endurance, reduction of fatigue, and enhancing mental alertness and concentration. Caffeine has also been recently linked to weight loss and consequent reduction of the overall risks for developing the metabolic syndrome. However, the caloric contribution of caffeine-sweetened beverages needs to be considered in the overall energy balance. Despite all these benefits the potential negative effects of excessive caffeine intake should also be considered, particularly in children and pregnant women.

Keywords: caffeine, fatigue, functional beverages, mental alertness, metabolic syndrome, regulation

Introduction

Caffeine has been used for thousands of years and is one of the most widely consumed active food ingredient throughout the world. It is found in common beverages including coffee, tea and soft drinks, as well as products containing cocoa or chocolate, and a variety of medications and dietary supplements (Barone and Roberts 1996; Andrews and others 2007). Caffeine, the common name for 1,3,7-trimethylxanthine, was derived from the German word *kaffee* and the French word *café*, each meaning coffee. Historians suggest that caffeine was consumed as far back as 2737 BC when Chinese Emperor Shen Nung boiled drinking water and leaves from a nearby bush, creating a pleasant aroma and the first pot of tea (Arab and Blumberg 2008). Coffee originated many years later in the 9th century in Ethiopia when a shepherd began consuming wild coffee berries after observing that his goats had increased energy after eating them (Griffin 2006). It was not until the late 1800's that caffeinated soft drinks began appearing with the introduction of Dr. Pepper, followed by Coca-Cola and then Pepsi-Cola (ABA 2008). The caffeinated soft drink market grew enormously during the 2nd half of the 20th century with increased popularity occurring among the beverages containing higher amounts of caffeine. The increased popularity inspired the arrival of energy drinks, which have become very prevalent. Today, approximately 80% of the world's population consumes a caffeinated product every day and 90% of adults in North America consume caffeine on a daily basis (Ogawa and Ueki 2007). The attractiveness and recognition of these beverages are due to the effect that caffeine has on the body and mind. It has properties that aid in staying awake and improving mental alertness after fatigue (Smit and Rogers 2002). In addition, other findings show that caffeine can be a potential contributor to reducing risk factors involved in the metabolic syndrome, including type 2 diabetes mellitus (DM) and obesity (Westerterp-Plantenga and others 2006; Hino and others 2007). Due to the popularity and wide consumption of caffeinated beverages, the objective of this review was to compile and comprehensively analyze updated scientific information about dietary caffeine, including its consumption, health related functionality, safety, and regulations.

MS 20091104 Submitted 11/4/2009, Accepted 1/13/2010. *Authors Heckman and de Mejia are with Dept. of Food Science and Human Nutrition, Univ. of Illinois Urbana-Champaign, IL, U.S.A. Author Weil is with School of Medicine, University of Buenos Aires, Argentina. Direct inquiries to author de Mejia (E-mail: edemejia@illinois.edu).*

Sources of Caffeine

Caffeine is a naturally occurring alkaloid that is found in varying quantities in the beans, leaves, and fruits of more than 60 plants. Some common sources of caffeine are the kola nut (*Cola acuminate*), cacao bean (*Theobroma cacao*), yerba mate (*Ilex paraguariensis*), and guarana berries (*Paullinia cupana)*; however, roasted coffee beans (*Coffea Arabica* and *Coffea robusta*), and tea leaves (*Camelia siniensis*) are the world's primary sources of dietary caffeine (Barone and Roberts 1996). In the United States, most of all dietary caffeine consumed is imported in the form of coffee and tea; cocoa, kola nuts and synthetic caffeine account for a small portion (Bonita and others 2007; Frary and others 2005). There is no chemical difference between synthetic caffeine and naturally sourced caffeine. Caffeine is consumed most frequently in beverages such as coffee (71%), soft drinks (16%), and tea (12%) (Channel Check 2008). The market for caffeinated beverages has increased in the past decade with the introduction of functional beverages, including the energy drinks category, as well as other beverages such as caffeinated sport drinks, juices, and waters (Channel Check 2008). In addition to these beverages, caffeine is also found in cocoa, chocolate, and in a variety of medications such as in some pain reliever formulations and in dietary supplements.

doi: 10.1111/j.1750-3841.2010.01561.x

Caffeine Concentration in Beverages

Caffeine concentration varies among different beverages with coffee having in general the highest value compared to tea, soft drinks, and some energy drinks. A significant variation in caffeine concentration within a beverage category can also exist, as in the case of coffee and tea. Green tea contains caffeine; nevertheless, there is a large variability in caffeine content according to the type of green tea as well as the brewing method. Given that caffeine occurs naturally in those beverages the caffeine content will vary due to the plant variety, environmental growing conditions or the brewing method used (McCusker and others 2003; Heck and de Mejia 2007). For example, a standard 8 oz (240 mL) cup of coffee is thought to have an average of 100 mg of caffeine; however, in a study that analyzed the caffeine content of 20 different specialty coffees purchased at coffee shops in the United States found that the amount of caffeine in brewed coffee ranged from 76 to 112 mg/8 oz (McCusker and others 2003). In addition, it was found that the caffeine content of the same type of coffee purchased from the same store on 6 separate occasions ranged from 130 to 282 mg/8 oz (McCusker and others 2003). The analysis of 7 decaffeinated coffee products was also done with each product containing ≤17.7 mg/serving. Table 1 outlines a variety of caffeinated beverages that are available in the market and their average and ranges in caffeine content. The caffeine content in espresso coffee is the highest. Figure 1 shows a comparison of the amount of caffeine found in commonly consumed beverages. Among tea beverages,

Table 1 — Concentration of caffeine in selected beverages.

	Caffeine (mg)			Caffeine range (mg)	
Sources of caffeine	1 oz	8 oz	12 oz	8 oz	Reference
Coffee					
Decaffeinated		5		3 to 12	CSPI (2007)
Instant	12	93	140	27 to 173	
Plain, brewed	17	133	200	102 to 200	
Espresso	40	320	480	240 to 720	
Tea					
Tea, brewed	7.0	53	80	40 to 120	www.nal.usda.gov
Green	5.6	45	68	30 to 50	www.nal.usda.gov
Black	6.0	47	72	25 to 110	www.stashtea.com
Yerba Mate	9.8	78	117	65 to 130	Heck and de Mejia (2007)
Soft Drinks					
Coca-Cola Classic	2.9	23	35	NA	http://www.energyfiend.com/the-caffeine-database
Pepsi-Cola	3.1	25	37	NA	
Sunkist	3.5	28	42	NA	
Diet Coke	3.9	31	47	NA	
Mountain Dew	4.6	37	55	NA	
Energy drinks					
Amp	8.9	72	107	NA	
Full Throttle	9.0	72	108	NA	http://www.energyfiend.com/the-caffeine-database
Red Bull	9.5	76	114	NA	
Monster	10.0	80	120	NA	
Rockstar	10.0	80	120	NA	
Other					
Water Joe	3.6	28	43	NA	http://www.energyfiend.com/the-caffeine-database
Cranergy	8.8	70	105	NA	

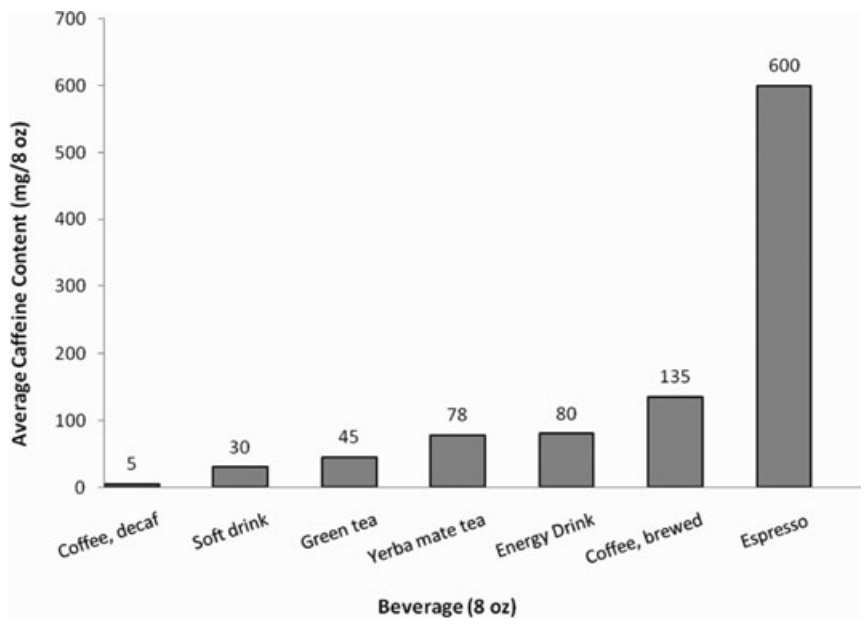

Figure 1 — Caffeine (mg/8 oz) comparison in a variety of beverages.

yerba mate tea has a considerably higher content of caffeine with an average of 78 mg/8 oz compared to black (55 mg/8 oz) and green (35 mg/8 oz) teas. The caffeine concentration of yerba mate is more comparable to that of energy drinks. The 2 most abundant compounds in yerba mate are polyphenols (chlorogenic acid) and xanthines (caffeine and theobromine), followed by purine alkaloid, amino acids, flavonoids, minerals, and vitamins (Heck and de Mejia 2007). Table 2 shows the caffeine concentration of a variety of yerba mate teas from different origins of the world, ranging from 8.6% ± 0.004% to 15.5% ± 0.01% (w/w) (Kennedy and de Mejia 2007).

Caffeine Consumption

Caffeinated beverages are consumed frequently by different segments of society including children, adolescents, and adults from both genders; however, within these segments the daily caffeine intake varies as well as the types of caffeinated products consumed. In the United States, adults consume on average 4 mg/kg body weight (bw)/d of caffeine, which equates to 280 mg/d for a 70-kg person; less is consumed in adolescents and children (Barone and Roberts 1996). In the United States, ordinary soft drinks, rather than beverages with increased caffeine content, account for the main source of caffeine among children and adolescents, while coffee is the main source of caffeine consumption for adults (Frary and others 2005).

In addition, caffeine consumption varies around the world. Table 3 presents the average daily caffeine intake from coffee, tea, mate, and cocoa among adults in various countries (Fredholm and others 1999). These averages are most likely lower than in reality since caffeinated cola products were not included in the data collection. Additionally, the caffeine content present in coffee, tea, mate, and cocoa is highly variable. In the United States, the average of 4 mg/kg bw/d is very comparable to the average in the U.K. of 3.98 mg/kg bw/d. These levels are somewhat higher than the consumption of caffeine in the Republic of Ireland, which is 3.05 mg/kg bw/d (equivalent to 214 mg/d for a 70-kg person) (Fredholm and others 1999; Finnegan 2003; Knight and others 2004). The reported intake in Denmark is much greater with an average of 7 mg/kg bw/d (Nawrot and others 2003). As a result of the variation among countries, it is difficult to develop a standard for what constitutes a moderate level of intake since the average in the United States is by far less than Denmark's average. Much of the variance that is seen between countries is due to the rate of coffee and tea consumption in those given areas. In the United States and Canada as well as in many European countries such as Finland, Denmark, and Switzerland coffee consumption is very prevalent and accounts for the majority of the daily caffeine consumption among adults; whereas in the U.K. tea is the beverage of choice (Nawrot and others 2003). In addition, the United States is the largest per capita consumer of soft drinks, accounting for over 20% of the global total, followed by Mexico and Chile (AICRWCRF 2007). There is not reliable data of caffeine consumption in Latin American countries; however, it is believed that caffeine intake in countries such as Brazil and Argentina is high due to the popular consumption of coffee and yerba mate tea. A similar situation may occur in China due to the high consumption of green tea.

Table 2—Caffeine concentration among a variety of yerba mate teas.

Origin	Description	Caffeine in tea powder concentrate (%)
Paraguay, Itabo Reservation	Wood dried, organic	15.5 ± 0.01
Paraguay, Asuncion	Organic	13.5 ± 0.006
Brazil, Canarias	Wood-charred, air dried	13.0 ± 0.01
Paraguay, Asuncion	Wild organic, wood dried	12.6 ± 0.01
Argentina, Corrientes	Organic, wood dried	10.8 ± 0.009
Brazil, San Mateo do Sol	Air dried, organic	10.4 ± 0.002
Argentina, Misiones	Wood dried	8.6 ± 0.004

A standard curve of pure caffeine in water was developed to quantify caffeine content in teas ($Y = 0.8979x - 0.0002$; $R^2 = 0.999$).
Source: Univ. of Illinois Champaign, Urbana, Ill., U.S.A. (Kennedy and de Mejia 2007).

Table 3—Average daily caffeine consumption.

Country	Adults (mg/d)
China	16
South Africa	40
Kenya	50
United States	168
Japan	169
United Kingdom	202
Canada	210
Australia	232
France	239
Switzerland	288
Brazil	300
Finland	329
Denmark	390

This data was adapted from the 1995 food balance sheets of the Food and Agriculture Org. of the United Nations (FAO) (Fredholm and others 1999).

Caffeine is rapidly and completely absorbed and eliminated with an average half-life of 5 h (Charles and others 2008). Pharmacokinetics and bioavailability of caffeine in extremely premature infants showed that caffeine is completely absorbed after orogastric administration of a caffeine citrate solution (Charles and others 2008). In healthy humans, the range of gastric emptying of caffeine was 50 to 175 min; 50% of the dose being emptied in 1 to 2 h and over 90% by 3.5 h following dosing. The absorption kinetics of caffeine was closely related to gastric-emptying suggesting that gastric emptying is an important determinant of absorption rate (Higaki and others 2008). Based on absorption, the bioavailability of caffeine is assumed to be 100% (Blanchard and Sawers 1983a, 1983b). Since the pharmacokinetics of caffeine after bolus injection can be described by a one-compartment model excretion from the intestine as feces can be ignored because caffeine is absorbed completely (Newton and others 1981; Blanchard and Sawers 1983a, 1983b; Rump and others 1997). Several studies have been conducted to compare various caffeine doses and modes of delivery (capsule, oral solution, gum), with the aim of determining which is the safest, most reliable, and most rapidly absorbed (Kamimori and others 2002). When caffeine was administered in a gum formulation, a quick onset of action was obtained (within 5 to 10 min of administration) and researchers suggested that the gum provides an effective and convenient means of maintaining effective concentrations of caffeine that would in some operational scenarios be desirable for maintaining alertness and performance in sleep deprived individuals (Syeda and others 2005).

Metabolism

Once ingested, caffeine is rapidly absorbed from the gastrointestinal tract into the bloodstream and becomes metabolized in the liver (Nawrot and others 2003). Bonati and others found that caffeine is extensively metabolized by the liver (99%) to form 3 major metabolites 3,7-dimethylxanthine, 1,7-dimethylxanthine, and 1,3-dimethylxanthine showing that 70 to 100 mg of caffeine exhibit a linear pharmacokinetics (Bonati and others 1982). For higher doses (250 to 500 mg), the clearance of caffeine is significantly reduced and its elimination half-life is prolonged, indicating nonlinearity (Kaplan and others 1997). Figure 2A shows an overview on

how caffeine undergoes demethylation, resulting in paraxanthine (84%), theobromine (12%), and theophylline (4%), with the xanthenes theobromine and theophylline having very similar chemical structures compared to caffeine (Figure 2B) (Safranow and Machoy 2005). These metabolites are then broken down further in the liver by additional demethylations and oxidation to urates with about 3% of those metabolites being caffeine when recovered in the urine (Mandel 2002). Approximately 90% of the caffeine contained in 1 cup of coffee is cleared from the stomach within 20 min and peak plasma concentration is reached within approximately 1 to 1.5 h (Chvasta and Cooke 1971; Nawrot and others 2003). Once absorbed, caffeine exerts a variety of physiological actions to diverse organs of the body. In doses typically contained in coffee, tea, and soft drinks caffeine's main mechanism of action is to work as an adenosine receptor antagonist in the brain resulting in inhibitory effects to the central nervous system (Dunwiddie and Mansino 2001; Pettenuzzo and others 2008). Since caffeine has a similar molecular structure to adenosine, with both having a comparable double bond ring structure, caffeine has the potential to occupy adenosine receptor sites, primarily A_1 and A_{2a} (Fisone and others 2004). The A_1 receptors are located in all parts of the brain with the heaviest concentration in the hippocampus, cerebral, and cerebellar cortex and certain thalamic nuclei (Fredholm and others 1999). The A_{2a} receptors are located in the dopamine rich areas of the brain (Fredholm and others 1999). After caffeine connects to those receptors an adenosine blockage forms. The blockage of adenosine to the neurons causes the sleep promoting effects of adenosine to stop, resulting in the neurons speeding up instead of slowing down (Ferre 2008).

Caffeine Consumption and Human Health

Caffeine has been widely studied in a variety of areas regarding human health and performance (Smit and Rogers 2002). Many studies confirm caffeine's ability to enhance mood and alertness (Kaplan and others 1997; Lorist and Tops 2003), exercise performance (Doherty and Smith 2004), the speed at which information is processed, awareness, attention, and reaction time (Cysneiros and others 2007). Additionally, research has suggested that caffeine can aid in reducing symptoms associated with Parkinson's disease (PD) such as the deterioration of gross and small motor skills, and tremors (Blandini and others 2000; Trevitt and others 2009). Since PD is a neurodegenerative disease which results in progressive loss of dopaminergic neurons of the substantia nigra, caffeine a nonselective adenosine antagonist is thought to aid in improving the performance of the dopaminergic system by blocking the A_{A2} receptors, thus, stimulating dopamine release (Trevitt and others 2009). Caffeine has also been found to play a preventative role against the onset of PD. A large prospective study in men showed

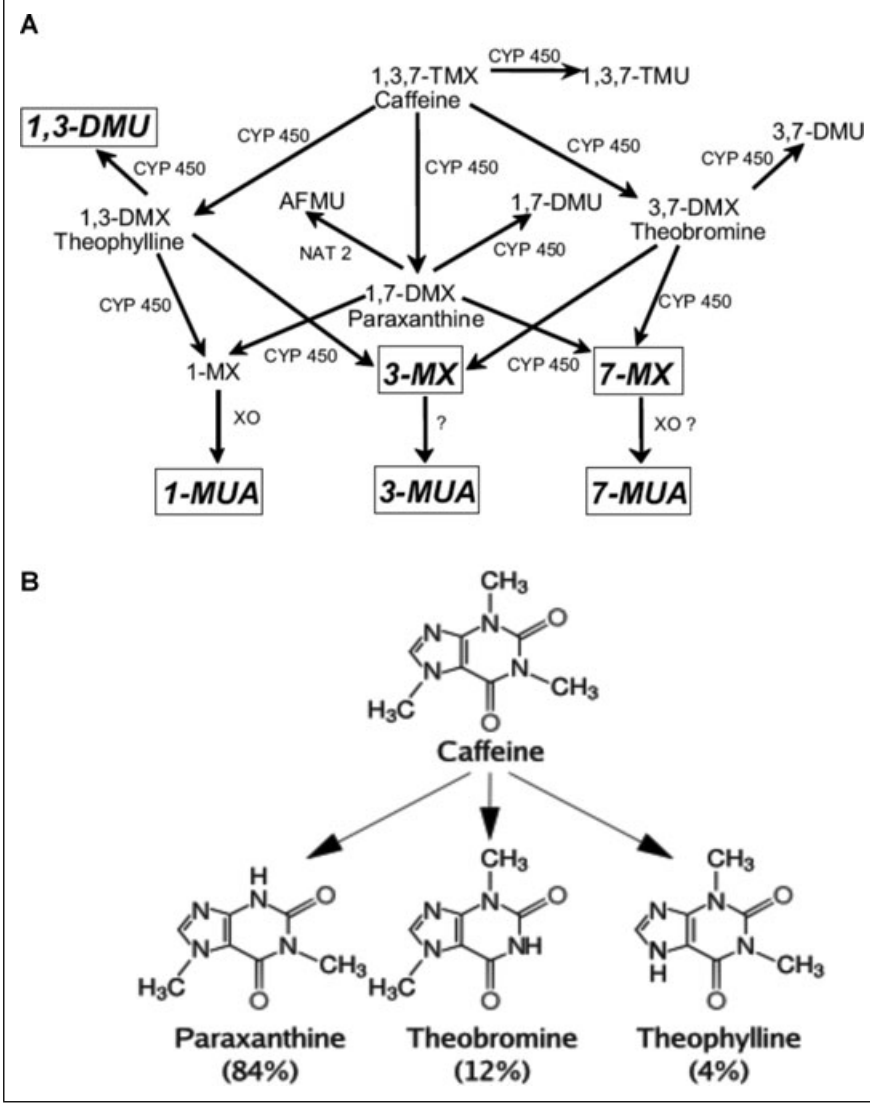

Figure 2—Structure of caffeine and its metabolism (Safranow 2005). A) Metabolism, B) chemical structures. AFMU: 5-acetylamino-6-formylamino-3-methyluracil, CYP 450: Cytochrome P450, DMU: dimethyluric acid, DMX: dimethylxanrthines, MUA: monomethyluric acid, MX: monomethylxanthines, NAT 2: N-acetyltransferase 2, TMU: trimetylxanthines, TMX: trimethylxanthines, XO: xanthine oxidoreductase.

an inverse relationship between PD and coffee consumption, caffeine from non-coffee sources, and tea but not with decaffeinated coffee (Ascheiro and others 2001).

Another area in which caffeine may play a positive role is in the prevention of sunlight-induced skin cancer. The main mutagenic effect of UV radiation is DNA damage in which research suggests caffeine has a protective role in both mice and humans (Hakim and others 2000; Abel and others 2007; Rees and others 2007; Kerzendorfer and O'Driscoll 2009). Potential antiinflammatory properties of caffeine have also been studied, although, less extensively. A study investigated the effect coffee consumption on inflammation biomarker in 3042 randomly selected healthy men and women who resided in Attica, a region in Greece (Zampelas and others 2004). The study concluded that moderate coffee drinking was associated with an increase in the concentration of several inflammatory biomarkers, which included C-reactive protein, interleukin 6, tumor necrosis factor α, and amyloid A compared to non-coffee drinkers (Zampelas and others 2004). Although this particular study found a positive association between inflammatory biomarker levels and coffee consumption, metabolic studies are needed to confirm these findings. A review of literature is controversial with no strong evidence supporting an association between coffee consumption and increased inflammation (Nawrot and others 2003).

Although caffeine is being researched in a variety of areas regarding human health the focus of this review will be on its potential as an aid in weight loss, thus reducing the overall risk for developing the metabolic syndrome (Ballard and others 2006; Fujioka and others 2006). The metabolic syndrome is a significant and growing health concern affecting approximately 25% of the United States population (Ford and others 2002; Zimmet and Alberti 2008). The World Health Organization (WHO) has developed a list of specific criteria necessary for the diagnosis of the metabolic syndrome. It includes the presence of type 2 DM, altered fasting glucose, impaired glucose tolerance, insulin resistance, obesity, increased triglycerides, high-density lipoprotein cholesterol, hypertension, fasting plasma glucose, and microalbuminuria (Hollander and Mechanick 2008; Temple 2009). Table 4 has a compiled list of various studies regarding obesity and type 2 DM. They addressed the potential role that caffeine has in reducing the various factors that contribute to the metabolic syndrome. In the majority of the studies, caffeine consumption was recorded by tracking the subjects coffee intake. Additional studies were included regarding caffeine and its correlation to cardiovascular disease. In most studies, caffeine and coffee consumption were highly interrelated regarding the potential health benefits. As a result, further research should be focused on pure dietary caffeine as opposed to caffeine through the consumption of coffee. However, other components in coffee or teas should not be ignored. Several studies that looked at caffeinated coffee as well as decaffeinated coffee have been completed, and concluded that components in coffee, other than caffeine, could be the contributors to the decreased risk of type 2 DM (Table 4).

There are also negative health aspects attributed to caffeine intake that must be considered in both adults and children (Temple 2009). Caffeine affects children in a similar way as adults, and may disturb their sleep patterns and thus impair their normal development. Additionally, caffeine often comes as part of sugar-sweetened beverages that may contribute to increased weight gain and dental cavities (Lim and others 2009). It has been found that children and adolescents with high daily caffeine consumption, at least 1.5 L of cola drinks per day (192.88 mg of caffeine daily), and an average of 11 L (range 10.5 to 21 L) of cola drinks a week, which average 1414.5 mg of caffeine may suffer from caffeine-induced daily headaches. Gradual withdrawal was achieved leading to complete cessation of all headaches (Hering-Hanit and Gadoth 2003).

In pregnancy, results are conflicting in relation to the association of increased caffeine intake and fetal growth restriction and low birth weight. The main inconsistencies have been associated to the sensitivity of the methods used in the quantification of caffeine and assessments at different stages of pregnancy, among many other factors. It is well known that caffeine is rapidly absorbed and crosses the placenta freely and no enzymes involved in caffeine metabolism are present in the placenta or fetus. The main concerns are possible causes of spontaneous abortion and impaired fetal growth. A large prospective observational study of maternal caffeine intake and fetal growth restriction by the CARE Study Group (2008) concluded that caffeine intake before conception and during pregnancy should be reduced (CARE Study Group 2008). In this study there was an association between maternal caffeine intake and an increase risk of fetal growth. Even though the threshold of higher risk was not well characterized, the CARE study found that the fetal growth restriction risk is reduced for women consuming $<$100 mg/d. In summary, high levels of caffeine consumption may have adverse effects on fertility and the recommendation is for women who are trying to become pregnant to limit caffeine to $<$300 mg/d (Nawrot and others 2003; Kuczkowski 2009). In addition, pregnant women are advised to drink no more than 2 cups of coffee or 4 cups of tea per day.

Obesity

Globally, according to the WHO over 1 billion adults are overweight and over 300 million are obese, overweight ranking in the top 10 health risk conditions and the top 5 in developed nations (Hill and others 2003). Caffeine consumption, as contained in green tea, has been associated with weight reduction Kovacs and others 2004; Westerterp-Plantenga and others 2005). Caffeine supplementation has also been recently considered as an effective means of weight management (Greenberg and others 2006; Turk and others 2009).

Energy balance is the main determinant of weight regulation. In this context, research on caffeine has demonstrated its role in increasing metabolic rate, energy expenditure (EE), lipid oxidation, and lipolytic and thermogenic activities; all favorable components in regards to weight management and possible weight loss in humans (Acheson and others 2004; Ballard and others 2006; Dallas and others 2008). Although the role of thermogenic activity in weight control is in the process of being analyzed, multiple studies have shown that caffeine can influence energy balance in humans. In a recent investigation, the 24-h increased energy expenditure from the caffeine consumption of 300 mg/d was found to be approximately 79 kcal/d, which may appear insignificant; however, it has been found to be sufficient in maintaining weight balance (Rudelle and others 2007). The American population has an average weight gain of approximately 1 kg/y, equivalent to 15 kcal/d of excess energy (Hill and others 2003). It is also known that for 90% of the population, about 50 kcal/d are in excess of their daily EE, which means that a 50 kcal/d reduction could offset weight gain (Hill and others 2003). That being said, an increased EE of approximately 79 kcal/d, can act as a positive contributor to maintaining, if not losing weight for active individuals (Rudelle and others 2007). One potential mechanism that could explain the thermogenic effect of caffeine is through the inhibition of cyclic AMP- phosphodiesterase (PDE) and the antagonizing adenosine receptors which negatively affect increased norepinephrine (NE) release (Westerterp-Plantenga and others 2006). The consumption

Table 4— Human studies examining the association of caffeine and/or coffee consumption and risk factors of the metabolic syndrome.

Model	Subjects	*N*	Duration and dose	Main results	Reference
Type 2 Diabetes Mellitus					
Prospective cohort study examining long term coffee consumption and incidence of type 2 DM	Healthy men and woman; 30-75 y old	126210	13 and 18 y; 0, <1, 1 to 3, 4 to 5, and ≥6 cups/d	5418 incident cases of type 2 DM confirmed; inverse association between caffeinated coffee intake and risk of type 2 DM	Salazar-Martinez and others (2004)
A prospective follow up study examining association of coffee consumption in combination with other factors (alcohol, obesity, exercise) and type 2 DM	Finnish men and woman with no history of stroke, CHD, diabetes; 35 to 74 y old	21385	13.4 y; 0 to 2, 3 to 6, ≥7 cups/d	964 incident cases of type 2 DM confirmed; inverse association between coffee consumption and risk of type 2 DM, regardless of weight, exercise level and alcohol intake	Hu and others (2006)
Prospective cohort study examining association between total caffeinated and decaffeinated coffee intake and risk of type 2 DM	Postmenopausal woman; no CVD or diabetes at baseline; 55 to 69 y old	28812	11 y; 0, <1, 1 to 3, 4 to 5, ≥6 cups/d	1418 incident cases of diabetes; coffee intake primarily decaffeinated was associated with a decreased risk	Pereira and others (2006)
Prospective cohort study examining caffeinated food and drink consumption and incidence of type 2 DM	Healthy U.S. female nurses; 24 to 46 y old	88259	10 y; 0, 1, 2 to 3, ≥4 cups/d	1263 incident cases confirmed for type 2 DM; protective effect from caffeinated, decaffeinated coffee and caffeine	van Dam and others (2006)
Systematic review examining coffee intake and risk of type 2 DM	9 cohort studies	193473	Duration varied among studies; lowest dose 0 or ≤2 cups/d, highest dose ≥6 or ≥7 cups/d	8394 incident cases of type 2 DM confirmed; inverse association between habitual coffee consumption and risk of type 2 DM	van Dam and Hu (2005)
15 epidemiological studies (cohort or cross-sectional; for 1 study, both longitudinal and cross-sectional data were reported)	7 cross-sectional studies	20654			
Cross sectional study examining effects of coffee consumption on type 2 DM and serum GGT levels	Healthy, Finnish men and woman; 35 to 74 y old	21826	5 y; 0 to 2, 3 to 4, 5 to 6, ≥7 cups/d	862 incident cases of type 2 DM confirmed; protective effect seen from coffee consumption especially for those with a higher baseline serum GGT level; GGT levels inversely associated with coffee consumption	Bidel and others (2008)
Cross sectional study examining effects of coffee consumption on serum C-reactive protein (CRP) levels	Japanese women, 23 to 83 y old	459	1 day clinical analysis; <1, 1 to 3, ≥4 cups/d	Benefits of coffee consumption were seen in ≥1 cup/d resulting in decreased CRP levels	Kotani and others (2008)
Obesity					
A study examining the metabolic effect of caffeine on EE	Healthy, lean and postobese females and males; 18-46 yr old	18	100 mg each every 2 h for 12 h (600 mg); indirect calorimetry measurement for 24 h	24 h EE ↑ by 109 kcal/d (5.5%) in lean and 78 kcal/d (4.9%) in postobese subjects	Dulloo and others (1989)
A double blind, placebo controlled dose-response study examining caffeine consumption and its effect on EE	Healthy, men and woman; 20 to 32 y old	6	100, 200, or 400 mg single dose, resting metabolic rate measured for 180 m	The EE ↑ by 7.2, 9.2, and 32.4 kcal/3 h above placebo response after 100, 200, and 400 mg of caffeine	Astrup and others (1990)
Examined metabolic effect of caffeine on energy metabolism through caffeinated and decaffeinated coffee intake	Females (10 lean, 10 obese) aged 20 to 35 y old	20	5 × 4 mg/kg or 5 times 4 mg/kg ideal wt; indirect calorimetry measurement for 24 h	24 h EE ↑ by 7.6% (lean), 4.9% (obese); lipid oxidation ↑ during the next day by 29% (lean), 10% (obese) woman	Bracco and others (1995)
Measurements of EE and lipid oxidation and turnover after caffeine consumption	Healthy males; 20 to 26 y old	8	observed 90 min before, 240 min after intake of 10 mg/kg of caffeine	↑ in EE (13%), lipid oxidation (44%) and doubled lipid turnover rate after caffeine consumption	Acheson and others (2004)
Double bind, placebo controlled, cross over design studied the effect of a beverage containing caffeine, green tea catechins and calcium on 24 h EE	Healthy, lean men and woman; 18 to 35 y old	32	3 d; 3 × 250 mL servings/d of beverage; 100 mg/serving caffeine (300 mg/d)	EE ↑ 106 ± 31 kcal/d (4.6%); linear regression found 300 mg/d of caffeine would ↑ EE by approximately 79 kcal/d	Rudelle and others (2007)

Continued

Table 4—Continued

Model	Subjects	*N*	Duration and dose	Main results	Reference
A longitudinal cohort study examining weight gain in association with internet time, sleep, caffeinated coffee, and alcohol consumption	Girls; 14 to 21 y old	>5000	1 y; 0, 1 to 3 cups/mo, 1 cup/wk, 2 to 4 cups/wk, ≥5 cups/wk	No evidence that coffee consumption promoted weight gain	Berkey and others (2008)
An epidemiological study examining association between coffee intake and the metabolic syndrome (BP, waist circumference, fasting plasma glucose, lipid profiles)	Japanese men and woman; ≥40 y old	1902	1 d health check up in 1999	Coffee and not green tea consumption is inversely associated with factors of the metabolic syndrome; high frequency of metabolic syndrome seen in subjects with low coffee intake	Hino and others (2007)
Cardiovascular Disease					
A prospective longitudinal study examining association between coffee consumption, ↑ BP and long term hypertension	Former male medical students; mean age 26 y	1017	33 y; o, 1 to 2, 3 to 4, ≥5 cups/d	Coffee consumption associated with small ↑ BP and a small ↑ risk of developing hypertension long term	Klag and others (2002)
A cohort study examining the association of caffeinated coffee and mortality in post MI patients	Patients confirmed with having an acute MI; 41 to 87 y old	1902	5 y; 0, ≤7, >7 to 14, >14 cups/wk coffee; 0, ≤2, >2 to 7, >7 cups/wk cola	Coffee consumption had no association with mortality of post MI patients	Mukamal and others (2004)
Prospective cohort study examining association of coffee consumption with risk of CHD	Males 42 to 60 y old with no CHD at baseline	1971	14 y; 0 mL/d, 1 to 375 mL/d, 376 to 813 mL/d, >814 mL/d	269 cases of a coronary event confirmed; heavy coffee consumption associated with an ↑ risk of CHD	Happonen and others (2004)
Meta-analysis of randomized controlled trials examining coffee or caffeine intake and BP from Jan 1966 to Jan 2003	A meta-analysis of randomized controlled trials (16 studies)	1010	≥7 d intervention; median caffeine intake 410 mg/d and coffee intake 725 mL/d	↑ BP was larger in pure caffeine intake (systolic: 4.16 mmHg, diastolic: 2.41 mmHg) compared with coffee intake (systolic: 1.22 mmHg, diastolic: 0.49 mmHg)	Noordzij and others (2005)
Prospective cohort study examining association of caffeine consumption and hypertension	Woman with no hypertension at baseline; 25 to 55 y old	155594	12 y	33077 cases of hypertension confirmed; no linear association seen between caffeine and hypertension; coffee intake showed no ↑ risk; cola beverages (regular and diet) showed ↑ risk	Winkelmeyer and others (2005)
Prospective cohort study examining association between long term coffee consumption and risk of CHD	Healthy, men and woman with no history of CVD or cancer	128493	14 & 20 y; <1cup/mo, 1 cup/mo-4 cups/wk, 5 to 7 cups/wk, and 2 to 3, 4 to 5, ≥6 cups/d	4427 incidences of CHD confirmed; coffee consumption was not associated with an increased risk of CHD in either gender	Lopez-Garcia and others (2006b)
Prospective cohort study examining association between coffee consumption and disease specific mortality, including CVD	Healthy, postmenopausal woman; 55 to 69 y old	27312	15 y; 0 to 2, 3 to 4, 5 to 6, ≥7 cups/d	Inconclusive, coffee consumption may reduce risk for CVD	Andersen and others (2006)
Longitudinal study examining the effect of caffeine on the risk of nonfatal myocardial infarction (MI)	-Hispanic-Americans men and women survivors of a first acute MI as diagnosed by a cardiologist	2014	10 y; <1 cup/d, 1 cup/d, 2 to 3 cups/d, ≥4 cups/d	Coffee intake associated with an increased risk of nonfatal MI, seen in subjects who had slow caffeine metabolism	Cornelis and others (2006)
	-Control (no MI)	2014			
A study examining association between coffee consumption and mortality due to CVD, cancer, and other causes	Men and woman with no history of CVD or cancer at baseline	127950	18 and 24 y; <1 cup/mo, 1 cup/mo- 4 cups/wk, 5 to 7 cups/wk, and 2 to 3, 4 to 5, ≥6 cups/d	4417 incident cases of mortality due to CVD confirmed; regular coffee consumption had no association to increased mortality; research needed	Lopez-Garcia and others (2008)

of caffeine would consequently result in increased cyclic AMP, causing a heightened level of NE allowing the adrenoceptors to be continually stimulated (Dulloo and others 1999; Dulloo and others 2000). However, the effect of caffeine on weight reduction should be interpreted with caution since green tea drinking is effective only in individuals with originally low caffeine intake (< 300 mg/d) (Kovacs and others 2004). Furthermore, in a long term observational study, caffeine intake was only associated with less weight gain (Lopez-Garcia and others 2006a). The use of caffeine to manage weight should consider the calorie contribution of the vehicle that contains caffeine and the potential negative effects of caffeine.

Type 2 diabetes mellitus

Type 2 DM is a global health concern estimated to have affected 2.2% of the world population in 2000 and is forecasted to increase to 4.4% by 2030 (Wild and others 2004). There are several studies that have investigated the association between caffeine, particularly caffeine from coffee consumption, and the relative risk for developing type 2 DM. In a systematic review of 9 prospective cohort studies and 7 cross-sectional studies, which included over 200000 men and women, it was found that the majority of the studies showed an inverse relationship between caffeinated coffee and type 2 DM (van Dam and Hu 2005). In addition, the review found that the risk of type 2 DM was 35% lower in those who consumed at least 6 cups/d of coffee and 28% lower in those who consumed between 4 and 6 cups/d compared to those who consumed less than 2 cups/d (van Dam and Hu 2005). It was concluded that routine coffee consumption is associated with a lower risk of type 2 DM although it was considered premature to recommend increasing coffee consumption as a means to prevent type 2 DM until more research becomes available (van Dam and Hu 2005). The reason why the existing studies have been focused primarily on the effect of coffee consumption on type 2 DM and not exclusively on caffeine, is probably due to the fact that coffee is the main source of caffeine for adults. Two U.S. cohort studies examined both regular and decaffeinated coffee separately (Salazar-Martinez and others 2004). These studies concluded that a significant inverse association existed between regular coffee consumption and a risk for type 2 DM, whereas only a modest inverse association was seen with decaffeinated coffee (Salazar-Martinez and others 2004). Coffee contains many other ingredients such as potassium, niacin, chlorogenic acid, and magnesium, which all could have been attributed to the modest inverse association seen in the decaffeinated coffee (Devasagayam and others 1996). Although, as seen in Figure 1, decaffeinated coffee still contains on average 5 mg/8 oz of caffeine. Additional studies conducted after 2005 (Table 4), showed inconsistent results, thus requiring additional investigation. A 22% lower risk of type 2 diabetes mellitus in postmenopausal women who consumed 6 or more cups of coffee per day, in comparison to women who reported 0 cups of coffee per day, was largely explained by decaffeinated coffee ($R^2 = 0.67$; 95% CI, 0.42-1.08; P for trend, 0.006) rather than for regular coffee ($R^2 = 0.79$; 95% CI, 0.59-1.05; P for trend, 0.90) (Pereira and others 2006). Although the role of caffeine in regards to lowering the risk of type 2 DM is not totally clear, it is certain that the consumption of caffeinated beverages is not associated with increasing the risk for type 2 DM as suggested by some investigators (Pereira and others 2006).

Cardiovascular disease

A direct link between increased caffeine consumption and cardiovascular disease, including the risk for coronary heart disease (CHD), could not be established due to inconsistencies in research findings, a position also shared by the AHA (2008). Data from 2 separate meta-analyses, although performed over a decade ago, showed that people who consumed 5 or more cups of coffee per day had a 40% to 60% increased risk of developing CHD than those who drank no coffee (Greenland 1993; Kawachi and others 1994). However, more recently the results from a prospective cohort study found no association between caffeine and CHD (Lopez-Garcia and others 2006b). In addition, a study that looked at the effect coffee consumption had on the mortality of people with a confirmed diagnosis of acute myocardial infarction was found to have no overall association (Mukamal and others 2004). Additional studies have examined the association between coffee consumption and caffeine and CHD have concluded inconsistent findings, confirming that further research in this area is necessary (Cornelis and El-Sohemy 2007).

Safety and Adverse Effects

As one of the most-researched substances in the food supply, caffeine has a long history of safe use and overwhelming scientific evidence maintains that when consumed in moderation, caffeine has no adverse health effects (Clark 1997). It is extremely rare to hear of a fatality due to a caffeine overdose, with only a few reported cases being known (Nawrot and others 2003). In general, life-threatening caffeine overdoses involve the ingestion of caffeine containing medications, not caffeinated foods or beverages (Higdon and Frei 2006).

Reissig and others (2009) have reported negative effects of excessive caffeine consumption due to overdose, dependence or withdrawal. Signs of caffeine intoxication include tachycardia, anxiety, restlessness and tremors.

A research review regarding caffeine consumption concluded that among the healthy adult population a moderate daily caffeine intake of ≤400 mg (equivalent to 6.5 mg/kg bw/d for a 70-kg person) was not associated with any adverse effects (Nawrot and others 2003). These recommendations were based primarily on published human data obtained through a comprehensive literature search made on the basis of no 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, and effects on male fertility (Nawrot and others 2003). This review also concluded that pregnant woman should limit their caffeine intake to ≤300 mg/d (equivalent to 5 mg/kg bw/d for a 70-kg person) and children should consume ≤2.5 mg/kg bw/d (Nawrot and others 2003). In children, controlled clinical trials showed no adverse effects when consuming caffeine at levels up to 3 mg/kg bw/d (Higdon and Frei 2006). The exact amount of caffeine necessary to produce an adverse effect varies from person to person depending on their weight and sensitivity to caffeine (Higdon and Frei 2006). For those who are highly sensitive to caffeine it is recommended to consume no more than 400 mg/d to avoid adverse effects, such as headache, drowsiness, anxiety, and nausea (Smith 2002). An acute effect of caffeine intake in the general population is an increase in blood pressure (Riksen and others 2009). In particular, hypertensive individuals are more sensitive to caffeine and show progressively longer responses in blood pressure with increased risk of hypertension, even if under hypertensive medication (Smits and others 1983; Hartley and others 2000). Therefore, consumption of caffeinated beverages in these individuals should be made with caution. Differences in the caffeine effects on blood pressure in caffeine naive persons as compared to regular consumers have also been reported (Reissig and others 2009). Individuals that do not consume caffeine daily are at a greater risk of the negative physiological effects of caffeine than the habitual caffeine consumers.

The acute toxic level of caffeine consumption is not well established, but for adults it is approximately 10 g/d, which is comparable to consuming approximately 100 cups of coffee (Nawrot and others 2003). In a study about caffeine intake of adolescents (12 to 15 y old), the results showed that their average consumption was 52.7 mg/d with an average of 1.1 caffeinated products consumed per day (Pollak and Bright 2003). The findings also showed that 57.1% of the respondents averaged 0 to 50 mg/d of caffeine, while only 6.8% averaged 150 mg/d or more. The largest reported mean caffeine intake was from a 13.3-y-old male consuming 379.4 mg/d (Pollak and Bright 2003). The 1999, U.S. Share of Intake Panel study showed that 56% of American children aged 1 to 5 y consumed caffeinated beverages daily with an average intake of 13.5 mg/d, equivalent to 0.82 mg/kg/d (Knight and others 2006). The children in the 90th percentile averaged 37.3 mg/d, which is still below safe limits for children aged 4 to 6 y of 2.5 mg/kg/d or 45 mg/d (Knight and others 2006).

Caffeine is approved globally by numerous regulatory authorities as a safe dietary ingredient for use mainly in carbonated beverages and dietary supplements. The evaluation and approval process that caffeine underwent has been based on scientific evidence that supported its safety. In 1959, the U.S. Food and Drug Administration (FDA) classified the caffeine in cola drinks to be generally recognized as safe (GRAS, code #21CFR). In 1987, caffeine underwent another extensive review in which the FDA declared its safety for all consumers, including children. Since then, the FDA continues to meet and hold expert reviews to reevaluate caffeine's safety as a food ingredient. There was no evidence to show that the use of caffeine would cause any negative health effects; therefore, caffeine continues to have GRAS status (FDA 2003a).

The continuous research that is being done on caffeine and its potential health impacts does not go unnoticed and causes continued assessment on caffeine's safety. For example, the Intl. Life Sciences Inst. (ILSI) sponsored a review in 2001 that focused on the reproductive effects of caffeine (Christian and Brent 2001). After reviewing over 200 scientific studies it was concluded that woman who consumed moderate amounts of caffeine, less than 5 to 6 mg/kg bw/d, do not have an increase in reproductive risks. In 2002, ILSI assembled another expert panel, to focus on recent caffeine-related research in the area of behavior and development in children and adults, withdrawal and related issues, bone, and calcium physiology, and reproductive risks in women (Mandel 2002). The weight of evidence from their research findings supported the conclusion that a moderate intake of caffeine does not elevate the risks for adverse effects.

In regards to concerns about caffeine being addictive, people need to recognize that the term "addiction" can be used very loosely and has different meanings to different people. According to the *Diagnostic and Statistical Manual of Mental Disorders*, the authoritative text of the American Psychiatric Assoc., caffeine is not present in the category of substances classified as causing "substance dependence."

Finally, the World Anti-Doping Agency (WADA) published the 2008 "Prohibited List-International Standard," which states that caffeine is not considered a prohibited substance, a position accepted by the Intl. Olympic Committee (World Anti-Doping Agency 2008).

Approaches and Regulations on the Addition of Caffeine to Beverages in Different Countries

Since caffeine occurs naturally in 2 commonly consumed beverages, coffee and tea, it is difficult to regulate their labeling or their permissible maximum levels. In addition, the regulation of caffeine has become difficult because coffee and tea are not always consumed on their own as they have been incorporated into hundreds of new beverage formulations. Also, because of the varying amounts of caffeine consumed in each country, it is difficult to set an international standard. However, daily intake guidelines as well as regulatory upper limits have been set for those beverages to which caffeine does not occur naturally, and is instead added either from a synthetic or a natural source. In general, soft drinks, energy drinks, and other caffeinated beverages are generally regulated by specific caffeine levels ranging from 100 to 350 ppm. The U.S. Code of Federal Regulations lists caffeine as GRAS with respect to cola type beverages, allowing 200 ppm or 0.02%, totaling 71 mg for a 12 oz soft drink (FDA 2003b). Additionally, higher concentrations of caffeine in other beverages have also been considered GRAS, subject to compliance of relevant federal regulations.

Several countries have addressed caffeine addition and upper limits gradually over time. Due to historical reasons, many countries have initially set upper limits for soft drinks and at a later stage they introduced different and separate upper limits for other beverages added with higher amounts of caffeine, such as energy drinks. For example, the Australian Food Standards Code allows the addition of caffeine to cola-type soft drinks and flavored syrups, up to 145 mg/L, and in New Zealand this limit goes up to 200 mg/kg (ANZFA 2000). Following the emergence of energy drinks, the Australia New Zealand Food Authority (ANZFA) has defined a distinct category of beverages called "formulated caffeinated beverages," which must contain no less than 145 mg/L and no more than 320 mg/L of caffeine, which includes "all caffeine present from whatever source."

In Canada, caffeine is allowed at levels up to 200 mg/L in cola-type beverages (CFDA). Beverages containing 320 mg/L have been approved by the Canadian Health Authority as Natural Health Products. Additionally, in February 2006, Health Canada issued general consumption recommendations for caffeine based on the newest available research. Health Canada concluded that for the general population of healthy adults a daily caffeine intake of 450 mg was considered safe. They further recommended for children between 10 to 12 y limiting their caffeine intake to 85 mg/d whereas for pregnant women the recommended threshold was set at 300 mg caffeine per day (Health Canada 2009).

At the European Union level there is no upper limit of caffeine being set. Directive 2002/67/EC establishes that beverages containing caffeine from whatever source (including natural and synthetic caffeine) in excess of 150 mg/L must bear the message "High Caffeine Content" followed by the amount of caffeine expressed by milligrams per 100 mL, on the label (European Union 2002).

In Asian countries such as South Korea, recommended upper daily levels of caffeine have been set by the Korean Food and Drug Administration; for adults less than 400 mg of caffeine per day, for pregnant women less than 300 mg and for children less than 2.5 mg/kg of body weight (KFDA 2006). Taiwan has recently amended its regulations and set an upper limit of caffeine in 320 mg/L for beverages other than coffee and tea (TLGFS 2008).

In Latin America, Mexican regulations do not foresee any upper limit for the addition of caffeine to beverages. However, flavored nonalcoholic beverages containing more than 20 mg/100 mL (200 mg/L) are considered "beverages with added caffeine," which must be printed on the label (RSCM 2006). In Brazil, beverages containing 80 mg of caffeine (320 mg/L) are considered "liquid compounds ready for consumption" and the regulations foresee an upper limit of 350 mg/L (SVNA 2005). In Chile, beverages containing 80 mg of caffeine (320 mg/L) were classified as sports drinks and the regulation does not foresee an upper limit but rather states

that producers should not recommend on their labels a daily consumption higher than 500 mg of caffeine (Chile's Ministry if Health 1997).

Conclusions

The total daily intake, as well as the leading source of caffeine, varies throughout the world. Caffeine is a widely consumed dietary ingredient that will continue to keep its presence in products that fill grocery store shelves. The majority of the human studies that have been conducted in the past decade have demonstrated that moderate (<400 mg/d) caffeine consumption poses no significant health risks to most consumers (Nawrot and others 2003). Caffeine acts mainly upon the central nervous system, stimulating wakefulness, increasing concentration and decreasing the sensation of fatigue. Although coffee intake slightly increases blood pressure, and plasma concentrations of homocysteine and cholesterol, there is no association with the incidence of hypertension or promoting the development of atherosclerosis in the general population. Additionally, many of these studies show that caffeine intake at varying higher levels is linked to a number of potential health benefits as well as to some health concerns of high caffeine consumption in children and pregnant women. Positive effects include a negative association with the incidence of type 2 DM, as well as assisting in weight management. It is too early to assume that an increased intake of caffeine will prevent the metabolic syndrome from developing and therefore future research in this area is required. Several authoritative regulatory agencies around the world have reviewed, regulated and authorized the addition of caffeine to specific beverages where caffeine does not occur naturally. Such addition was generally authorized up to levels of caffeine of 350 mg/L, which are comparable to those provided by coffee and yerba mate. Additionally, some regulatory agencies have set guidelines on caffeine daily intakes up to 450 mg/d for adults.

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