Documents Submitted to Committee


Herrera, 18 scientists urge FDA action on Monster, other caffeinated energy drinks

City Attorney calls letters an ‘important step we can take at the national level,’ while City’s investigation of Monster Energy Drinks’ business practices continues

SAN FRANCISCO (March 19, 2013)—City Attorney Dennis Herrera today joined 18 scientists and public health professionals in urging the U.S. Food and Drug Administration to take prompt regulatory action to protect children and adolescents from the dangers of highly caffeinated energy drinks—including requiring manufacturers to publish caffeine content on product labels.

In separate letters to FDA Commissioner Margaret Hamburg this morning, Herrera and scientific experts cite federal law requiring that food additives like caffeine be “Generally Recognized As Safe,” or GRAS, for their intended use based on a consensus of scientific opinion. Contradicting manufacturers’ safety claims, the scientists’ letter finds that the caffeine levels in popular energy drinks such as Monster Energy, Rockstar, and Red Bull do not meet the GRAS standard required by federal law because they pose serious risks to public health, especially for young people to whom the products are marketed.

Young consumers of caffeinated energy drinks are particularly vulnerable to the documented health risks cited in the letters, including seizures, cardiac arrhythmia, altered heart rates, elevated blood pressure, sleeplessness, anxiety and childhood obesity. According to FDA data cited in the letter, consumption of Monster Energy has been implicated in the reported deaths of at least five individuals, with 13 additional deaths believed possibly linked to 5-Hour Energy.

“Caffeine-dosed energy drinks will never give you wings—but they may give you deadly health problems, especially if you’re a young person targeted so aggressively by marketers,” said Herrera. “The evidence doesn’t support the manufacturers’ safety claims. To the contrary, nationally renowned experts have found that energy drinks pose serious health risks, which are exacerbated by manufacturers’ marketing tactics to youth. I’m glad to join with respected scientists, academics
and public health professionals nationwide in urging the FDA to take steps to protect consumers. This is an important step we can take at the national level, even as my office continues to investigate the business practices of Monster Energy Drinks here in California.”

In November, Herrera invoked California’s tough Unfair Competition Law to demand evidence from the Corona, Calif.-based Monster Beverage Corporation to substantiate its marketing claims that the dosages of caffeine contained in its products are “completely safe” for consumption by adolescents and adults. The City Attorney is continuing his investigation into Monster Energy, which is the largest manufacturer in a growing U.S. energy drink industry projected reach $19.7 billion in sales this year.

# # #
The Honorable Margaret Hamburg, M.D.
Commissioner
U.S. FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: The Use of Caffeine in Energy Drinks

Dear Dr. Hamburg:

I write with regard to the attached letter from 18 scientists, academics, clinicians, and public health professionals who have concluded, based on their expertise and review of published studies, that the caffeine levels in energy drinks pose serious health and safety risks. Because the letter concludes that there is no consensus among qualified experts supporting the safety of the high levels of added caffeine in energy drinks, I urge the Food and Drug Administration (“FDA”) to take action to protect consumers from these products.

My office has been investigating the safety of highly caffeinated energy drinks, such as Monster Energy, as well as the marketing practices and advertising claims made by energy drink companies. In the wake of recent reports of illness, injury, and even death allegedly linked to the consumption of energy drinks, I understand that the FDA is also investigating the safety and health risks associated with the products.

Because energy drinks are conventional beverages, the caffeine added to these drinks is a food additive that must be generally recognized as safe under the conditions of its intended use (i.e., Generally Recognized As Safe (“GRAS”)). For a food additive to be safe under this standard, there must be “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.” 21 C.F.R. 170.3(i). Under GRAS guidelines,

---

2 Many energy drink manufacturers mislabel their products as dietary supplements in an apparent attempt to avoid the requirements of the GRAS standard. We note that Monster Energy recently announced that it is reclassifying its drinks as conventional beverages.
The burden is on the manufacturer to prove that (1) an additive is safe for its intended use based on published scientific literature, and (2) there is a consensus of scientific opinion regarding the safety of the use of the substance. 21 C.F.R. §§ 170.3, 170.30. The FDA has approved caffeine as GRAS only for use in cola-type beverages in concentrations no greater than 200 parts per million, which is substantially less than the amount of caffeine added to energy drinks. 21 C.F.R. § 182.1180.

As the accompanying letter demonstrates, the large amount of added caffeine in energy drinks does not meet the requirements of the GRAS standard because it is neither safe based on scientific evidence, nor is there expert consensus regarding its safety. To the contrary, as the letter makes clear, there is a strong consensus of scientific opinion that the caffeine levels in energy drinks have not been demonstrated to be safe, but rather pose a serious public health risk, particularly to young people to whom energy drinks are aggressively marketed.

California’s food safety and labeling laws adopt the requirements of the Federal Food, Drug and Cosmetic Act (“FDCA”), including the GRAS standard. My office has statutory authority to file suit for violations of California law. However, the harms posed by energy drinks are not limited to California. Therefore, I urge the FDA to exercise its authority under the FDCA to protect consumers from the dangerously high levels of caffeine found in many energy drinks.

Thank you for your prompt attention to this matter.

Sincerely,

DENNIS J. HERRERA
City Attorney of San Francisco

DJH/msd

Enclosure
March 19, 2013

The Honorable Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: The Use of Caffeine In Energy Drinks

Dear Commissioner Hamburg:

Recent reports of health complications, emergency department visits, injuries, and deaths related to energy drink consumption have spawned widespread concern among scientists, health professionals, legislators, state and local law enforcement officials, and consumers regarding the safety of highly caffeinated energy drinks. As researchers, scientists, clinicians, and public health professionals who have studied and conducted research on energy drinks, we are writing this letter to summarize the scientific evidence on this issue and encourage action.

Given the evidence summarized below, we conclude that there is neither sufficient evidence of safety nor a consensus of scientific opinion to conclude that the high levels of added caffeine in energy drinks are safe under the conditions of their intended use, as required by the FDA’s Generally Recognized as Safe (GRAS) standards for food additives. To the contrary, the best available scientific evidence demonstrates a robust correlation between the caffeine levels in energy drinks and adverse health and safety consequences, particularly among children, adolescents, and young adults.

DESCRIPTION OF ENERGY DRINKS AND RELATED PRODUCTS

Energy drinks are a relative newcomer to the U.S. marketplace and have surged in popularity in recent years, particularly among adolescents. Energy drinks are flavored beverages that contain added amounts of caffeine as well as other additives such as taurine, guarana (a natural source of caffeine), and ginseng.1-3

The U.S. energy drink industry has grown rapidly since the drinks were first introduced,3,4 and is projected to reach $19.7 billion in sales by 2013.2 Between 2006 and 2012, Monster Energy®, the largest U.S. energy drink manufacturer, tripled its sales.5 As a result of aggressive marketing, energy drinks are particularly popular among adolescents.4,6,7 As noted in a 2010 study commissioned by the FDA,a “[e]nergy drinks are typically attractive to young people,” and 65% of energy drink consumers are 13- to 35-year-olds.8 More recent reports show that 30 to 50% of

---

a This report discusses the mean per capita daily caffeine intake from energy drinks as calculated by estimates from data provided by the Beverage Marketing Corporation. The mean per capita daily intake tells us nothing about the number of individuals who are ingesting large quantities of these products. The report relied on data that is now out of date and made assumptions based on caffeine levels in 16 oz serving sizes, rather than the new 24 oz sizes. Further, the report also acknowledged that “very limited reliable information is available of the number and age distribution of regular energy drink consumers” and “there may be underreporting for young person[s]”.8

1
adolescents and young adults consume energy drinks.\textsuperscript{7,9-11} According to Monitoring the Future, the federally funded national annual survey of students in grades eight through twelve, 35\% of eighth graders and 29\% of both tenth and twelfth graders consumed an energy drink during the past year, and 18\% of eighth graders reported using one or more energy drinks every day.\textsuperscript{12}

Energy drinks vary with respect to caffeine content and concentration.\textsuperscript{1,13} The caffeine content of many energy drinks is not disclosed on the product label,\textsuperscript{2} and in these cases, information about caffeine content must be derived from Internet sources of unknown validity. In general, the caffeine concentration of energy drinks is much higher than that of sodas, for which the FDA has recognized 200 parts per million of caffeine (approximately 71 mg per 12 fl oz serving) as GRAS.\textsuperscript{14} By contrast, the most popular energy drinks, like Monster Energy\textsuperscript{®}, contain between 160 and 240 milligrams of caffeine per can. Many energy drinks contain as much as 100 mg of caffeine per 8 fl oz serving\textsuperscript{2} with some containing as much as 300 mg per 8 fl oz serving.\textsuperscript{13} In addition, many energy drink brands are sold in larger, containers that hold multiple servings (16 to 24 fl oz/473 to 710 mL).\textsuperscript{1} While some energy drink manufacturers properly classify their drinks as beverages, others label their beverages as dietary supplements.\textsuperscript{b}

Although some brands of coffee contain amounts of caffeine that exceed the FDA’s established GRAS levels for soda, energy drinks differ from coffee in three important ways. First, the caffeine in coffee is naturally occurring, while the caffeine in energy drinks is added by the manufacturer and is thus subject to regulation by the FDA as a food additive. Second, many energy drinks and related products containing added caffeine exceed the caffeine concentration of even the most highly caffeinated coffee.\textsuperscript{13,15} Third, coffee is typically served hot, tastes bitter, and is consumed slowly by sipping. By contrast, energy drinks are typically carbonated, sweetened drinks that are served cold and consumed more rapidly. Indeed, energy drinks are often marketed in a manner that encourages consumers to ingest large quantities quickly (\textit{e.g.}, “pound down,” “chug it down”). Unlike coffee, energy drinks are marketed in a manner designed to appeal to youth and are highly popular with youth. A scientific review funded by the National Institutes of Health has concluded that the risk for energy drink overdose is increased by the combination of marketing that specifically targets youth and the developmental risk-taking tendencies of adolescents.\textsuperscript{7}

\textsuperscript{b}Energy “shots” are a subset of energy drinks that come in smaller containers (usually 1.4 to 3 oz) and have even higher caffeine concentration than regularly-sized energy drinks. Many contain B vitamins, taurine, flavoring, and sweeteners. Other “energy products” available for purchase include gel packs, candies, gum, snacks, energy powders, inhalers, and strips, all containing various amounts of added caffeine.

\textsuperscript{c}Labels of Monster Energy\textsuperscript{®} products.
HEALTH COMPLICATIONS ASSOCIATED WITH THE CONSUMPTION OF ENERGY DRINKS

We are particularly concerned about the health effects of energy drink consumption by children and adolescents. Younger individuals tend to have greater sensitivity to a given serving of caffeine than adults because they are more likely to have a lower body mass and are less likely have already developed a pharmacological tolerance from regular caffeine consumption. The American Academy of Pediatrics’ Committee on Nutrition and the Council on Sports Medicine and Fitness recently concluded that “rigorous review and analysis of the literature reveal that caffeine and other stimulant substances contained in energy drinks have no place in the diet of children and adolescents.”

The Institute of Medicine has similarly recommended that any drinks containing caffeine should not be sold to children at school. Pediatric professionals concur and further state that energy drinks “are not appropriate for children and adolescents and should never be consumed.” Other experts have concluded that children and adolescents should not consume more than 100 mg of caffeine per day, less than the amount in a single can of most energy drinks.

With respect to adults, the FDA has noted that consumption of 400 mg of caffeine by healthy adults in the course of a day is not associated with adverse health effects. That standard for “healthy adults” does not take into consideration that individuals have varying sensitivities to caffeine. Moreover, consumption of 400 mg “in the course of the day” is an important qualification because consumers can ingest 400 mg of caffeine from energy drinks very quickly. Metabolism of caffeine appears to be non-linear at high doses. In one study using caffeine-experienced human subjects, an increase in caffeine dose from 250 to 500 mg was associated with significant increases in the half-life as well as a decrease in the clearance of caffeine from the blood, resulting in higher caffeine levels that were sustained much longer compared with the lower dose. An additional consideration is that the negative effects of caffeine at high blood levels could be compounded by the accumulation of its metabolites (e.g., paraxanthine, theophylline, theobromine), which are active stimulants themselves.

Our work as public health professionals has included examination of the surveillance methods used to track adverse health effects associated with energy drink consumption (e.g., emergency department visits for caffeine-related cardiac events). Despite widespread use of energy drinks, there are no systematic data collection methods to ascertain the prevalence of possible adverse health complications related to energy drinks and related products. Therefore, the following information likely underestimates the actual prevalence of adverse health effects associated with these beverages.

Fatalities and Injuries: According to information submitted to the FDA through its voluntary Adverse Event Reporting System, consumption of Monster Energy® was implicated in the deaths of five individuals, and reports of 13 deaths have cited the possible involvement of 5-Hour Energy®. The FDA has not disclosed the ages of the deceased individuals in these cases. However, details reported elsewhere indicate that in one case, a 14-year-old girl reportedly died of a cardiac arrhythmia induced by caffeine after consuming two 24 oz Monster Energy®
beverages over two consecutive days.\textsuperscript{28} Also reported to the FDA were 21 claims of adverse reactions, some requiring hospitalization, which were reportedly associated with the consumption of Red Bull\textsuperscript{\textregistered}.\textsuperscript{29} These reports only refer to three of the energy products on the market, and of course do not include injuries and deaths that were not voluntarily reported to the FDA. Also, between October 2010 and September 2011, about half of all calls to the National Poison Data System for energy-drink-related caffeine toxicity concerned children under 6 years old. This incidence is far greater than for accidental ingestion of other forms of caffeine.\textsuperscript{30}

**Emergency Department Visits:** The Drug Abuse Warning Network (DAWN) reports U.S. emergency department (ED) visits using a probability sampling strategy. DAWN conducted a special analysis of the data related to energy drink consumption, which revealed a ten-fold increase in ED visits from 2005 to 2009 (1,128 to 13,114).\textsuperscript{31} DAWN recently issued an update to that report which showed that the number of energy-drink-related ED visits doubled between 2007 and 2011, from 10,068 to 20,783.\textsuperscript{32}

**Cardiovascular Complications:** Caffeine produces a number of cardiac effects, which appear in a more pronounced manner in caffeine-naïve subjects and in those consuming higher doses of caffeine. The consumption of highly caffeinated energy drinks has been associated with elevated blood pressure, altered heart rates, and severe cardiac events in children and young adults, especially those with underlying cardiovascular diseases. A few studies have examined the effects of caffeine consumption on heart rate and blood pressure in children and adolescents.\textsuperscript{33,34}

Higher doses of caffeine have been associated with caffeine intoxication, resulting in tachycardia, elevated blood pressure, vomiting, hypokalemia (from beta-adrenergic stimulation), and cardiac arrhythmias (atrial flutter, atrial fibrillation, atrioventricular nodal reentrant tachycardia, and ventricular fibrillation).\textsuperscript{1,3}

A study of young adults found that the consumption of a sugar-free energy drink containing 80 mg of caffeine was associated with changes in platelet and endothelial function great enough to increase the risk for severe cardiac events in susceptible individuals.\textsuperscript{35} These findings show how acute effects of caffeine administration on heart rate might result in cardiovascular events requiring hospitalization, especially in at-risk youth. Caffeine’s effects on blood pressure have been found to be more pronounced among African American children than White children.\textsuperscript{36,37}

The consumption of energy drinks before or during exercise might be linked to an increased risk for myocardial ischemia. In healthy individuals who consume caffeine and then exercise afterwards, significant reductions in myocardial blood flow have been noted by indirect laboratory measures.\textsuperscript{38} Several mechanisms have been postulated to explain this effect, including the ability of caffeine to block adenosine receptors that modulate coronary vasomotor tone.\textsuperscript{38} This vasoconstrictive effect might be more pronounced among caffeine-naïve individuals or those who acutely ingest higher doses of caffeine, such as are present in energy drinks.
Seizures: In addition to cardiac events, cases have been reported of new-onset seizures attributed to energy drink consumption among 15- to 28-year-olds. In all of these cases, seizures ceased after the individuals abstained from consuming energy drinks.

Childhood Obesity: Energy drinks have also been shown to contribute to youth obesity due to their high calorie and sugar content. One 24-oz can of Monster Energy® contains 81 grams of sugar, which is equivalent to 6.75 tablespoons. The American Academy of Pediatrics' Committee on Nutrition reports findings that the consumption of excessive carbohydrate calories from energy drinks increases risk for pediatric overweight and that "energy drinks have no place in the diet of children and adolescents." In addition, adolescents are at risk for increased consumption of high-calorie energy beverages due to marketing claims that they enhance physical and mental performance and increase energy.

Other Health Issues: Youth with higher caffeine intake commonly report troubling neurological symptoms, including nervousness, anxiety, jitteriness, and headache. In one review, youth consuming 100 to 400 mg of caffeine daily from dietary sources report jitteriness and nervousness. Studies have shown negative behavioral effects among youth including jitteriness, anxiety, and dizziness, which might undermine students' ability to stay on task, focus, and perform well. Although many energy drink manufacturers assert that additives such as taurine and B-vitamins improve physical or cognitive performance, current evidence does not support these claims. Finally, energy drinks that have higher titratable acidity levels than sports drinks have been associated with comparatively more tooth enamel loss.

Health and Safety Effects of Combining Energy Drinks with Alcohol: Energy drinks also pose unique dangers when combined with alcohol. Although the FDA and CDC have concluded that the combination of alcohol and energy drinks is unsafe and poses serious health risks, the latest available national data from Monitoring the Future indicated that 26% of high school seniors consumed an alcoholic beverage containing caffeine during the past year. Because individuals who consume energy drinks with alcohol underestimate their true level of alcohol-related impairment (i.e., a "wide-awake drunk"), the bulk of scientific evidence suggests that individuals who combine energy drinks with alcohol are more likely to engage in risky behavior than if they were only consuming alcohol. Accordingly, consuming energy drinks mixed with alcohol is associated with serious alcohol-related consequences such as sexual assault and driving while intoxicated. One study found that individuals who mix alcohol and energy drinks are more likely to report heavy drinking, while another study documented a link between frequent consumption of energy drinks and increased risk for alcohol dependence among college students.
CONCLUSION

Based on our own research and our review of the published literature cited herein, we conclude that there is no general consensus among qualified experts that the addition of caffeine in the amounts used in energy drinks is safe under its conditions of intended use as required by the GRAS standard, particularly for vulnerable populations such as children and adolescents. On the contrary, there is evidence in the published scientific literature that the caffeine levels in energy drinks pose serious potential health risks, including increased risk for serious injury or even death. We therefore urge the FDA to take prompt action to protect children and adolescents from the dangers of highly caffeinated energy drinks, including applying the existing GRAS standard for sodas to energy drinks and other beverages that contain caffeine as an additive. We also urge the FDA to require that manufacturers include caffeine content on product labels.

Sincerely,

Amelia M. Arria, Ph.D.
Director
Center on Young Adult Health and Development
University of Maryland School of Public Health
8400 Baltimore Avenue, Suite 100
College Park, MD 20740
aarria@umd.edu

Mary Claire O'Brien, M.D.
Associate Professor
Department of Emergency Medicine
Department of Social Science and Health Policy
Wake Forest School of Medicine
One Medical Center Boulevard
Winston-Salem, NC 27157
mobrien@wakehealth.edu

Roland R. Griffiths, Ph.D.
Professor
Departments of Psychiatry and Neuroscience
Johns Hopkins University School of Medicine
5510 Nathan Shock Drive
Baltimore, MD 21224
rgriff@jhmi.edu
Patricia B. Crawford, Dr.P.H., R.D.
Adjunct Professor and Director
Atkins Center for Weight and Health
C E Nutrition Specialist
119 Morgan Hall
University of California
Berkeley, CA 94720
pbcraw@berkeley.edu

Additional Signatories

Kavita Babu, M.D., FACEP, FACMT
Fellowship Director
Division of Medical Toxicology
Assistant Professor
Department of Emergency Medicine
UMass Memorial Medical Center
55 Lake Avenue North
Worcester, MA 01655
kavitambabu@gmail.com

Bruce A. Goldberger, Ph.D.
Professor and Director of Toxicology
Departments of Pathology and Psychiatry
University of Florida College of Medicine
4800 S.W. 35th Drive
Gainesville, FL 32608
bruce-goldberger@ufl.edu

William C. Griffin III, Ph.D., R.Ph.
Research Assistant Professor
Center for Drug and Alcohol Programs
Department of Psychiatry and Behavioral Sciences
Medical University of South Carolina
MSC 861
67 Presidential Street
Charleston, SC 29425
griffinw@musc.edu
John P. Higgins, M.D., M.B.A. (Hons), M.Phil., ACC, FACP, FAHA, FACSM, FASNC, FSGC
Associate Professor of Medicine, The University of Texas Health Science Center at Houston
Director of Exercise Physiology, Memorial Hermann Ironman Sports Medicine Institute
Chief of Cardiology, Lyndon B. Johnson General Hospital
Principal Investigator HEARTS (Houston Early Age Risk Testing & Screening Study)
Division of Cardiology
6431 Fannin Street, MSB 4.262
Houston, TX 77030
john.p.higgins@uth.tmc.edu

C. Tissa Kappagoda, M.D.
Professor Emeritus
Heart and Vascular Services
Lawrence J. Ellison Ambulatory Care Center
University of California Davis Health System
4860 Y Street, Suite 0200
Sacramento, CA 95817
ctkappagoda@ucdavis.edu

Steven E. Lipshultz, M.D., FAAP, FAHA
George E. Batchelor Professor of Pediatrics and Endowed Chair in Pediatric Cardiology
Professor of Epidemiology and Public Health
Professor of Medicine (Oncology)
Leonard M. Miller School of Medicine, University of Miami
Chief-of-Staff, Holtz Children’s Hospital of the University of Miami-Jackson Memorial Medical Center
Director, Batchelor Children’s Research Institute
Member, Sylvester Comprehensive Cancer Center, Miami, Florida
Department of Pediatrics (D820)
University of Miami, Leonard M. Miller School of Medicine
P.O. Box 016820
Miami, Florida 33101
slipshultz@med.miami.edu

Kristine Madsen, M.D., M.P.H., FAAP
Fellow, American Academy of Pediatrics
Assistant Professor
School of Public Health, University of California Berkeley
Department of Pediatrics, University of California San Francisco
King Sweesy and Robert Womack Endowed Chair in Medical Research and Public Health
219 University Hall
Berkeley, CA 94720
madsenk@berkeley.edu
Cecile A. Marczinkski, Ph.D.
Assistant Professor
Department of Psychological Science
Northern Kentucky University
349 BEP, 1 Nunn Drive
Highland Heights, KY 41099
marczinskc1@nku.edu

Kathleen E. Miller, Ph.D.
Senior Research Scientist
Research Institute on Addictions
University at Buffalo
1021 Main Street
Buffalo, NY 14203
kmiller@ria.buffalo.edu

Jeffrey Olgin, M.D., FACC
Gallo-Chatterjee Distinguished Professor of Medicine
Professor of Medicine & Chief, Division of Cardiology
University of California San Francisco
505 Parnassus Avenue
Room M-1182A, Box 0124
San Francisco, CA 94143
olgin@medicine.ucsf.edu

Kent A. Sepkowitz, M.D.
Physician
Infectious Disease Service
Department of Medicine, Infection Control
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10065
sepkowik@mskcc.org

Jennifer L. Temple, Ph.D.
Assistant Professor
University at Buffalo
Departments of Exercise and Nutrition Sciences and Community Health and Behavior
3435 Main Street
1 Farber Hall
Buffalo, NY 14214
jltemple@buffalo.edu
Dennis L. Thombs, Ph.D., FAAHB
Professor and Chair
Department of Behavioral & Community Health
EAD 709N School of Public Health
3500 Camp Bowie Boulevard
University of North Texas Health Science Center
Fort Worth, TX 76107
dennis.thombs@unthsc.edu

Charles J. Wibbelsman, M.D.
President
California Chapter 1, District IX
American Academy of Pediatrics
Kaiser Permanente
2200 O’Farrell Street, Teen Clinic
San Francisco, California 94115
charles.wibbelsman@kp.org

Acknowledgements:
Special thanks are extended to Brittany A. Bugbee, Kimberly M. Caldeira, Kaitlin A. Hippen, and Kathryn B. Vincent.
References


8. Somogyi LP. *Caffeine intake by the US population.* Silver Spring, MD: Food and Drug Administration; 2010.


Effects of caffeine on human health


Toxicological Evaluation Section, Chemical Health Hazard Assessment Division, Bureau of Chemical Safety, Food Directorate, Health Canada, Tunney’s Pasture, P.O. Box 2041, Ottawa, Ontario, Canada K1A 0L2

(Received 19 November 2001; revised 17 June 2002; accepted 18 June 2002)

Caffeine is probably the most frequently ingested pharmacologically active substance in the world. It is found in common beverages (coffee, tea, soft drinks), in products containing cocoa or chocolate, and in medications. Because of its wide consumption at different levels by most segments of the population, the public and the scientific community have expressed interest in the potential for caffeine to produce adverse effects on human health. The possibility that caffeine ingestion adversely affects human health was investigated based on reviews of (primarily) published human studies obtained through a comprehensive literature search. Based on the data reviewed, it is concluded that for the healthy adult population, moderate daily caffeine intake at a dose level up to 400 mg day\(^{-1}\) (equivalent to 6 mg kg\(^{-1}\) body weight day\(^{-1}\) in a 65-kg person) is not associated with adverse effects such as general toxicity, cardiovascular effects, effects on bone status and calcium balance (with consumption of adequate calcium), changes in adult behaviour, increased incidence of cancer and effects on male fertility. The data also show that reproductive-aged women and children are ‘at risk’ subgroups who may require specific advice on moderating their caffeine intake. Based on available evidence, it is suggested that reproductive-aged women should consume \(\leq 300\) mg caffeine per day (equivalent to 4.6 mg kg\(^{-1}\) bw day\(^{-1}\) for a 65-kg person) while children should consume \(\leq 2.5\) mg kg\(^{-1}\) bw day\(^{-1}\).

Keywords: behaviour, bone, caffeine, calcium balance, cardiovascular effects, children, coffee, congenital malformations, development, fertility, foetal growth, pregnancy, spontaneous abortion, tea

Introduction

Caffeine (1,3,7-trimethylxanthine) is a natural alkaloid found in coffee beans, tea leaves, cocoa beans, cola nuts and other plants. It is probably the most frequently ingested pharmacologically active substance in the world, found in common beverages (coffee, tea, soft drinks), products containing cocoa or chocolate, and medications, including headache or pain remedies and over-the-counter stimulants (Murphy and Benjamin 1981, IARC 1991h, Dlugosz and Bracken 1992, Carrillo and Benitez 1996).

The possibility that caffeine consumption can have adverse effects on human health was assessed based on the results of (primarily) published human studies obtained through a comprehensive literature search. The results of this assessment are summarized here.

Sources and prevalence of caffeine consumption

In North America, coffee (60–75%) and tea (15–30%) are the major sources of caffeine in the adult diet, whereas caffeinated soft drinks and chocolate are the major sources of caffeine in the diet of children. Coffee is also the primary source of caffeine in the diet of adults in some European countries, such as Finland, Sweden, Denmark and Switzerland. Brewed coffee contains the most caffeine (56–100 mg/100 ml), followed by instant coffee and tea (20–73 mg/100 ml) and cola (9–19 mg/100 ml). Cocoa and chocolate products are also important sources of caffeine (e.g. 5–20 mg/100 g in chocolate candy), as are a wide variety of both prescription (30–100 mg/tablet or capsule) and non-prescription (15–200 mg/tablet or capsule) drugs (Dlugosz and Bracken 1992, Barone and Roberts 1996, Shils et al. 1999, Tanda and Goldberg 2000).
In Canada, published values for the average daily intake of caffeine from all sources is about 2.4 mg kg\(^{-1}\) body weight (bw) for adults and 1.1 mg kg\(^{-1}\) bw for children 5–18 years old (Chou 1992). Recently, Brown et al. (2001) reported daily caffeine intakes ranging from 288 to 426 mg (equivalent to 4.5–6.5 mg kg\(^{-1}\) bw in a 65-kg person) in the adult population (481 men and women aged 30–75 years) residing in southern Ontario, Canada. Elsewhere, mean daily caffeine intake for adults among the general population has been given as approximately 3 mg kg\(^{-1}\) bw in the USA, 4 mg kg\(^{-1}\) bw in the UK and 7 mg kg\(^{-1}\) bw in Denmark. For high-level consumers, daily intakes range from 5 to 15 mg kg\(^{-1}\) bw. For children, daily caffeine intakes have been given as 1 mg kg\(^{-1}\) bw in the USA, <3 mg kg\(^{-1}\) bw in the UK and <2.5 mg kg\(^{-1}\) bw in Denmark (IARC 1991b, Ellison et al. 1995, Barone and Roberts 1996, Hughes and Oliveto 1997).

Note that the caffeine content of coffee and tea is dependent on their method of preparation and the product brand. In addition, variations in caffeine intake can occur due to differences in the size of the serving ‘cup’ (Stavric et al. 1988). The impact of these variations should be considered in the interpretation and comparison of clinical studies, particularly when cultural differences may be involved.

Pharmacokinetics

Following ingestion, caffeine is rapidly and essentially completely absorbed from the gastrointestinal tract into the bloodstream. Maximum caffeine concentrations in blood are reached within 1–1.5 h following ingestion. Absorbed caffeine is readily distributed throughout the entire body. It passes across the blood–brain barrier, through the placenta into amniotic fluid and the foetus, and into breast milk. Caffeine has also been detected in semen (Berger 1988, Arnaud 1999).

The liver is the primary site of caffeine metabolism (Stavric and Gilbert 1990, Arnaud 1999). In adults, caffeine is virtually completely metabolized to 1-methylxanthine and 1-methyluric acid from the paraxanthine intermediate. Only 1–5% of ingested caffeine is recovered unchanged in the urine. Infants up to the age of 8–9 months have a greatly reduced ability to metabolize caffeine, excreting about 85% of the administered caffeine in the urine unchanged (Nolen 1989, Stavric and Gilbert 1990).

The elimination half-life of caffeine ranges between 3 and 7 h and can be influenced by many factors, including sex, age, use of oral contraceptives, pregnancy and smoking. Caffeine’s half-life has been reported to be 20–30% shorter in females than in males. The half-life in newborns ranges from 50 to 100 h, but it gradually approaches that of an adult by 6 months of age. The half-life in females using oral contraceptive steroids is approximately twice that observed for ovulatory females. During pregnancy, the metabolic half-life increases steadily from 4 h during the first trimester to 18 h during the third trimester. Cigarette smoking is associated with about a twofold increase in the rate at which caffeine is eliminated (Aranda et al. 1979, Dalvi 1986, Gilbert et al. 1986, Stavric and Gilbert 1990, James 1991a, Dolgosz and Bracken 1992, Eskenazi 1993, Hinds et al. 1996, Arnaud 1999, Karen 2000).

General toxicity

Death due to excessive caffeine ingestion is not common, and only a few cases have been reported in the literature. The acute lethal dose in adult humans has been estimated to be 10 g/person. Death has been reported after ingestion of 6.5 g caffeine, but survival of a patient who allegedly ingested 24 g caffeine was also reported (Stavric 1988, James 1991b).

Caffeine toxicity in adults can present a spectrum of clinical symptoms, ranging from nervousness, irritability and insomnia to sensory disturbances, diuresis, arrhythmia, tachycardia, elevated respiration and gastrointestinal disturbances. Caffeine toxicity in children is manifested by severe emesis, tachycardia, central nervous system agitation and diuresis. Chronic exposure to caffeine has been implicated in a range of dysfunctions involving the gastrointestinal system, liver, renal system and musculature (Stavric 1988, James 1991b).

The most important mechanism of action of caffeine is the antagonism of adenosine receptors. Adenosine is a locally released purine which acts on different receptors that can increase or decrease cellular concentrations of cyclic adenosine monophosphate (cAMP). Caffeine selectively blocks adenosine receptors and competitively inhibits the action of adeno-
Effects of caffeine on human health

Caffeine at concentrations found in people consuming caffeine from dietary sources. Caffeine results in the release of norepinephrine, dopamine and serotonin in the brain and the increase of circulating catecholamines, consistent with reversal of the inhibitory effect of adenosine (Benowitz 1990).

It is now widely believed that habitual daily use of caffeine >500–600 mg (four to seven cups of coffee or seven to nine cups of tea) represents a significant health risk and may therefore be regarded as 'abuse'. Sustained abuse may in turn result in 'caffeinism', which refers to a syndrome characterized by a range of adverse reactions such as restlessness, anxiety, irritability, agitation, muscle tremor, insomnia, headache, diuresis, sensory disturbances (e.g. tinnitus), cardiovascular symptoms (e.g. tachycardia, arrhythmia) and gastrointestinal complaints (e.g. nausea, vomiting, diarrhoea) (James and Pauli 1985).

Excessive caffeine intake (>400 mg day⁻¹) may increase the risk of detrusor instability (unstable bladder) development in women. For women with pre-existing bladder symptoms, even moderate caffeine intake (200–400 mg day⁻¹) may result in an increased risk for detrusor instability (Arya et al. 2000).

Cardiovascular effects

Clinical studies have investigated the effects of caffeine or coffee on cardiac arrhythmia, heart rate, serum cholesterol and blood pressure. Epidemiological studies have largely focused on the association between coffee intake and cardiovascular risk factors, including blood pressure and serum cholesterol levels, or the incidence of cardiovascular disease itself.

Clinical studies have shown that single doses of caffeine <450 mg do not increase the frequency or severity of cardiac arrhythmia in healthy persons, patients with ischaemic heart disease or those with serious ventricular ectopia (Myers 1998). Studies conducted in healthy or hypertensive subjects suggest that when a change in heart rate is observed, it is typically a decrease at doses >150 mg/person (James 1991c, Green et al. 1996, Myers 1998). The rapid development of tolerance to the heart rate effect of caffeine (Green et al. 1996) complicates data interpretation. The generally modest decrease in heart rate is likely not clinically relevant (Myers 1998).

Several clinical and epidemiological studies have suggested that coffee consumption is associated with significant increases in total and low-density lipoprotein cholesterol levels. Recent studies, however, suggest that it is not the caffeine in coffee that is responsible for its hypercholesterolaemic effect (Thelle et al. 1987, James 1991c, d, Thelle 1993, 1995, Gardner et al. 1998). Two diterpenoid alcohols, cafestol and kahweol, found at significant levels in boiled coffee have been identified as hypercholesterolaemic components. Although these components are largely trapped by the use of a paper filter in coffee preparation, there is some evidence that consumption of filtered coffee is associated with small increases in serum cholesterol levels (Thelle 1995).

The effect of caffeine on blood pressure in habitual caffeine consumers and abstainers has been investigated in more than 50 acute and 19 repeated-dose clinical trials with healthy or hypertensive subjects (reviewed by Myers 1988, 1998, James 1991c, Green et al. 1996). The results of the acute studies indicate that caffeine induces an increase in systolic (5–15 mmHg) and/or diastolic (5–10 mmHg) blood pressure, most consistently at doses >250 mg/person, in adults of both sexes, irrespective of age, race, blood pressure status, or habitual caffeine intake. The effect is most pronounced in elderly, hypertensive or caffeine-naïve individuals. The pressor effect of caffeine was also observed in many of the repeated-dose studies, but not as consistently as in the acute studies. It is generally agreed that tolerance to these pressor effects develops within 1–3 days, but is partially lost after abstinence for as little as 12 hours. The clinical significance of caffeine’s pressor effects and the development of tolerance continues to be discussed in the literature (James 1991c, Green et al. 1996, Myers 1998).

Epidemiological studies investigating associations between caffeine and blood pressure (reviewed by Myers 1988, 1998, James 1991c, 1997, Green et al. 1996) have yielded conflicting results (i.e. positive, negative or no association). These inconsistencies may reflect methodological problems, including misclassification resulting from the use of dietary recall data, tolerance to the pressor effects of caffeine and the effect of smoking on the plasma half-life of caffeine. While James (1991c, 1997) and Green et al. (1996) indicated that further research was needed, Myers (1998) concluded that there was no epidemiological evidence to support any relationship between caffeine use and blood pressure.
Epidemiological studies addressing the possible association between consumption of caffeine-containing beverages, usually coffee, and coronary heart disease include case-control, longitudinal cohort and prospective studies (reviewed by James 1991d, Lynn and Kissinger 1992, Myers and Basinski 1992, Franceschi 1993, Thelle 1995, Myers 1998); meta-analyses of case-control and/or prospective study data were published by Greenland (1987, 1993) and Kawachi et al. (1994); and a recent case-control was published by Palmer et al. (1995) and two recent prospective studies were published by Stensvold and Tverdal (1995) and Hart and Smith (1997). Most relied on self-administered questionnaires to determine intakes of caffeinated beverages. Cardiovascular disease was assessed by a variety of outcome variables, including death from myocardial infarction or coronary heart disease, non-fatal myocardial infarction or coronary event, angina pectoris and/or hospitalization for coronary heart disease. The results of both case-control and prospective epidemiological studies yielded inconsistent results, although case-control studies were more likely to show a significant relationship between coffee consumption and cardiovascular disease, with an increased risk generally observed at intakes of five or more cups of coffee per day (≥ 500 mg caffeine day⁻¹). Longitudinal cohort studies published from 1986 yielded more consistent positive associations than those published up to 1981 (Greenland 1993). The inconsistencies both within and between case-control and prospective studies have resulted in controversies regarding study methodologies and data interpretation (James 1991d, Myers and Basinski 1992, Franceschi 1993, Greenland 1993, Myers 1998). While recognizing the ambiguity of the epidemiological data, Greenland (1993) and Franceschi (1993) concluded that the possibility of heavy coffee consumption (defined as 10 or more cups per day by Greenland 1993; probably four or more cups per day in Franceschi 1993) adversely affecting the incidence of coronary heart disease or mortality cannot be ruled out.

None of the epidemiological data determine whether it is caffeine per se or other components of coffee that are responsible for coffee’s association with cardiovascular disease. Although no significant association has been found between tea consumption and cardiovascular disease (Franceschi 1993, Thelle 1995, Myers 1998), it has been suggested that the beneficial effects of the flavonoids present in tea may offset any adverse effect of caffeine (Thelle 1995). Support for the idea that caffeine in coffee is not responsible for cardiovascular effects comes from epidemiological studies showing an increased risk of coronary events with consumption of decaffeinated coffee (Grobbee et al. 1990, Gartside and Gruen 1993).

In summary, the data currently available indicate that moderate caffeine intake (four or fewer cups of coffee per day, or ≤ 400 mg caffeine day⁻¹) does not adversely affect cardiovascular health. There are insufficient epidemiological data to draw any conclusions about the risk for coronary heart disease or mortality associated with consumption of 10 or more cups of coffee per day (≥ 1000 mg caffeine day⁻¹).

Effects on bone and calcium balance

The database on caffeine’s potential to adversely influence bone metabolism includes epidemiological studies investigating the relationship between caffeine and/or coffee intake and the risk of osteoporosis as characterized by low bone mineral density and increased susceptibility to fractures, as well as metabolic studies examining the effect of caffeine on calcium homeostasis.

Caffeine intake of 150–300 mg after a 10-h fast increased urinary calcium excretion 2–3 h after exposure in adolescent men and women (Massey and Hollingbery 1988), women 22–30 years of age (Massey and Wise 1984, Massey and Opryszek 1990), men 21–42 years of age (Massey and Berg 1985), and women 31–78 years of age consuming ≥ 200 mg caffeine day⁻¹ (Bergman et al. 1990). Tolerance to the renal effects of caffeine does not develop, as habitual coffee intake had no effect on the increase in calcium excretion associated with an acute caffeine dose (Massey and Opryszek 1990). Caffeine-induced hypercalciuria was not affected by oestrogen status (Bergman et al. 1990), gender or age (Massey and Wise 1992). Barger-Lux et al. (1990) reported that caffeine intakes of 400 mg person⁻¹ day⁻¹ for 19 days led to evidence of altered bone remodelling in healthy premenopausal women between the ages of 35 and 44, but had no effect on fractional calcium absorption, endogenous faecal calcium or urinary calcium excretion. An earlier study in the same population suggested that caffeine consumption of 175 mg person⁻¹ day⁻¹ was positively associated with increased 24-h urinary calcium excretion (Heaney and Recker 1982).
Effects of caffeine on human health

Whether it is through increased urinary calcium excretion (Massey and Whiting 1993) or decreased intestinal calcium absorption (Heaney 1998), caffeine does appear to have a negative effect on calcium balance (Hasling et al. 1992, Barger-Lux and Heaney 1995). Barger-Lux et al. (1990) concluded that a daily intake of 400 mg caffeine by healthy premenopausal women with a calcium intake of at least 600 mg day\(^{-1}\) has no appreciable effect on calcium excretion. Hasling et al. (1992) derived a model from data collected from postmenopausal women that indicated coffee intakes >1000 ml day\(^{-1}\) (760 mg caffeine day\(^{-1}\)) could induce excess calcium loss, while intakes of 150–300 ml coffee day\(^{-1}\) (112–224 mg caffeine day\(^{-1}\)) would have little impact on calcium balance. The biological significance of caffeine's negative effect on calcium balance has been debated (Barger-Lux et al. 1990, Massey and Whiting 1993).

Several epidemiological studies have been conducted to assess the relationship between caffeine intake and bone density. Increasing caffeine intakes were not associated with significant decreases in bone density in adolescent women (Lloyd et al. 1998), young women 20–30 years of age (Ellef et al. 1983, McCulloch et al. 1990, Packer and Recker 1996, Conklin and Galuska 2000), premenopausal women (Pearl et al. 1988, Lacey et al. 1991, Lloyd et al. 1991, Hansen 1994), perimenopausal women (Slemenda et al. 1987, 1990), postmenopausal women (Slemenda et al. 1987, Hansen et al. 1991, Reid et al. 1994, Lloyd et al. 1997, 2000, Hannan et al. 2000) or men (Ellef et al. 1983, Glynn et al. 1995, Hannan et al. 2000). Some negative associations between caffeine intake and bone density have been observed; these associations disappeared when confounders such as calcium intake were adjusted for in some studies (Cooper et al. 1992, Johansson et al. 1992), but not others (Hernández-Avila et al. 1993). Some researchers have found that caffeine's effects on bone density were dependent on calcium intake. Harris and Dawson-Hughes (1994) concluded that two to three servings of coffee (280–420 mg caffeine day\(^{-1}\)) may accelerate bone loss in healthy postmenopausal women with calcium intakes <800 mg day\(^{-1}\). Barrett-Connor et al. (1994) found that only postmenopausal women who did not report drinking at least one glass of milk per day between the ages of 20 and 50 years exhibited a coffee-associated decrease in bone mineral density.

Caffeine intake has been investigated as a potential risk factor for bone fracture, the major cause of morbidity and mortality associated with osteoporosis. In case-control studies, caffeine intakes were not associated with an increased risk of hip fracture in women >55 years of age (Nieves et al. 1992), women 18–70 years of age (Tavani et al. 1995), or men or women >65 years of age (Cumming and Klineberg 1994). In a cross-sectional study, Travers-Gustafson et al. (1995) were also unable to show that caffeine intakes were related to an increased incidence of low-trauma fractures. In contrast, data from the Nurses Health Study found that women who consumed more than four cups of coffee per day (>544 mg caffeine day\(^{-1}\)) had a higher risk of hip fracture than those who 'almost never' consumed coffee (Hernández-Avila et al. 1991). Although other studies have shown an increase in the risk of hip fracture with dietary caffeine, it was not clear whether the analysis adjusted for differences in calcium intake (Holbrook et al. 1988) or whether calcium intake data were unavailable (Kiel et al. 1990).

Interpretation of caffeine's effects on bone metabolism are complicated because coffee intake is associated with other risk factors for osteoporosis: calcium intake (Heaney and Recker 1982, Massey and Hollingbery 1988, Hasling et al. 1992, Hernández-Avila et al. 1993), age (Barger-Lux and Heaney 1995), cigarette smoking (Cooper et al. 1992, Johansson et al. 1992, Barrett-Connor et al. 1994) and alcohol consumption (Cooper et al. 1992, Barrett-Connor et al. 1994). Collectively, the available data suggest that an increased caffeine intake is associated with a slight but biologically real deterioration in calcium balance. The majority of evidence indicates that this effect is through caffeine-induced hypercalciuria. The biological significance of caffeine's negative effect on calcium balance continues to be the topic of scientific debate, as studies on both bone density and fracture risk have revealed conflicting results. Bruce and Spiller (1998) suggest that a lifetime pattern of high caffeine intake (more than four cups of coffee per day or >400 mg caffeine day\(^{-1}\)) in women contributes to a negative impact on calcium and bone metabolism and is correlated with bone loss or fracture risk, particularly when there is a low calcium intake. Heaney (1998) suggests that the epidemiological studies showing a negative association between caffeine intake and bone mass may be explained by an inverse relationship between consumption of milk and consumption of caffeine-containing beverages, concluding that there is no evidence that caffeine has any harmful effect on bone status or...
calculated economy in individuals ingesting recommended levels of calcium.

To date, the evidence indicates that the significance of caffeine's potential to affect calcium balance and bone metabolism adversely is dependent on lifetime caffeine and calcium intakes and is biologically more relevant in women. Current data suggest that caffeine intakes of $<400\,\text{mg \, day}^{-1}$ do not have significant effects on bone status or calcium balance in individuals ingesting at least $800\,\text{mg \, calcium \, day}^{-1}$ (an intake that $<50\%$ of Canadian women achieve).

**Effects on human behaviour**

**Mood and performance in adults**

The results of studies on the effects of caffeine on various psychomotor tasks (reviewed by James 1991e, Smith 1998) are sometimes conflicting. For example, some studies have shown no effects of caffeine on hand steadiness, whereas others have associated caffeine consumption with poorer performance in this parameter (Bovim et al. 1995). Studies showing both positive effects (Jacobson and Edgley 1987, Roache and Griffiths 1987) and no effects (Zahn and Rapoport 1987) on reaction time have also been reported.

Inconsistent results can be encountered in the literature in terms of the impact of caffeine on cognitive functioning, including alertness, vigilance, memory, and mood. These inconsistencies may be due to methodological differences, personality differences (e.g. introverts versus extroverts), the time of day when tests were conducted, and uncontrolled confounding factors (e.g. habitual caffeine, alcohol or tobacco use) (James 1991e, Smith 1998). In general, caffeine ($100\,\text{mg \, day}^{-1}$ for 4 days, Leathwood and Pollet 1982/83; 1.5–3\,\text{mg \, kg}^{-1} \text{bw}$ as single doses, 2h apart, or $105–210\,\text{mg}$ for a 70-kg adult, Smith et al. 1993; $250\,\text{mg \, day}^{-1}$ for 2 days, Johnson et al. 1990; two doses of $200\,\text{mg}$, Regina et al. 1974) has been shown to increase the alertness of individuals, especially in situations where arousal is low (e.g. night-shift workers, early in the morning). Caffeine can also increase vigilance in the daytime. In a double-blind placebo-controlled study in males, statistically significant increases were observed in two of three vigilance tests, including both visual and auditory tests, at all caffeine doses employed (as low as $32\,\text{mg \, caffeine \, up \, to \, 256\,\text{mg}}$) (Lieberman et al. 1987). In another investigation of the effects of caffeine on alertness, subjects given caffeine ($250\,\text{mg \, twice \, per \, day}$) performed significantly better in an auditory vigilance test than did the placebo group (Zwyghuizen-Doorenbos et al. 1990).

Most studies on the effects of caffeine on psychomotor and cognitive parameters deal with acute administration. In a study on regular consumers of coffee and tea (Jarvis 1993), higher levels of coffee consumption were associated with improved performance in reaction time, verbal memory and visuospatial reasoning. The consumption of tea was related to an improved performance in one test of reaction time and in visuospatial reasoning, but not in the other tests. The best performance was noted at an intake of five to six cups of coffee or tea per day.

Although the results of studies on the effects of caffeine on alertness, vigilance and memory are sometimes contradictory in terms of whether caffeine produces beneficial effects or no effects, there is little indication that intake of caffeine (up to approximately 250 mg in a single dose or over a few days) affects these processes in a negative manner (Smith 1998). However, a single caffeine dose of $100\,\text{mg}$ was shown to affect short-term memory adversely in one study (Terry and Phifer 1986).

Some studies have noted little or no change in mood after the consumption of single doses of caffeine of 32 mg (Lieberman et al. 1987), 100 mg (Svensson et al. 1980) or 200 mg (Swift and Tiplady 1988). Larger amounts of caffeine (200, 400 or 600 mg as a single dose) have been associated not only with slight increases on an anger/hostility scale, but also with reduced ratings for drowsiness and incoordination (Roache and Griffiths 1987). Caffeine has little effect in producing depression, even at the consumption of more than eight cups of coffee per day (James 1991f). It is unclear why some studies have found effects on mood and others have not.

The consumption of caffeine by adults has been associated with an increase in anxiety in several studies. Many studies conducted on psychiatric inpatients, for example, have shown significantly increased anxiety levels in heavier users of caffeine (James 1991f); however, some of these studies did not control for alcohol and tobacco use, and patients may have been primed to report more symptoms. James et al. (1987) remedied these methodological
problems in a survey of 173 psychiatric in-patients, reporting no association between the consumption of caffeine and anxiety. In patients with generalized anxiety disorder, the administration of caffeine increased their already high anxiety level in a dose-related manner (Bruce et al. 1992). Note that the results of studies using psychiatric patients or patients with anxiety disorders may not be applicable to the general population (James and Crosbie 1987). Other studies have shown no effects of caffeine (e.g. regular consumption of up to seven or more cups of coffee or tea per day) on anxiety in psychiatric patients, non-clinical subjects or patients with anxiety disorders (Lynn 1973, Hare 1978, Eaton and McLeod 1984, Mathew and Wilson 1990, James 1991f, Smith 1998).

The literature suggests that caffeine can produce anxiety or exacerbate anxiety in adults with pre-existing anxiety disorders; however, the doses associated with these effects are large (1–2 g caffeine day\(^{-1}\)) and would likely be consumed only by a small segment of caffeine consumers. In addition, it has been suggested that people experiencing the anxiogenic effects of caffeine are likely to avoid the use of this substance (James 1991f); thus, the self-limiting nature of caffeine intake would reduce any potential that caffeine had to produce anxiety in adults.

Studies have shown that caffeine can increase the time taken to fall asleep (sleep latency) and reduce sleep duration, especially if large amounts of caffeine (>3 mg kg\(^{-1}\) bw, >210 mg for a 70-kg person) are ingested close to the usual bedtime of the individual (Smith 1998). High consumers of caffeine are less likely to report sleep disturbances than individuals consuming caffeine more infrequently (Snyder and Sklar 1984, Zvyghuizen-Doorenbos et al. 1990), suggesting the development of tolerance to the effects of caffeine on this parameter. It is apparent that if caffeine ingestion (especially in the late evening) affects the sleep of the individual, a self-limiting reduction in caffeine intake will likely occur to avoid any effects on sleep.

In summary, the moderate consumption of caffeine in normal adults has not been associated with any major adverse effects on mood or performance, and most effects associated with higher consumption rates would be self-limiting. However, in light of inconsistent results in the literature and individual differences in sensitivity to caffeine, some people (e.g. those with anxiety disorders) need to be aware of the possible adverse effects of caffeine and to limit their intake accordingly.

**Tolerance, physical dependence, and withdrawal**

The literature on the development of tolerance to the effects of caffeine during prolonged ingestion is sparse and inconsistent (James 1991c). Any tolerance that may be present is likely to be dependent on the biological or behavioural effect produced by caffeine and by the level and pattern of caffeine consumption.

Cessation of caffeine ingestion has been associated with a wide variety of mainly subjective effects, in particular headache (Rubin and Smith 1999) and fatigue, characterized by such symptoms as mental depression, weakness, lethargy, apathy, sleepiness and decreased alertness (Griffiths and Woodson 1988). The general caffeine withdrawal pattern appears to be an onset from 12 to 24 h after cessation, a peak at 20−48 h, and a duration of about 1 week (Griffiths and Woodson 1988). The strength of the association between caffeine cessation and withdrawal is supported by the fact that symptoms can be ameliorated by administration of caffeine tablets in a dose-dependent manner (Griffiths and Woodson 1988). The intensity of the symptoms has been described as mild to extreme. The presence or absence of withdrawal symptoms is not always predictable, as some heavy users have ceased ingestion of caffeine with no apparent withdrawal (Griffiths and Woodson 1988).

Symptoms associated with caffeine withdrawal have been noted in studies involving the cessation of regular consumption of high (≤1250 mg day\(^{-1}\)), Griffiths et al. 1986; ≤2548 mg day\(^{-1}\); Strain et al. 1994) and much lower doses (100 mg day\(^{-1}\), Griffiths et al. 1990; 235 mg day\(^{-1}\), Silverman et al. 1992; 290 mg day\(^{-1}\), Weber et al. 1993; 428 mg day\(^{-1}\), Bruce et al. 1991; four to six cups of coffee per day, van Dusseldorp and Katan 1990; five cups of coffee per day, Hughes et al. 1991). While some studies have shown a dose-dependent increase in the effects of withdrawal (increased headaches after the stoppage of regular consumption of >700 mg caffeine day\(^{-1}\) compared with ≤700 mg day\(^{-1}\); Weber et al. 1993), others have shown little correlation between daily intake and withdrawal symptoms (in a range of regular intake of 231−2548 mg day\(^{-1}\); Strain et al. 1994). In Strain et al. (1994), the most severe effects upon cessation were noted with the lowest consumption, while the individual with the highest regular consumption reported only moderate effects.

Dews et al. (1998) hypothesized that bias and priming of the subjects in caffeine withdrawal studies led to
the exaggeration of the incidence and severity of symptoms of caffeine withdrawal. They suggested that the prevalence and severity of withdrawal symptoms have been exaggerated in the literature, as illustrated by the variability among published reports of both the symptoms associated with caffeine withdrawal and the incidence rates, and concluded that the true level of caffeine withdrawal is low and near background levels. Also, there are reports of caffeine withdrawal continuing for long periods, which may be the result of a return of performance and alertness to pre-caffeine conditions. Since caffeine has been shown to improve these parameters, the return to normalcy may be associated with reduced performance and alertness compared with caffeine use, and these effects may be attributed to a caffeine withdrawal syndrome or as a sign that physical dependence has been produced during caffeine consumption.

In a blinded study by Dewes et al. (1999), subjects were given coffee and then subjected to continued caffeine intake, abrupt caffeine cessation or gradual caffeine cessation (from 100 to 0% over 7 days). Subjects in the gradual cessation group reported no adverse effects of caffeine cessation, while females (but not males) in the abrupt cessation group had adverse effects, as evidenced by reduced mood/attitude scores on no-caffeine days (reductions in scores were small). This study showed that the binding of subjects to caffeine cessation reduced the incidence of reported symptoms of caffeine withdrawal, as about half of the subjects reporting severe withdrawal symptoms in a prior telephone interview experienced no symptoms of withdrawal in the blinded study.

The literature thus supports the existence of caffeine withdrawal in some individuals, with variability in the severity of symptoms. When withdrawal occurs, it is short-lived and relatively mild in the majority of people affected.

Effects on children

Scientific studies have shown a variety of effects of caffeine consumption in children, although it is surprising that so few studies have specifically addressed effects in this population.

At low doses, an increased performance in attention tests has been noted in children. A double-blind and placebo-controlled study was conducted in which 21 children (mean body weight 38.1 ± 12.5 kg; average age 10.6 ± 1.3 years) were administered a placebo, a low dose of caffeine (single dose of 2.5 mg kg⁻¹ bw) or a high dose of caffeine (single dose of 5.0 mg kg⁻¹ bw) (Bernstein et al. 1994). The authors noted a statistically significant, dose-dependent improvement in a performance test of attention after caffeine administration compared with the placebo group. A significant but non-dose-related improvement in a manual dexterity test was also noted. In a double-blind placebo-controlled cross-over study (Elkins et al. 1981, Rapoport et al. 1981b), a group of 19 pre-adolescent boys were tested for a number of parameters after the ingestion of a placebo or a single caffeine dose of 3 or 10 mg kg⁻¹ bw on three separate occasions (each separated by 48 h). The children in the high-dose group showed a significant increase in motor activity compared with the control and low-dose groups, an increase in speech rate compared with the low-dose group, a significant reduction in reaction time in a vigilance test, and a reduced number of errors in a sustained attention measure test compared with the placebo group. Stratification of usual, pre-study caffeine use was not conducted for the subjects in this study.

Anxiety, measured both subjectively and objectively, has also been associated with the administration of low doses of caffeine in children in a number of studies. In the Bernstein et al. (1994) study described above, there was a trend (although it was statistically non-significant) towards a higher level of anxiety in one of the subsets of the Visual Analogue Scale for state anxiety (‘how I feel right now’) just after caffeine administration. There was a statistically significant correlation between salivary caffeine concentration and the severity of the state anxiety as measured by the Visual Analogue Scale. It was noted in this study that the levels of salivary caffeine were significantly correlated with the dose of caffeine administered. Other anxiety measurements conducted in this study (all self-reported, including other measurements of state and trait anxiety) showed no difference after caffeine administration. While this study randomized the order of testing, there was a lack of participant stratification based on regular, pre-study caffeine consumption. Even so, the level of caffeine administered to children in the Bernstein et al. (1994) study is the lowest in the available literature, and this study should be considered along with the wider body of evidence.
Other reviewed studies showing manifestations of anxiety in children associated with caffeine were those by Rapoport et al. (1981a) (10 mg kg\(^{-1}\) bw day\(^{-1}\)), Rapoport et al. (1981b) (3 and 10 mg kg\(^{-1}\) bw day\(^{-1}\)) and Rapoport et al. (1984) (10 mg kg\(^{-1}\) bw day\(^{-1}\)). In all of these studies, effects on anxiety were noted at all doses tested. Other effects in these studies included being nervous, fidgety, jittery, and restless and experiencing hyperactivity and difficulty sleeping. Positive dose–response were noted for skin conductance (a measure of anxiety) as well as for nervous/jittery behaviour in the children in the Rapoport et al. (1981b) study. When subjects were stratified by pre-study caffeine intake (Rapoport et al. 1981a), differences between low and high dose consumers (pre-study intake of <50 and ≥ 300 mg caffeine day\(^{-1}\), respectively) were apparent. High dose consumers were more easily frustrated, with a greater feeling of nervousness on baseline tests, than the low consumer group, possibly pointing to caffeine withdrawal during this period of testing. In terms of reported side-effects, the low users could distinguish between the placebo and the caffeine treatment (according to a variety of self-reported side-effects), while the high users could not. The high users given placebo and then caffeine experienced more side-effects during the initial placebo administration than they did when administered caffeine. The study by Rapoport et al. (1981a) appears to provide evidence of tolerance in the high regular consumers, and this group also appeared to show withdrawal in the baseline and placebo conditions. In Rapoport et al. (1984), a number of differences were noted between high and low consumers in terms of behaviour. During the screening, baseline and initial pre-study caffeine-free periods, the high consumers reported significantly more symptoms of anxiety and were reported to be more ‘disobedient’ than the low consumers. There appeared to be many differences between the groups when caffeine was administered for 2 weeks. Low consumers exhibited a significant increase in restlessness and fidgety behaviour, while the high-dose group showed a decrease in this behaviour. Statistically significant differences between the groups were mood changes, excitability, inattentiveness, restlessness and crying (the direction of these changes between the two groups was not mentioned in the paper). In terms of side-effects during this period, the low consumers reported headache, stomach-ache and nausea. These effects were not noted in the high consumers. A feeling of faintness and of being flushed was significantly increased in the low consumers and significantly decreased in the high consumers. Also, the low consumers had difficulty sleeping and a decreased appetite compared with the high consumer group. It was suggested by the authors that child consumers of high-caffeine diets differ inherently from those consuming low-caffeine diets in certain ways, namely having lower autonomic arousal and being more impulsive, leading to the self-administration of caffeine. In this study the initial pre-study stratification of subjects into high and low consumers (18 ± 18 and 641 ± 350 mg day\(^{-1}\), respectively) was based on a 24-h recall; however, based on a 7-day food diary for the pre-study baseline period, it was observed that there was a large overlap between the low and high consumer groups (95 ± 84 and 290 ± 275 mg week\(^{-1}\) or about 41.4 and 13.6 mg day\(^{-1}\), respectively). The overlap in pre-study caffeine intake may reduce the ability to evaluate the differential effects of caffeine on high and low consumers that were noted.

Other studies dealing with the effects of caffeine on children were those by Baer (1987), Hale et al. (1995) and Davis and Osorio (1998). The study by Baer (1987) used six 5-year-old children who were administered either a caffeine-free or a caffeinated soft drink each day for 2 weeks, resulting in a dose of 1.6–2.5 mg kg\(^{-1}\) bw day\(^{-1}\) when caffeine was administered. Drink conditions were reversed at the end of the 2 weeks. Effects noted on behaviour (e.g. off-task behaviour, motor activity, continuous performance) were inconsistent and small. No testing for anxiety was conducted. Hale et al. (1995) examined the self-administration of caffeine in 18 adolescent children of both sexes (age 11–15) in a double-blind, placebo-controlled study. Soft drinks containing either caffeine (33.3 mg/8 ounce serving) or a placebo were supplied to the participants. The children consumed a particular drink one day (either caffeinated or placebo) followed by another drink (either the same as the previous day or different) the next day. Consumption of all drinks was ad libitum. Four children met the criteria for repeatable self-administration, preferring the caffeinated drink to the placebo; however, only one child had a statistically significant self-administration. In these four children, the average intake of caffeine was 169 mg day\(^{-1}\) compared with 62 mg day\(^{-1}\) in those where self-administration was not evident. No behavioural symptoms were consistently reported in any participant. When the results were analysed across all participants, it was noted that on caffeine-free beverage days, there was significantly more depression, drowsiness and fatigue. No differences between the consumption of caffei-
inated or non-caffeinated drinks were observed in the children when a parent rating scale for anxiety, hyperactivity or impulsivity was employed. No information was provided in this study about the pre-study intake of caffeine. Davis and Osorio (1998) reported that caffeine intake can worsen and trigger the appearance of tics in children, based on two children aged 11 and 13. The authors concluded that consumption of caffeine can trigger the appearance of tics in susceptible children, although they made no indication of how the determination of a 'susceptible' child could be made. It is possible that genetic factors play a role, since the two children in this study were related. It should be recognized that with only two children, this study is only suggestive of a problem; however, it is an area that deserves further research.

In a meta-analysis of nine studies (Stein et al. 1996), caffeine showed no significant deleterious acute effects on behaviour or cognition in children. The results of the meta-analysis with respect to anxiogenic effects are difficult to interpret, for several reasons. For example, tests of anxiety were grouped with a number of other tests to form an 'internalizing' category. This may have diluted any effects of anxiety. In addition, the tests used to assess anxiety were not the same in each study, making comparisons between these studies more difficult. Of the nine studies used for the meta-analysis, four dealt with normal children, while the remainder used children who had attention deficit hyperactivity disorder. Again, this makes the inter-comparison of studies difficult.

The cessation of caffeine intake in normally high consuming children (≥ 300 mg day\(^{-1}\)) or those administered larger amounts of caffeine (10 mg kg\(^{-1}\) bw day\(^{-1}\)) over a period of weeks has resulted in the production of symptoms associated with caffeine withdrawal (Rapoport et al. 1981a). Bernstein et al. (1998) studied the single-blinded withdrawal of caffeine in 30 normal pre-pubertal children (mean age 10 years) having an average pre-study consumption of at least 20 mg caffeine day\(^{-1}\). Children were administered 150 mg caffeine day\(^{-1}\) for 13 days followed by a non-caffeinated drink for 1 day, then resumed their normal diet. While on caffeine, the subjects responded significantly faster in the test of attention than in the withdrawal period and resumption to normal diet period. During the withdrawal period, the response time was significantly increased compared with the pre-caffeine (baseline) period. This increased response time was still significantly elevated 1 week post-caffeine cessation. The authors suggested that the children had developed a physical dependence on the caffeine and exhibited withdrawal effects upon removal of the caffeine. Anxiety was observed to be higher during the baseline period in this study, with scores decreasing over time, possibly related to an increasing familiarity of the children with the testing procedure.

Caffeine has been tested for use in the treatment of hyperactivity/attention deficit disorder in children (James 1991e, Leviton 1992). A few early studies showed beneficial effects of caffeine intake at doses ranging from 175 to 600 mg day\(^{-1}\); in these studies, few adverse effects were noted, although some effect on sleep (dose-dependent insomnia) was noted in one study (100–400 mg caffeine day\(^{-1}\)), and minor group increases in blood pressure and heart rate were noted in another (300 mg day\(^{-1}\)). Many other studies, however, have shown no benefit of caffeine use in children with attention deficit disorder. Some studies, in fact, suggest that caffeine ingestion can lead to symptoms of hyperactivity in natural low consumers. In a study in which the 7-day food diaries from 30 low- and 30 high-caffeine-consuming school children were analysed, 30% of the high consumers met criteria for attention deficit disorder with hyperactivity, and the high consumers were perceived as being more restless than the low consumers (Rapoport et al. 1984). Problems with this study in terms of overlap between the low and high consumers’ pre-study intake of caffeine have been noted above.

The studies reviewed here and their sometimes conflicting results can be difficult to compare, since they employed either different endpoints or different ways to assess similar endpoints. In addition, most studies used a small number of subjects. The problems associated with differing groups of caffeine consumers within the population of children and the potential differential susceptibility to caffeine of certain subpopulations need to be clarified. Another difficulty with some studies is the non-stratification of children based on their usual (pre-study) caffeine intake, since high consumers and low consumers may not always respond in the same manner to additional administered caffeine. In addition, no studies have been designed to test for potential chronic effects of caffeine consumption by children.

In conclusion, it is unknown if long-term daily consumption of caffeine would produce effects similar to those observed in the studies reviewed above. However, it is known that the human nervous system (including the brain) continues to develop and mature
throughout childhood. It is possible that the protracted development of the nervous system may render children more sensitive to any adverse effects of caffeine.

**Mutagenicity/genotoxicity**

Caffeine not only induces mutations in bacteria in the absence of mammalian metabolic activation, but also can exhibit weak antimutagenic activity in some microorganisms (Legator and Zimmering 1979, Brusick et al. 1986, Rosenkranz and Ennever 1987, Pons and Muller 1990). In eukaryotic organisms, including fungi and yeasts (Legator and Zimmering 1979, Osman and McCready 1998), higher plants (Gonzalez-Fernandez et al. 1985, Manandhar et al. 1996), rodent cell lines (Jenssen and Ramel 1980, Aeschbacher et al. 1986, Brusick et al. 1986, Haynes et al. 1996, Kiefer and Wiebel 1998), and human cell lines (Lachance 1982, Bernhard et al. 1996, Roldan-Reyes et al. 1997), caffeine inhibits cell cycle-dependent DNA repair induced by a variety of physical and chemical mutagens, leading to the potentiation of clastogenic effects (D’Ambrosio 1994, Puck et al. 1998, Harish et al. 2000, Jiang et al. 2000). In chick embryo cells, DNA damage was induced (Müller et al. 1996) at dose levels in the \( \geq 1 \mu M \) range, not considered toxicologically relevant (Tempel and von Zallinger 1997). Genotoxic activity in *Drosophila* was weakly positive or inconclusive for chromosomal effects, dominant lethals, the somatic mutation and recombination test, and chromatid aberrations (Legator and Zimmering 1979, Graf and Würgler 1986, 1996), while X-ray damage was enhanced (De Marco and Cozzi 1980). Only at high levels of caffeine were clastogenic effects reported in somatic cells of rodents (Jenssen and Ramel 1980, Aeschbacher et al. 1986, Haynes et al. 1996), while no specific locus mutations or chromosomal effects were induced in germ cells or embryonic cells (Legator and Zimmering 1979, Mailhes et al. 1996, Müller et al. 1996). Antigenotoxic activity on somatic or germ cells exposed to a variety of physical and chemical mutagens, following ingestion of caffeinated or decaffeinated coffees was weak or negative (Legator and Zimmering 1979, Everson et al. 1988, Reidy et al. 1988, Chen et al. 1989, MacGregor 1990, Smith et al. 1990, Robbins et al. 1997, Vine et al. 1997, Abraham and Singh 1999).

Although evidence for the mutagenic potential of caffeine is conflicting (Lachance 1982, Grice 1987, Rosenkranz and Ennever 1987, D’Ambrosio 1994), it appears to be unlikely that at normal, physiologically relevant levels of consumption (i.e. at less than systemic toxicity ranges), caffeine would result in mutagenic effects in humans.

**Carcinogenicity**

The evidence from several oral oncogenic/chronic toxicity studies in mice (Bauer et al. 1977, Macklin and Szot 1980, Stalder et al. 1990) and rats (Wurzner et al. 1977, Johansson 1981, Takayama and Kuwabara 1982, Mohr et al. 1984) indicate that caffeine is not a carcinogen, up to dose levels of 391 and 230 mg kg\(^{-1}\) bw day\(^{-1}\), respectively. The most common clinical sign observed in these studies was a decrease in body weight, with no concomitant decrease in food consumption.

Epidemiological studies on the carcinogenicity of caffeine as present in coffee have consistently shown that caffeine is not associated with cancer development at several tissue and organ sites. For example, caffeine consumption, from three or more cups of coffee per day (\( \geq 300 \text{ mg caffeine day}^{-1} \)) was not associated with cancer development in the following sites: large bowel in 13 case-control studies (cited in IARC 1991a, Lee et al. 1993, Olsen and Kronborg 1993); stomach in six case-control studies (cited in IARC 1991a, Agudo et al. 1992); prostate in one case-control study (cited in IARC 1991a); liver in one case-control study (cited in IARC 1991a); lung in two cohort studies and one case-control study (cited in IARC 1991a); and vulva in one case-control study (Sturgson et al. 1991). Higher caffeine consumption, specifically drinking seven or more cups of coffee per day (\( \geq 700 \text{ mg caffeine day}^{-1} \)) was not associated with breast cancer in 11 case-control studies (cited in Rohan et al. 1989, IARC 1991a, McLaughlin et al. 1992, Folsom et al. 1993, Smith et al. 1994, Tavani et al. 1998).

On the other hand, caffeine intake, as measured by coffee consumption, was occasionally associated with cancer development at some sites. In the urinary bladder, four cohort studies showed no effect with doses of five or more cups of coffee per day (\( \geq 500 \text{ mg caffeine day}^{-1} \)) (cited in IARC 1991a, Chyou et al.
1993, Stensvold and Jacobsen 1994). In 26 case-control studies, 17 studies showed no effect with doses of five or more cups of coffee per day. Nine studies were positive, and three of these studies showed a dose-response (cited in IARC 1991a, Vena et al. 1993, Donato et al. 1997). Of these three studies, two showed a positive increase with any coffee consumption, and the third study was significant only when consumption was five or more cups of coffee per day. In the pancreas, out of nine cohort studies, eight showed no significant effect with doses of five or more cups of coffee per day (≥500 mg caffeine day⁻¹), while one study was positive for any coffee consumption (cited in IARC 1991a, Stensvold and Jacobsen 1994, Harnack et al. 1997). Of 24 case-control studies, 21 showed no effect on pancreas with doses of five or more cups per day. In one of the three positive case-control studies, a significant effect was observed only when four cups of coffee per day were drunk (400 mg caffeine day⁻¹). In a second study, doses exceeding two cups of coffee per day (200 mg caffeine day⁻¹) were associated with an increase. In the third positive study, any level of coffee drinking resulted in an increased risk. Of the three positive studies, two studies showed a dose-related response. When smoking was taken into consideration, the positive responses in these studies were weakened (cited in IARC 1991a, Bueno de Mesquita et al. 1992, Lyon et al. 1992, Partanen et al. 1995, Nishi et al. 1996). In the ovary, two case-control studies showed a significant increase in cancer incidence with doses of more than one cup of coffee per day, while five case-control studies showed no effect with doses of five or more cups per day (cited in IARC 1991b, Polychronopoulou et al. 1993). In the skin, a case-control study showed that the risk of basal cell carcinoma was increased with doses of more than two-and-a-half cups of coffee per day (>250 mg caffeine day⁻¹) (Sahl et al. 1995).

Overall, the evidence indicates that caffeine, as present in coffee, is not a chemical that causes breast or bowel cancer. Results on the association between caffeine and the development of urinary bladder and pancreatic cancer are inconsistent and the data are not conclusive. At other sites (e.g. ovary, stomach, liver) the data are insufficient to conclude that caffeine consumption is related to carcinogenesis. Based on the studies reviewed in this report, caffeine is not likely to be a human carcinogen at a dose less than five cups of coffee per day (<500 mg caffeine day⁻¹).

Reproductive and developmental effects

There is evidence that many women spontaneously reduce their caffeine intake during pregnancy, some apparently developing a temporary 'loss of taste' for the substance. Nevertheless, caffeine consumption in this group can remain relatively high. About 98% of women of reproductive age regularly consume caffeine in the form of caffeinated beverages or in caffeine-containing medications, while 72% of them continue to do so during pregnancy (James 1991g). Epidemiological investigations reviewed for this paper showed that a majority of women consumed caffeine during pregnancy in a range of 100–300 mg day⁻¹ (Fenster et al. 1991a, Fortier et al. 1993, Mills et al. 1993, Dominguez-Rojas et al. 1994, Rondo et al. 1996). A small proportion of pregnant women in the population may ingest a much greater amount, >400 mg caffeine day⁻¹ (Kurppa et al. 1983, Toubaras et al. 1986, Olsen et al. 1991, Armstrong et al. 1992, McDonald et al. 1992a).

During the past 20 years, a great deal of evidence has accumulated concerning the effects of caffeine consumption on reproduction and pre- and postnatal development. Although the results from studies reviewed for this publication have not been entirely consistent, the bulk of evidence suggests that caffeine intake at dose levels of >300 mg day⁻¹ may have adverse effects on some reproductive/developmental parameters when exposure takes place during certain periods (Dlugosz and Bracken 1992).

Christian and Brent (2001) reviewed published animal and human epidemiological studies investigating the association between caffeine ingestion and adverse reproductive/developmental effects and concluded that pre-pregnant or pregnant women who do not smoke or drink alcohol and who consume moderate amounts of caffeine (≤5–6 mg kg⁻¹ bw day⁻¹ spread throughout the day) will be unlikely to develop reproductive problems.

The effects of caffeine on the outcome of pregnancy appear biologically plausible. Published data suggest that the human foetus and neonate may be exposed to substantial amounts of caffeine or its metabolites, as caffeine ingested by the mother is rapidly absorbed from the gastrointestinal tract, readily crosses the placenta and is distributed to all foetal tissues, including the central nervous system. Caffeine is also excreted in mother's milk. In addition, exposure of the foetus and newborn to caffeine is enhanced due to
Effects of caffeine on human health

Effects on conception and female fertility

Caffeine consumption is one of many factors implicated in the reduction of fecundity, or the capacity to reproduce. There are several plausible biological mechanisms by which caffeine could delay conception. Caffeine consumption has been associated with alteration of hormone levels (e.g. oestradiol), with tubal disease or endometriosis, with altered tubal transport time, and with reduced viability of the fertilized ovum (Alderete et al. 1995). Caffeine metabolism varies during the menstrual cycle, with reduced clearance during the luteal phase, resulting in greater accumulation during the period of implantation and early embryonic development. Caffeine consumption may lead to pregnancy loss, which might result in prolongation of the waiting time required to achieve a clinically recognized pregnancy (Stanton and Gray 1995).

Thirteen epidemiological studies (retrospective and prospective data collection) investigating the relationship between coffee/caffeine consumption and time to conception (fecundability) present conflicting results. Five studies reported no delay in conception in women who consumed up to \( \geq 700 \text{mg caffeine day}^{-1} \) before pregnancy. In a multicentre study conducted in the USA and Canada, caffeine consumption was not associated with decreased fertility in a group of 2817 women whose caffeine consumption from all sources ranged from 100 to \( \geq 240 \text{mg day}^{-1} \) (Joesoef et al. 1990). Results of a study by Olsen (1991) showed no association between subfecundity and consumption of coffee or tea at any dose level (none to eight cups per day) among non-smoking women. Florack et al. (1994) showed that participants (male and female partners) with caffeine intake of 400–700 mg day\(^{-1} \) had a higher fecundability than those with a lower intake level; only heavy caffeine intake (\( >700 \text{mg day}^{-1} \)) among partners was negatively related to fecundability when compared with the lowest intake level (\( <300 \text{mg day}^{-1} \)). Caan et al. (1998) found no association between caffeine intake at a mean dose level of about 90 mg day\(^{-1} \) and a reduction in fertility of women trying to conceive for at least 3 months. Alderete et al. (1995) examined the independent and combined effects of smoking and coffee consumption on time to conception in 1341 primigravid women and found that women who consumed more than three cups of coffee per day (\( >300 \text{mg caffeine day}^{-1} \)) but did not smoke showed no decrease in fertility when compared with non-coffee-drinking women (adjusted odds ratio [OR] = 1.0–1.2) who did not smoke.

Results from two studies showed a significant decrease in monthly probability of pregnancy among women who consumed the equivalent of three or more cups of coffee per day (\( \geq 300 \text{mg caffeine day}^{-1} \)). In a retrospective study of 2465 women, Stanton and Gray (1995) found that the adjusted OR of delayed conception for \( >1 \) year was not increased among women who consumed \( \leq 300 \text{mg caffeine day}^{-1} \), but the OR was 2.65 (95% confidence interval [CI] = 1.38–5.07) among non-smokers who consumed \( \geq 301 \text{mg caffeine day}^{-1} \). In this study, no effect of high caffeine consumption was observed among women who smoked. In a study of 430 Danish couples planning their first pregnancy, Jensen et al. (1998) found that compared with non-smoking couples with caffeine intake <300 mg day\(^{-1} \), non-smoking females and males who consumed 300–700 mg caffeine day\(^{-1} \) had fecundability ORs of 0.88 and 0.87 (95% CI = 0.60–1.31 and 0.62–1.22), respectively, whereas females and males with a higher caffeine intake (\( >700 \text{mg day}^{-1} \)) had ORs of 0.63 and 0.56 (95% CI = 0.25–1.60 and 0.31–0.89), respectively. No dose–response relationship was found among smokers. Smoking women whose only source of caffeine was coffee (\( >300 \text{mg day}^{-1} \)) had a reduced fecundability OR = 0.34 (95% CI = 0.12–0.98), and non-smoking women with a caffeine intake of \( >300 \text{mg day}^{-1} \) from other sources had a low, but non-significant, OR = 0.43 (95% CI = 0.16–1.13) compared with non-smoking women consuming \( <300 \text{mg caffeine day}^{-1} \). The authors concluded that the results indicated a possible association between male and female caffeine intake and decreased fecundability only among non-smokers.

Another four studies reported delayed conception in women who consumed \( \geq 400, \geq 500, \text{or } \geq 800 \text{mg caffeine day}^{-1} \). Data collected by Christiason et al. (1989) showed a dose-related effect of coffee consumption on reported difficulties in becoming pregnant. Women who were heavy coffee drinkers before pregnancy (four to seven or more cups of coffee per day) experienced almost double the time in becoming
pregnant compared with women who consumed none or one cup of coffee per day. Williams et al. (1990) examined data from a large cross-sectional study on 3010 postpartum women, finding that times to conception for women who consumed three, two, one or no cups of coffee per day were similar (ranging from 4.8 to 5.0 months), whereas time to conception was longer (6.6 months) for the 129 women who consumed four or more cups of coffee per day (approximately 400 mg caffeine day⁻¹). In a retrospective study by Bolumar et al. (1997), a significantly increased OR (1.45, 95% CI = 1.03–2.04) for subfecundity in the first pregnancy was observed among women consuming >500 mg caffeine day⁻¹. Women in this highest level of consumption had an increase of 11% in the time leading to the first pregnancy. The effect of drinking >500 mg caffeine day⁻¹ was relatively stronger in smokers [OR = 1.56, 95% CI = 0.92–2.63] than in non-smokers [OR = 1.38, 95% CI = 0.85–2.23]. In Olsen (1991), a statistically significant association was observed (OR = 1.35, 95% CI = 1.02–1.48) for a delay of ≥1 year in women who smoked and also consumed at least eight cups of coffee per day (or an equivalent amount of caffeine from 16 cups of tea).

Three studies found modest positive associations with delayed conception from maternal consumption of more than one caffeinated beverage per day. A prospective study by Wilcox et al. (1988) showed that women who consumed more than one cup of coffee per day (126 mg caffeine day⁻¹) were half as likely to conceive during a given menstrual cycle. In a cross-sectional study, Hatch and Bracken (1993) found that intake of caffeine from coffee, tea and caffeinated soft drinks was associated with an increased risk of a delay of conception of ≥1 year. Compared with no caffeine use, consumption of 1–150 mg caffeine day⁻¹ resulted in an OR for delayed conception of 1.39 (95% CI = 0.90–2.13), consumption of 151–300 mg day⁻¹ was associated with an OR = 1.88 (95% CI = 1.13–3.11), and consumption of >300 mg day⁻¹ resulted in an OR = 2.24 (95% CI = 1.06–4.73). Women who reported drinking >300 mg caffeine day⁻¹ had a 27% lower chance of conceiving for each cycle, and those who reported drinking <300 mg day⁻¹ had a 10% reduction in conception rates per cycle compared with women who consumed no caffeine. Hakim et al. (1998) examined the effects of caffeine consumption on conception in a prospective study of 124 women, finding that the consumption of the equivalent of more than one cup of coffee per day among the sample of women who neither smoked nor drank alcohol was associated with a decreased risk of conception (18.0%, adjusted OR = 0.56, 95% CI = 0.23–1.33), which did not reach statistical significance.

In one of the above-described studies, delayed conception was observed among non-smoking women who consumed >300 mg caffeine day⁻¹, but not among women who smoked (Stanton and Gray 1995). Also, Jensen et al. (1998) found no dose–response relationship among smokers at caffeine doses of up to ≥700 mg day⁻¹, whereas non-smoking males and females who consumed 300–700 mg day⁻¹ exhibited decreased fecundability compared with non-smoking couples with caffeine intake of <300 mg day⁻¹. However, in Olsen (1991), no association was found among non-smokers at any dose level of caffeine, just for women who smoked and also consumed at least eight cups of coffee per day. Bolumar et al. (1997) also found that the effect of drinking >500 mg caffeine day⁻¹ was relatively stronger in smokers than in non-smokers. An interaction between caffeine and smoking is biologically plausible. Reports in the literature have shown that cigarette smoking significantly increases the rate of caffeine metabolism (see Pharmacokinetics). The enhanced caffeine metabolism in smokers also accelerates caffeine clearance and, as a result, reduces the duration and magnitude of the exposure.

Most epidemiological studies reviewed here were affected by methodological issues, including inadequate measurement of caffeine intake, failure to distinguish among different types of preparation and different strengths of coffee, inadequate control for possible confounding effects, recall bias in retrospective studies, lack of data on frequency of unprotected intercourse, and, in some studies, inadequate sample size. Despite these limitations, epidemiological studies are an important source of information on potential adverse effects of caffeine on fertility (delayed conception) in humans.

The evaluated epidemiological studies generally indicate that consumption of caffeine at dose levels of >300 mg day⁻¹ may reduce fecundability in fertile women.

Effects on sperm and male fertility

Although ingested caffeine is capable of crossing the blood–testis barrier, caffeine consumption as a factor
that could alter male reproductive function has not been investigated extensively. Data from *in vitro* studies suggest that caffeine has variable, dose-related effects on human sperm motility, number and structure (Dlugosz and Bracken 1992). It has been reported that women undergoing artificial insemination were twice as likely to become pregnant if their husbands’ semen had been treated with caffeine than if it had not. Scanning electron microscopic examination of fresh semen showed no morphological changes caused by *in vitro* treatment with caffeine (IARC 1991b, Dlugosz and Bracken 1992).

In an investigation of semen quality and its association with coffee drinking, cigarette smoking and alcohol consumption in 445 men attending an infertility clinic, coffee drinking was correlated with increases in sperm density and percentage of abnormal forms, but not in a dose-dependent manner. Men who drank one to two cups of coffee per day had increased sperm motility and density compared with subjects who drank no coffee. However, men who drank more than two cups per day had decreased sperm motility and density. The combination of drinking more than four cups of coffee per day (>400 mg caffeine day\(^{-1}\)) and smoking >20 cigarettes per day diminished spermatozoan motility and increased the percentage of dead spermatozoa. No alteration in the fertility of individuals who consumed these substances was observed (Marshburn et al. 1989, IARC 1991b, Dlugosz and Bracken 1992).

Jensen *et al.* (1998) found no association between caffeine intake and semen quality in men exposed to caffeine for an extended period at dose levels as high as \( \geq 700 \text{ mg day}^{-1} \).

Based on the limited data, it is concluded that caffeine consumption at dose levels of \( >400 \text{ mg day}^{-1} \) may decrease sperm motility and/or increase the percentage of dead spermatozoa (only in heavy smokers), but will be unlikely to adversely affect male fertility in general.

**Spontaneous abortion (miscarriage)**

The influence of caffeine on the risk of spontaneous abortion in humans is difficult to assess. A number of studies have been conducted that show either a positive effect or a lack of effect of caffeine on this pregnancy outcome. Shortcomings in the literature include small sample size and inadequate adjustment for potential confounders. A major potential confounder is the presence of nausea in the first trimester of pregnancy, as a lack of nausea early in pregnancy has been associated with a significantly increased risk of miscarriage (Stein and Susser 1991). Nausea in pregnancy may cause a reduction in the consumption of coffee/caffeine, while a lack of nausea may lead to continued ingestion. This may result in an erroneous association of caffeine intake with increased risk of spontaneous abortion. Another drawback is the general lack of accurate measurement of actual caffeine consumption by the participants in the epidemiological studies. Stavric *et al.* (1988), for example, found a marked variation in caffeine content of coffee and tea depending on the method of preparation and brand, and errors also arise from differences in the size of the serving ‘cup’ used by different participants. Another serious limitation is the potential for poor identification of foetal loss due to enrolment of women later in the pregnancy or only those who presented to hospitals, as many early foetal losses go unnoticed by women. Studies measuring human chorionic gonadotrophin levels, such as those of Wilcox *et al.* (1990), Mills *et al.* (1993) and Hakim *et al.* (1993), should reduce any bias in this factor. In addition, the majority of the studies showing positive associations between caffeine and spontaneous abortion are retrospective in nature, and at least one study depended on information recalled after several pregnancies (Armstrong *et al.* 1992).

Most of the studies have shown no association between a caffeine intake of \(<300 \text{ mg day}^{-1}\) and an increased risk of spontaneous abortion (Watkinson and Fried 1985, Wilcox *et al.* 1990, Armstrong *et al.* 1992, Mills *et al.* 1993, Dlugosz *et al.* 1996, Wen *et al.* 2001). In the one study that accurately assessed caffeine intake (the prospective study by Watkinson and Fried 1985), 284 mothers were interviewed about their caffeine intake from coffee, tea, caffeinated soft drinks, chocolate bars, chocolate drinks and caffeine-containing medicines 3 years before pregnancy, during each trimester of pregnancy and the year after pregnancy. Caffeine consumption was measured and categorized into \(<100, 100–300 \text{ and } >300 \text{ mg day}^{-1}\). There was no association between caffeine consumption and risk of miscarriage. In this study, there was a long period for which the women had to recall their caffeine consumption, so all recalled intakes may not have been accurate. Another study that found no association between caffeine consumption at levels of \( \geq 300 \text{ mg day}^{-1} \) and an increase in spontaneous
abortion was the prospective study by Mills et al. (1993).

The meta-analysis conducted by Fernandes et al. (1998), using data from six original epidemiological studies (including 42,988 pregnancies), showed a positive association (small but statistically significant) of spontaneous abortion with the consumption of >150 mg caffeine day\(^{-1}\) (OR = 1.36, 95% CI = 1.29–1.45). No other more definitive consumption categories were used in this study, and adjusting for confounders was not possible. The authors described the increased risk as small and noted that 'a possible contribution to these results of maternal age, smoking, ethanol use or other confounders could not be excluded'.

Srisuphan and Bracken (1986) conducted a prospective cohort study with 3135 pregnant women whose caffeine consumption was estimated from their reported consumption of coffee, tea, caffeinated soft drinks and caffeine-containing drugs. In terms of a crude association, the rate of spontaneous abortion was 1.8% for those who did not use caffeine (<1 mg day\(^{-1}\)), 1.8% for the light users (1–150 mg day\(^{-1}\)) and 3.1% for the moderate/heavy users (>150 mg day\(^{-1}\)). When exposure was divided into 50-mg increments, there was a 'marked increase' in the relative risk for spontaneous abortion at use levels of >150 mg day\(^{-1}\), but no dose–response was noted, as no further risk was associated with exposures >200 mg caffeine day\(^{-1}\). This study also pointed out that coffee consumption rather than caffeine consumption per se may have contributed to the risk of spontaneous abortion, as those who had a caffeine consumption from coffee alone had an increased crude relative risk compared with those consuming tea or caffeinated soft drinks alone, although the differences were not statistically significant. In this study, there was no more definitive categorization of intake >150 mg day\(^{-1}\).

Al-Ansary and Babay (1994) conducted a retrospective case-control study with 226 women in Saudi Arabia and found an increased risk of miscarriage with the consumption of >150 mg caffeine day\(^{-1}\) (OR = 1.0 [referent] and OR = 1.9 [95% CI = 1.2–3.0] for consumption of 1–150 and >150 mg day\(^{-1}\), respectively). No subclassification of intake >150 mg day\(^{-1}\) was conducted in this study, and it appears that no confounders were taken into consideration in the analysis. Only cases that had presented to a hospital were included, which may not give a complete picture of all possible miscarriages.

The retrospective case-control study by Infante-Rivard et al. (1993) is one of the better papers of those showing an association between lower levels of caffeine consumption and the risk of spontaneous abortion. In total, there were 331 cases and 993 controls. The investigators found significant increases in OR for the risk of foetal loss in high consumers of caffeine when it was ingested before and during pregnancy (>321 mg caffeine day\(^{-1}\) before pregnancy, OR = 1.85, 95% CI = 1.18–2.89; 163–321 and >321 mg caffeine day\(^{-1}\) during pregnancy, OR = 1.95, 95% CI = 1.29–2.93, and OR = 2.62, 95% CI = 1.38–5.01, respectively). For caffeine consumption before pregnancy, the OR increased by a factor of 1.10 for each 100 mg caffeine ingested per day. For consumption during pregnancy, the OR increased by a factor of 1.22 for each 100 mg ingested per day. The conclusion was that the incidence of spontaneous abortions was strongly associated with caffeine intake during pregnancy and moderately associated with caffeine use before pregnancy.

The majority of papers that showed an increased risk of spontaneous abortion with caffeine consumption showed associations at levels of >300 mg caffeine day\(^{-1}\). In a prospective cohort study by Dlugosz et al. (1996), for example, only the highest use of coffee and tea (three or more cups per day, about >300 mg caffeine day\(^{-1}\)) was associated with an increased risk of spontaneous abortions (OR = 2.63, 95% CI = 1.29–5.34, for coffee; OR = 2.33, 95% CI = 0.92–5.85, for tea). Armstrong et al. (1992), in a retrospective study of 35,848 pregnancies in Quebec, Canada, found the percentage of subjects with spontaneous abortions to be 20.4, 21.3, 24.1, 28.1 and 30.9% for persons consuming none, one to two, three to four, five to nine and 10 or more cups per day, respectively. The ORs in these consumption categories were 1.00 (referent), 0.98 (95% CI = 0.93–1.04), 1.02 (0.94–1.12), 1.17 (1.03–1.32) and 1.19 (0.97–1.45), respectively. In this paper, the time lag between the actual abortion and the interview may have introduced errors in recall about the amount of coffee consumed in previous pregnancies. Subjects in this paper were questioned about the incidence of spontaneous abortion and caffeine intake in all previous pregnancies.

Wen et al. (2001) studied the association between caffeine consumption and nausea and the risk of spontaneous abortion. The categories of caffeine consumption (based on periodic food frequency questionnaires) were: <20, 20–99, 100–299 and
$\geq 300 \text{ mg day}^{-1}$. Caffeine consumption was calculated for the periods before pregnancy, in the first trimester of pregnancy, and up to the date of any spontaneous abortion if it occurred before the end of the first trimester. The presence and duration of nausea were monitored. Potential confounders were analysed, including demographic factors, smoking and the consumption of alcohol. Parity and body mass index were also considered. None of these parameters caused any important confounding and, therefore, the data were left unadjusted for these factors. Overall, 7.2 versus 29.6% of the women who experienced any nausea or no nausea, respectively, had spontaneous abortions. In this study, no increased risk of spontaneous abortion was noted with any level of pre-pregnancy intake of caffeine. The data showed that the consumption of caffeine did not increase the risk of spontaneous abortion in women who were already at risk due to a lack of nausea or a reduced frequency/duration of nausea. However, in those women who had nausea in their first trimester and who were consequently at a reduced risk of spontaneous abortion, increased caffeine consumption during the first trimester was associated with abortion. The risk ratios and 95% CIs were: $<20 \text{ mg caffeine day}^{-1}$, 1.0 (reference category); 20–99 mg day$^{-1}$, 1.8 (0.8–3.9); 100–299 mg day$^{-1}$, 2.4 (0.9–6.2); and $\geq 300 \text{ mg day}^{-1}$, 5.4 (2.0–14.6). The risk of spontaneous abortion was elevated significantly with a consumption of caffeine $\geq 300 \text{ mg day}^{-1}$.

Klebanoff et al. (1999), using actual serum measurements of paraxanthine, a major caffeine metabolite, showed an increased risk of spontaneous abortion at an estimated 600–1100 mg caffeine day$^{-1}$. In this retrospective study of 591 women who had spontaneous abortions and 2558 matched controls, women with spontaneous abortions had significantly higher serum paraxanthine levels than the controls (752 and 583 ng ml$^{-1}$ in women having spontaneous abortions and controls, respectively). The increased risk of spontaneous abortions (OR = 1.9, 95% CI = 1.2–2.8) was noted only in those women with serum paraxanthine concentrations $> 1845$ ng ml$^{-1}$. The authors concluded that the daily intake of caffeine needed to reach 1845 ng paraxanthine/ml serum in a 60-kg woman would be about 600 mg for those who do not smoke and 1100 mg in those who smoke. This would correlate with about six and 11 cups of coffee per day, respectively.

Some studies have revealed the possibility that constituents in coffee or tea other than caffeine may be related to an increased risk of spontaneous abortion in women (Watkinson and Fried 1985, Srisuphan and Bracken 1986, Dlugosz et al. 1996). The one study that accurately measured caffeine consumption (Watkinson and Fried 1985) found no association between caffeine intake and spontaneous abortion, but did find a statistically significant larger proportion of coffee and tea drinkers in the group of women who had spontaneous abortions. Dlugosz et al. (1996) found that caffeinated soft drink use (up to three or more cans per day) did not increase the risk of spontaneous abortions. Tea and coffee (at consumption of up to three or more cups of either drink per day) produced similar risks, despite these products having differing caffeine contents.

Although much epidemiological work has been conducted, additional prospective studies that measure actual caffeine intake in the participants and that adjust for potential confounders such as nausea and vomiting during pregnancy would be beneficial. In the absence of these data, however, there appear to be reasonable grounds for limiting the consumption of caffeine to $<300 \text{ mg day}^{-1}$ in women who are, or who are planning to become, pregnant.

**Foetal growth**

The potential adverse impact of caffeine consumption during pregnancy on foetal growth has been a concern for many years. Caffeine increases the levels of cAMP through inhibition of phosphodiesterases, and the rise in cAMP might interfere with foetal cell growth and development (Karen 2000). Caffeine may also block specific adenosine receptors. As adenosine is involved in maintaining the balance between the availability and the use of tissue oxygen, blockade of its receptors could increase the susceptibility of the cell to hypoxia. Consumption of two cups of coffee has been reported to increase maternal epinephrine concentration and decrease intervillous placental blood flow (Fortier et al. 1993). As smoking is closely associated with caffeine consumption, it is important to stress that caffeine and smoking impose similar adverse physiological effects on foetal development (Fortier et al. 1993).

Results from epidemiological studies investigating the association between caffeine consumption and foetal growth have been conflicting. Of 18 original epidemiological studies, three indicate an association be-
tween either low birth weight (body weight <2500 g at birth) or intrauterine growth retardation (defined as birth weight <10th percentile of the sex-specific and gestation age-specific distribution of birth weight) and caffeine consumption <300 mg day\(^{-1}\). In a population-based study by Fortier et al. (1993), caffeine intake by 7025 women living in the Quebec City, Canada, area was not related to low birth weight but was associated with an increased risk of intrauterine growth retardation. For women whose average daily caffeine consumption was 0–10, 11–150, 151–300 or >300 mg, the adjusted ORs for delivering a newborn with growth retardation were 1.00, 1.28 (95% CI = 1.04–1.59), 1.42 (1.07–1.87) and 1.57 (1.05–2.33), respectively. In a Brazilian unmatched case-control study by Rondo et al. (1996), results showed that the proportion of mothers who delivered babies with intrauterine growth retardation increased as the average consumption of coffee increased during pregnancy. Compared with mothers whose babies' size was appropriate for gestation age, the ORs of mothers with babies with intrauterine growth retardation were 1.55 (95% CI = 0.99–2.44), 2.25 (1.34–3.78) and 2.07 (1.14–3.78) for caffeine consumption levels of approximately <140, 141–280 and ≥ 281 mg caffeine day\(^{-1}\), respectively, following adjustment for confounders such as cigarette smoking, alcohol intake and per capita income. Vlaicu et al. (1997), in an investigation of the effect of caffeine consumption during the third trimester on birth weight, found that birth weight decreased as caffeine consumption increased at levels ranging from 71 to ≥ 140 mg day\(^{-1}\) in non-smokers.

Five studies reported an increased risk for foetal growth retardation in infants whose mothers were exposed to caffeine at dose levels of ≥ 300 mg day\(^{-1}\) during pregnancy after adjustment for potential confounders, including cigarette smoking and alcohol consumption (especially binge drinking). In the prospective study by Watkinson and Fried (1985) in which data were collected on maternal use of tea, coffee, caffeinated soft drinks, chocolate bars, chocolate drinks and caffeinated medication, the most marked effects associated with heavy caffeine use (>300 mg day\(^{-1}\)) were reduced birth weight and small head circumference; the associations were still significant after adjustment for maternal nicotine use. The mean weight of babies born to 12 heavy users was 3158 compared with 3537 g for the remaining sample. The results suggest that daily caffeine intake of ≥ 300 mg can interfere with normal foetal growth. In a prospective study investigating the effects of caffeine consumption on intrauterine growth retardation, Martin and Bracken (1987) found that low birth weight was most common among offspring of women consuming ≥ 300 mg caffeine day\(^{-1}\), the rate being 7.3% compared with the unexposed group rate of 4.1%. Heavy caffeine intake (>300 mg day\(^{-1}\)) was associated with a 120-g reduction in birth weight compared with the untreated group. Moderate use of caffeine (151–300 mg day\(^{-1}\)) was also associated with a decrease in birth weight, but to a lesser extent. When a comparison was made with women who had no caffeine exposure, the relative risks (RR) of low birth weight after adjustment for confounding factors (maternal age, ethnicity, education, previous spontaneous abortions, previous stillbirth, weight gain, body mass index, smoking and alcohol intake) were 1.4 (95% CI = 0.70–3.00) for 1–150 mg caffeine day\(^{-1}\), 2.3 (1.1–5.2) for 151–300 mg, and 4.6 (2.0–10.5) for >300 mg. Beauchac-Bailargeon and Desrosiers (1987) found that birth weight was significantly less for women who consumed >300 mg caffeine day\(^{-1}\) and who smoked 15 or more cigarettes per day. In a case-control study by Caan and Goldhaber (1989), the data showed no increased risk of low birth weight with light to moderate consumption of caffeine (<300 mg day\(^{-1}\)) (adjusted OR = 0.90, 95% CI = 0.4–1.92) but a small but measurable increased risk with heavy consumption of caffeine (>300 mg day\(^{-1}\)) (adjusted OR = 2.94, 95% CI = 0.89–9.65). One limitation of this study was its small sample size (131 cases, 136 controls). Fenster et al. (1991b) found that heavy caffeine consumption of >300 mg day\(^{-1}\) significantly increased the risk for foetal growth retardation. The mean birth weights for no, light (1–150 mg day\(^{-1}\)), moderate (151–300 mg day\(^{-1}\)) and heavy (>300 mg day\(^{-1}\)) caffeine use were 3327, 3311, 3288 and 3170 g (reduction of 0, 0.5, 1.2 and 4.7%), respectively. Adjusted ORs for low birth weight for women consuming 1–150, 151–300 and 300 mg caffeine day\(^{-1}\) were 0.78 (95% CI = 0.45–1.35), 1.07 (0.51–2.21) and 2.05 (0.86–4.88), respectively.

Three studies reported a reduction in birth weight for infants born to mothers who consumed caffeine during gestation at 400, 500 or ≥ 800 mg caffeine day\(^{-1}\). Olsen et al. (1991), in a study of 11858 pregnant women in Denmark, found that maternal caffeine consumption of four or more cups per day (400 mg caffeine day\(^{-1}\)) was associated with a moderate decrease in birth weight. The adjusted OR for women consuming 400–700 mg caffeine day\(^{-1}\) was 1.4 (95% CI = 1.10–1.70); for those consuming ≥ 800 mg day\(^{-1}\),
the OR was 1.2 (0.90–1.80). No dose–response relationship was observed. One explanation for the results might be that individuals who drink many cups of coffee may tend to drink weaker coffee, and therefore the caffeine intake may have been overestimated in the group drinking more coffee. In this study, the women assigned to the control group consumed 0–300 mg caffeine day⁻¹. McDonald et al. (1992a), in a study of 40455 pregnancies in Montreal, Canada, found that coffee consumption at levels of 10 or more cups per day was associated with low birth weights and that consumption at levels of five to nine cups per day was associated with lower birth weight for gestational age, after adjusting for such confounders as maternal age, smoking and alcohol consumption. Adjusted ORs for low birth weight at one to two, three to four, five to nine and 10 or more cups per day were 1.05 (95% CI = 0.95–1.16), 1.08 (0.93–1.25), 1.13 (0.92–1.39) and 1.43 (1.02–2.02), respectively. For low birth weight for gestational age, the ORs at one to two, three to four, five to nine and 10 or more cups per day were 1.05 (95% CI = 0.94–1.16), 1.15 (0.99–1.34), 1.34 (1.10–1.65) and 1.39 (0.97–1.98), respectively, when compared with the controls (no coffee consumption). Although Larroque et al. (1993) found no clear relation between caffeine consumption and birth weight in different groups of maternal tobacco use, there was a decreasing trend in non-smokers; women who drank >800 mg caffeine day⁻¹ had infants weighing 187 g less than the infants of those who drank ≤ 400 mg day⁻¹, and this difference was at the limit of significance. In this study, non-users and users of <400 mg caffeine day⁻¹ were combined and used as the control group.

Seven studies reported no association of caffeine consumption with birth weight or foetal growth retardation at levels of 300 to > 400 mg day⁻¹ during pregnancy. In a study of 12205 women in the Boston area in the USA, Linn et al. (1982) found no relation between low birth weight and coffee consumption of up to four cups per day after controlling for confounders, including smoking and alcohol intake. The adjusted OR among heavy coffee drinkers (four or more cups per day) was 1.19 (95% CI = 0.86–1.65). These negative results suggest that coffee consumption had a minimal effect, if any, on birth weight under the conditions of this study. Brooke et al. (1989) found no significant effects of caffeine consumption on birth weight in 1513 women in England after controlling for smoking with caffeine intakes of 0, 1–200, 201–400 and ≥ 401 mg day⁻¹. Barr and Streissguth (1991) reported no undesirable changes in birth weight, length or head circumference for infants born to mothers exposed to caffeine at doses up to 750 mg day⁻¹ during the entire pregnancy. Godel et al. (1992) found no association between caffeine ingestion (>300 mg day⁻¹) and birth weight, length or head circumference in the babies of 162 women in northern Canada when the data were adjusted for smoking and alcohol intake. Mills et al. (1993), in a prospective study of 423 women in the USA, found that moderate caffeine consumption (≤ 300 mg day⁻¹) was not associated with a reduction in early foetal growth. Although heavy caffeine consumption (>300 mg day⁻¹) appeared to have a negative effect on intrauterine growth and head circumference, the negative effect was no longer significant after adjusting for other risk factors, notably smoking and maternal age. In a prospective study by Shu et al. (1995), caffeine consumption at dose levels up to 300 mg day⁻¹ (three cups of coffee per day) showed no relation to foetal growth. Although heavy caffeine consumption (>300 mg day⁻¹) in the first or second trimester was related to a reduction of crude mean birth weight (93 g for the first trimester, 141 g for the second trimester), the study reported no decrease in foetal growth in any trimester when the data were adjusted for parity, pre-pregnancy weight, income, smoking and nausea. A matched case-control study by Santos et al. (1998) found no association between caffeine consumption at an average dose level of approximately 150 mg day⁻¹ and increased risk of low birth weight or intrauterine growth retardation.

The interaction of caffeine consumption and smoking and their association with low birth weight were also reported. Several studies have found a marked positive correlation between smoking and caffeine intake, including Godel et al. (1992), Fortier et al. (1993), and Vlajinac et al. (1997). Beaulac-Baillargeon and Desrosiers (1987) found that birth weight was not statistically different with a caffeine consumption of >300 mg day⁻¹ for non-smokers and women who smoked one to 14 cigarettes per day, but the birth weight of babies of women who consumed ≥ 300 mg caffeine day⁻¹ and smoked 15 or more cigarettes per day was significantly lighter (206 g less) than that of babies whose mothers consumed less caffeine. Contradictory results were found by Vlajinac et al. (1997): that caffeine intake had an effect only in non-smokers. Among non-smokers, women whose daily caffeine intake was 71–140 mg day⁻¹ had infants weighing 116 g less than the infants of women whose caffeine consumption was 0–10 mg day⁻¹. For
those whose caffeine intake was $\geq 140$ mg day$^{-1}$, the decrease in birth weight was 153 g. The authors suggested that the effect of smoking is more powerful than that of caffeine, so that caffeine intake does not produce any noticeable effect in women who smoke.

It is difficult to establish the cause of the inconsistencies in the results of studies investigating the association between caffeine consumption and foetal growth. They may have resulted from recall bias, particularly in retrospective studies, incomplete information on amounts and sources of caffeine consumption, misclassification of caffeine exposure, inadequate control for confounders or simply unknown study bias. In two studies (Olsen et al. 1991, Larroque et al. 1993), investigators combined non-users and users (consuming $<400$ mg caffeine day$^{-1}$ in Larroque et al. 1993) and used them as the control group. If, for example, exposure to caffeine at dose levels $<400$ mg day$^{-1}$ is associated with reduced birth weight, then comparing this control group with heavier users may obscure any positive association. Despite inconsistencies in the results, the persistent association between caffeine consumption during pregnancy and low birth weight observed in eight original studies strongly suggests that caffeine may adversely affect foetal growth. This conclusion is supported by a meta-analysis study incorporating seven original studies and involving a total of 64,268 pregnancies, which reported a statistically significant increase in the risk for low birth weight babies in pregnant women consuming $>50$ mg caffeine day$^{-1}$ (Fernandes et al. 1998). It should be indicated that due to the nature of data presentation in individual studies used in meta-analysis, the authors were unable to adjust for potential confounders (maternal age, smoking, alcohol intake or other confounders) that may have contributed to the final result.

Based on the above evaluated data, despite inconsistencies in the results, it is concluded that caffeine consumption during pregnancy at dose levels of $\geq 300$ mg day$^{-1}$ may interfere with foetal growth (decrease in birth weight or intrauterine growth retardation), particularly in smokers or heavy alcohol drinkers.

**Preterm delivery**

Relatively few epidemiological studies are available that address an association between caffeine consumption and preterm delivery. Nine of 11 studies reviewed showed that caffeine consumption at dose levels up to $\geq 300$ mg day$^{-1}$ was not an important risk factor for preterm delivery (Linn et al. 1982, Watkinson and Fried 1985, Fenster et al. 1991b, Olsen et al. 1991, McDonald et al. 1992a, Fortier et al. 1993, Mills et al. 1993, Pastore and Savitz 1995, Santos et al. 1998). In the case-control study performed by Pastore and Savitz (1995) to investigate the association between caffeinated beverage consumption and preterm delivery in women from North Carolina, USA, consumption at the 1–150 mg caffeine day$^{-1}$ level was associated with a moderately increased risk of preterm delivery, although there was no association between high levels of caffeine consumption and preterm delivery. The lack of a dose–response relationship strongly suggests that there is no association between caffeine consumption at dose levels as high as $\geq 400$ mg day$^{-1}$ and preterm delivery.

Only two studies (Berkowitz et al. 1982, Williams et al. 1992) suggested a possible relation between caffeine consumption ($\geq 300$ mg day$^{-1}$) and preterm delivery. Although Berkowitz et al. (1982) observed no association between coffee consumption (four or more cups per day) and preterm delivery in their case-control retrospective study, tea drinking, especially four or more cups per day in the first trimester, resulted in a slightly increased risk of preterm delivery (OR = 2.0, 95% CI = 1.0–4.0). The authors postulated that some other component of tea, if consumed in sufficient amounts, may have an adverse effect on gestation age. In Williams et al. (1992), women who consumed three or more cups of coffee per day during the first trimester had a 2.2-fold increase in risk of preterm premature rupture of the membranes compared with women who consumed two or fewer cups of coffee per day (OR = 2.2, 95% CI = 1.5–3.5). When only coffee drinkers were examined, there appeared to be a linear trend in the risk of preterm premature rupture of the membranes as coffee consumption increased. Maternal coffee consumption had relatively little relation to the risk of spontaneous preterm labour not complicated by premature rupture of the membranes. Women who drank three or more cups of coffee per day experienced a 1.4-fold increase in the risk of spontaneous preterm labour not complicated by premature rupture of the membranes compared with women who drank two or fewer cups of coffee per day (adjusted OR = 1.4, 95% CI = 1.0–1.9). It should be pointed out that low socio-economic status, history of adverse pregnancy outcome and antepar-
tum haemorrhaging have been reported consistently as risk factors of preterm delivery (Williams et al. 1992). Other factors, such as young and advanced maternal age, low maternal weight before pregnancy, and smoking during pregnancy, may also influence pregnancy outcome.

Based on the above evaluated data, it is concluded that caffeine consumption during pregnancy at dose levels of $\leq 300 \text{ mg day}^{-1}$ is unlikely to have an adverse effect on the length of gestation (preterm delivery).

**Congenital malformations**

The limited available epidemiological data show no increase in the incidence of congenital morphological malformations in infants born to mothers who consumed three to 10 or more cups of coffee per day (300–1000 mg caffeine day$^{-1}$) during the entire pregnancy.

Rosenberg et al. (1982) examined the association between drinking caffeine-containing beverages and five malformations (inguinal hernia, oral clefts, cardiac defects, pyloric stenosis, neural tube defects) in a case-control study of 2030 children in Canada and the USA. No association was found between coffee consumption at levels up to $\geq 400 \text{ mg caffeine day}^{-1}$ and any of the malformations investigated. In a case-control study of 706 children with birth defects in Finland (central nervous system defects, orofacial clefts, musculoskeletal defects, cardiovascular malformations), coffee consumption (up to 1000 mg caffeine day$^{-1}$) showed no significant association with malformations observed under the conditions of the study (Kurppa et al. 1983). Linn et al. (1982) reported no consistent association between coffee consumption (up to four or more cups per day) and the occurrence of malformations in a retrospective study of 12,205 women in the Boston area in the USA. Similarly, Olsen et al. (1991) found no association between coffee or tea consumption up to four or more cups per day and the occurrence of malformations in a Danish study.

Narod et al. (1991) reviewed the results from many epidemiological studies investigating potential teratogenic effects of caffeine and found that available data do not implicate coffee and/or caffeine as a likely human teratogen in the classical sense (development of morphological malformations), even at dose levels up to eight cups of coffee per day.

In one positive study, McDonald et al. (1992b) analysed the association of coffee consumption with congenital defects for 80,319 pregnancies in Montreal, Canada. A significant increase in the incidence of heart defects (RR = 1.52, 95% CI = 1.1–2.2) was observed among the children of women who drank three or more cups of coffee per day. However, no specific type of heart defect was over-represented in this group when compared with defects in babies born to women who did not drink coffee.

There is therefore little evidence to support the hypothesis that moderate consumption of caffeine during pregnancy can present a teratogenic (morphological malformations) risk in humans. It should, however, be noted that available data from reviewed literature show that caffeine can be teratogenic in animals when ingested at very high dose levels ($\geq 80 \text{ mg kg}^{-1} \text{ bw day}^{-1}$) in comparison with the range of typical human intakes (e.g. Collins et al. 1981, James 1991a, Purves and Sullivan 1993).

**Postnatal development**

The foetus is exposed to caffeine ingested by the pregnant mother, since caffeine is rapidly absorbed from the gastrointestinal tract, readily crosses the placenta, and is distributed to all foetal tissues. In addition, exposure of the foetus to caffeine is enhanced because caffeine’s half-life is markedly increased in the foetus and pregnant women in comparison with non-pregnant adults and older children (Dalvi 1986, Dlugosz and Bracken 1992, Eskenazi 1993). Because of the rapid growth that occurs during the late prenatal period, the impact of chronic caffeine exposure may be far greater than at any other time of life.

In a cohort study of 453 infants, caffeine ingested during pregnancy at dose levels up to 444 mg day$^{-1}$ did not adversely affect infant size at 8 months of age (Barr et al. 1984). A prospective study of 123 infants from three hospitals in Ottawa, Canada, showed that caffeine consumption at doses of $\geq 300 \text{ mg day}^{-1}$ had no adverse effects on postnatal growth at 12 and 24 months of age following adjustment for relevant confounders (Fried and O’Connell 1987). Barr and Streissguth (1991) investigated the effects of prenatal caffeine exposure on postnatal development from.
birth to 7 years of age and found that long-term prenatal exposure (during the entire pregnancy) to caffeine at dose levels ranging from 174 to 740 mg day$^{-1}$ had no adverse effects on the physical and/or behavioural development (e.g. orientation, reactivity, IQ, fine and gross motor skills) of children during the first 7 years of life.

Toubas et al. (1986) demonstrated that maternal exposure to caffeine (350 ± 370 mg day$^{-1}$, non-smokers, 185 cases) during gestation resulted in an increased incidence of central and obstructive infantile apnoea (cessation of breathing). The incidence of these symptoms was greater in infants born to mothers who smoked (85 cases) and consumed caffeine at dose levels of 610 ± 517 mg day$^{-1}$.

Two studies assessed the association between caffeine consumption and the risk of sudden infant death syndrome (SIDS). In Ford et al. (1998), heavy consumption of caffeine (≥ 400 mg day$^{-1}$, equivalent to four or more cups of coffee per day) was associated with a significantly increased risk for SIDS after adjustment for likely confounders. Although the results of this study have been criticized (Leviton 1998) on the grounds that parental smoking was not properly assessed, the authors responded that supplementary analysis of the data supported their results. The second study (Alm et al. 1999) found no association between caffeine ingestion and increased risk of SIDS at dose levels up to 800 mg day$^{-1}$ during and after pregnancy after adjustment either for smoking or for maternal age, education, parity and smoking in the first trimester. Many factors have been identified that may increase the risk of SIDS including, low maternal age, high live birth order, foetal prone sleep position, maternal smoking during pregnancy and postnatal exposure to passive smoke (MacDorman et al. 1997, Oyen et al. 1997, L’Hoir et al. 1998). The two factors, maternal smoking during pregnancy and infant prone sleeping position, appeared to be the major risk factors in SIDS (Golding 1997, MacDorman et al. 1997, Brouillette 2001, Nelson and Taylor 2001, Paris et al. 2001). Based on the data presented, it is difficult to establish what risk, if any, intake of caffeine during pregnancy may play in SIDS.

Based on limited epidemiological data, it can be concluded that it is unlikely that moderate intake of caffeine (≤ 300 mg day$^{-1}$) by pregnant and nursing mothers would pose adverse effects on postnatal development.

Summary and conclusions

Caffeine is widely consumed at different levels by most segments of the population. Both the public and the scientific community have expressed concern about the potential for caffeine to produce adverse effects on human health. The possibility that caffeine ingestion adversely affects human health was investigated based on reviews of published (primarily) human studies obtained through a comprehensive literature search. The following potential adverse effects of caffeine on human health were investigated: general toxicity, cardiovascular effects, effects on calcium balance and bone status, behavioural effects in adults and children, carcinogenic potential, genotoxic potential, and reproductive effects, including pre- and postnatal development. It should be pointed out that review of some of the epidemiological studies was complicated by one or more methodological issues, such as inadequate measurement of caffeine intake; a lack of consideration of all sources of caffeine intake; a lack of consideration of caffeine intake before study; the lack of distinction made between different types of preparation and different strengths of coffee in most studies; inadequate control for the possible confounding effects of variables such as smoking, alcohol consumption, age, nutrition and lifestyle factors in some studies; the low response rates in several studies; biased selection of adequate controls because of self-selection into groups of drinkers and non-drinkers of coffee; recall bias in retrospective studies; and insufficient statistical power in some of the studies. Despite these issues, the majority of the reviewed studies provided important and useful data with which to assess the potential effects of caffeine on human health.

Based on the data reviewed, it can be concluded that there is ample evidence indicating that for the general population of healthy adults, moderate caffeine intake at a dose level of 400 mg day$^{-1}$ is not associated with adverse effects such as general toxicity, cardiovascular effects, changes in adult behaviour, increased incidence of cancer and effects on male fertility. Nor are moderate intakes of caffeine associated with adverse effects on bone status and/or calcium balance if adequate intakes of calcium are being consumed. Data have also shown that reproductive-aged women can be defined as an 'at risk' group who may require specific advice on moderating their caffeine intake. It is therefore recommended that caffeine intake for women who plan to become pregnant and for women
Effects of caffeine on human health

during gestation should not exceed 300 mg day\(^{-1}\), equivalent to 4.6 mg kg\(^{-1}\) bw day\(^{-1}\) in a 65-kg person.

Children are another at-risk population identified in the literature. While data are lacking on adolescent children, some studies exist for pre-adolescents. Although this literature has its shortcomings, findings of altered behavior, including anxiety, are noted in a variety of studies using caffeine in children. The existing literature is difficult to compare due to differing methodologies as well as inadequacies in methodology in some cases; however, effects have been noted down to the lowest level of administered caffeine used (effects on state anxiety, correlated with salivary caffeine levels at an intake of 2.5 mg kg\(^{-1}\) bw, in Bernstein et al. 1994). The body of evidence, in totality, suggests that caffeine can elicit behavioral effects in children. Owing to these findings, as well as the fact that the nervous system in children is continually developing and the lack of available information on the longer-term effects of caffeine in this population, a cautious approach is warranted. It is judged that in the absence of more robust data associated with low levels of administered caffeine, an upper intake of 2.5 mg kg\(^{-1}\) bw day\(^{-1}\) is an amount on which to base risk assessments of caffeine consumption in children.

Acknowledgements

The authors gratefully acknowledge the assistance of Dr Sheila Dubois for statistical analysis, Elizabeth Vavasour for critical comments, Betty Anne Morrison for clerical assistance and Marla Sheffer for editorial assistance.

References


Effects of caffeine on human health


MACKLIN, A.W., and SZOTT, R.J., 1980, Eighteen month oral study of aspirin, phenacetin and caffeine in C57BL/6 mice. Drug and Chemical Toxicology, 3, 135–163.


MYERS, M. G., 1988, Effects of caffeine on blood pressure. Archives of Internal Medicine, 148, 1189–1193.


ROSENBERG, L., MITCHELL, A. A., SHAPIRO, S., and SŁONE, D., 1982, Selected birth defects in relation to caffeine-containing


July 22, 2013

Dr. Lynn R. Goldman, M.D., MPH, Dean,
School of Public Health and Health Services
The George Washington University
Suite 500
2175 K Street, NW
Washington, DC 20037

Re: IOM Caffeine Workshop

Dear Dr. Goldman:

I am writing on behalf of the American Beverage Association in connection with the IOM Workshop on Caffeine for which you chair the planning committee.

I write first to point out that the absence of a published agenda for the Workshop, which is scheduled to occur a little over two weeks from now, is directly impeding the ability of interested stakeholders to prepare for the Workshop. Continued delay in disclosing the agenda will only continue to exacerbate that problem.

Second, although I have been informed by the study director, Dr. Yaktine, that IOM will accept submission of materials from stakeholders up to the commencement of the Workshop, there is no clear indication of that on the Workshop website (unlike other IOM workshops), nor a ready means to submit those materials. It is also not clear what IOM intends to do with submitted materials. These issues should be corrected forthwith.

Finally, the delay in making an agenda available and the absence of a clear mechanism for the submission of materials creates concern that public participation in the Workshop is not desired by IOM and will be constrained. ABA sincerely hopes that is not the case and requests that there be a reasonable period of time for public participation during each session of the Workshop so that comments and input from the public can be received while a topic or issue is being discussed.
On behalf of the ABA, I appreciate your prompt consideration of these concerns.

Sincerely yours,

[Signature]

Stuart M. Pape
Counsel to the American Beverage Association

SMP:ro

cc: Ann Yaktine
This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier’s archiving and manuscript policies are encouraged to visit:

http://www.elsevier.com/copyright
A review of the epidemiologic evidence concerning the reproductive health effects of caffeine consumption: A 2000–2009 update

Jennifer David Peck, Alan Leviton, Linda D. Cowan

Article history:
Received 22 December 2009
Accepted 10 June 2010

Keywords:
Caffeine
Reproduction
Pregnancy outcomes
Spontaneous abortion
Fetal growth
Birth defects

ABSTRACT

This review of human studies of caffeine and reproductive health published between January 2000 and December 2009 serves to update the comprehensive review published by Leviton and Cowan (2002). The adverse reproductive outcomes addressed in this review include: (1) measures of subfecundity; (2) spontaneous abortion; (3) fetal death; (4) preterm birth; (5) congenital malformations; and (6) fetal growth restriction. Methodologic challenges and considerations relevant to investigations of each reproductive endpoint are summarized, followed by a brief critical review of each study. The evidence for an effect of caffeine on reproductive health and fetal development is limited by the inability to rule out plausible alternative explanations for the observed associations, namely confounding by pregnancy symptoms and smoking, and by exposure measurement error. Because of these limitations, the weight of evidence does not support a positive relationship between caffeine consumption and adverse reproductive or perinatal outcomes.

© 2010 Elsevier Ltd. All rights reserved.

Contents

1. Introduction
   1.1. Caffeine exposure assessment
   1.2. Pregnancy signal phenomenon
   1.3. Residual confounding by smoking
   1.4. Precision of results
2. Subfecundity
   2.1. Time to pregnancy studies
   2.2. Fecundability vs. Infertility
   2.3. Semen quality and timing of exposure assessment
   2.4. Selection bias in studies of semen quality
   2.5. Contribution of male exposures
   2.6. Review of individual studies of subfecundity
      2.6.1. Assisted reproductive technology (ART) outcomes
      2.6.2. Time to pregnancy studies
      2.6.3. Ovulatory infertility
      2.6.4. Sperm quality
3. Spontaneous abortion
   3.1. Missing early losses
   3.2. Role of abnormal karyotypes
   3.3. Pregnancy signal
   3.4. Proper control selection in case-control studies

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; CgA, chromogranin A; CYP1A2, cytochrome P450 1A2; CYP1B1, cytochrome P450 1B1; CYP2E1, cytochrome P450 2E1; GIFT, gamete intra-fallopian transfer; GST, glutathione S-transferase; HR, hazard ratio; IVF, in vitro fertilization; IUGR, intrauterine growth restriction; LMP, last menstrual period; OR, odds ratio; NAT2, N-acetylator type 2; RR, relative risk; SGA, small for gestational age.

* Corresponding author. Address: University of Oklahoma Health Sciences Center, 801 NE 13th St., Oklahoma City, OK 73104, USA. Tel.: +1 405 271 2229x48053; fax: +1 405 271 2068.
E-mail address: jennifer-peck@ouhsc.edu (J.D. Peck).

0278-6915/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.fct.2010.06.019
1. Introduction

This review of the literature on consumption of caffeine-containing products and reproductive health is an update of the comprehensive report previously published by Leviton and Cowan (2002). As such, this review is restricted to human studies of caffeine and reproductive health published in English between January 2000 and December 2009. The search strategy consisted of a Pubmed search using the keywords caffeine, coffee or paraxanthine in combination with the following terms: pregnancy, reproduction, fetal development, miscarriage, spontaneous abortion, pregnancy loss, fetal death, stillbirth, congenital malformations, birth defects, fetal growth, growth retardation, growth restriction, small for gestational age, low birth weight, low birth weight, IUGR, preterm, fertility, fecundity, time to pregnancy, sperm, semen, twins, twinning, multiple gestation, or multiple pregnancy. The references cited in all original studies and review papers identified were also examined to ensure completeness.

The reproductive outcomes addressed in this review are organized into six categories: (1) measures of subfecundity; (2) spontaneous abortion; (3) fetal death; (4) preterm birth; (5) congenital malformations; and (6) fetal growth. For each topic, we begin by summarizing study design considerations relevant to investigations of the specific reproductive endpoint. In keeping with the unique format of the previous summary, we then provide a detailed critical review of each study, identifying strengths as well as methodological limitations that may influence results and restrict inferences that can be drawn from individual studies. Individual studies are discussed by topic in chronological order. Table 1 lists the publications reviewed in this report by reproductive outcome evaluated. Two post-1999 publications (Chattingius et al., 2000; Grosso et al., 2001) were reviewed previously in Leviton and Cowan (2002) and, thus, are not summarized in this review.

We begin with a discussion of general methodological concerns that should be considered when reviewing studies of consumption of caffeine-containing products and reproductive health.

1.1. Caffeine exposure assessment

Total caffeine consumption is difficult to measure accurately. Caffeine exposure can occur from various sources including beverages (coffee, tea, soft drinks), chocolate, and some medications. Furthermore, the caffeine content of individual beverage servings varies considerably by method of preparation, product brand, and cup size (Bracken et al., 2002). The most common justification for assessing caffeine exposure from coffee alone or from coffee and...
tea is that coffee is the predominant source of caffeine exposure and fewer women report high doses from other beverages, foods or pharmaceuticals. Regardless of the population proportions consuming large quantities from other sources, consumption from all sources is important for accurate classification of total caffeine intake for individuals, since low to moderate intake from multiple sources can result in high cumulative caffeine exposure. Furthermore, because coffee also contains many chemicals other than caffeine, it is difficult to disentangle the potential effects of caffeine from those that may be attributed to other compounds.

Relying on coffee intake alone would likely result in underestimations of total caffeine exposure. The influence of this measurement error on observed associations would depend on whether use of caffeine from other sources was more, less or equally common among women experiencing the outcome under investigation. Exposure measurement error is commonly assumed to be similar among those with and without each reproductive disorder, resulting in an underestimation of any coffee/caffeine relationship with the reproductive adversity. This underestimation (biased toward the null) tends to be predictable only when the exposure is dichotomous and the association is independent of other errors (Greenland and Gustafson, 2006). Much of the caffeine literature assesses more than two categories of exposure and thus, misclassification of caffeine intake could produce a bias either toward or away from the null, depending on the nature of the errors.

Other critical aspects of caffeine exposure assessment include the importance of measuring exposures during the relevant

<table>
<thead>
<tr>
<th>Year</th>
<th>First author</th>
<th>Subfecundity/infertility</th>
<th>Spontaneous abortion</th>
<th>Fetal death</th>
<th>Gestational age/preterm birth</th>
<th>Congenital malformations</th>
<th>Fetal growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Natsume</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Torfs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Zusterzeel</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Grosso</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Signorello</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Wen</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Claussen</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Klebanoff</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Klonoff-Cohen</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Balat</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Bracken</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Giannelli</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Horak</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Orskou</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Rasch</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Tolstrup</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Tough</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Vik</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Wisborg</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Hassan</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Khoury</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Bech</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Parazzini</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Santos</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Sata</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Sobreiro</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Bech</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Chiaffarino</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Cole</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>George</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Grosso</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Karypidis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Matijasevich</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Tsoubouchi</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Bech</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Bille</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Browne</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Dieguez</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Infante-Rivard</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Maconochie</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Schmid</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>CARE Study Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Haugen</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Mikkelsen</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Mongraw-Chaflin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Ramblau-Hansen</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Savitz</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Slicers</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Weng</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Xue</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Chavarro</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Collier</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Johansen</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Killick</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Miller</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Schmidt</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
exposure time window and the need to capture changing intake patterns throughout pregnancy. Caffeine consumption tends to decrease during the early weeks of pregnancy, coinciding with increasing pregnancy symptoms and aversions (Gadsby et al., 1993; Cnattingius et al., 2000; Lawson et al., 2004). Retrospective reports of caffeine intake collected at a single time point as the average number of daily servings across a large time span such as the first trimester or entire pregnancy (typically converted to caffeine in mg/day) will not accurately characterize true exposure fluctuations. This type of measurement error is especially relevant when the critical window of exposure for selected outcomes occurs during the time interval when consumption patterns are changing in early gestation.

Although a few studies designed for the purpose of investigating caffeine exposure have implemented detailed improvements in exposure assessment, variations in caffeine exposure by source, portion size, brewing method, metabolism and fluctuations over the course of pregnancy continue to result in exposure misclassification. Furthermore, the comparison of findings across studies is difficult due to the use of different categories of caffeine intake and different reference groups.

Self-reported caffeine exposure is not only imprecise, it also fails to account for variability in rates of degradation. The measurement of caffeine metabolites in biologic fluids provides better information about biologic dose in part because it reflects individual differences in caffeine metabolism (Klebanoff et al., 1998c), but such methods are not without limitations. As the major metabolite of caffeine, serum paraxanthine has a short half-life, ranging from 2 to 5 h in early pregnancy to 10 h in late pregnancy (Aldridge et al., 1981). Thus, serum paraxanthine concentrations reflect recent exposures within the day immediately preceding specimen collection. Moreover, studies that incorporate caffeine biomarkers are typically limited to specimens collected at a single time point. Therefore, biomarker concentrations would accurately represent previous caffeine intake patterns only when consumption remains relatively constant over time. The problem with this assumption is that caffeine consumption is known to decrease throughout the first months of pregnancy (Lawson et al., 2004). Thus, biomarker concentrations may also be susceptible to exposure misclassification when a single measurement is intended to represent long-term or usual patterns of exposure during pregnancy.

The rate at which caffeine is cleared from the body may influence biologic dose and exposure interval. Caffeine metabolites might be more important than caffeine in producing a biologic effect. Caffeine clearance rates differ between individuals and are affected by pregnancy and genetics as well as environmental factors such as cigarette smoking, drugs and diet (Aldridge et al., 1981; Kalow and Tange, 1991; Carrillo and Benitez, 2000; Lampe et al., 2000). Variations in caffeine metabolism between individuals are mostly attributed to differences in cytochrome P450 1A2 (CYP1A2) enzyme activity (Arnaud, 1994). Assessments of CYP1A2 phenotypes and genotypes have been used to characterize study populations according to high or low metabolic activity. A comprehensive review of the metabolic considerations for caffeine exposure assessment during pregnancy was published by Grosso and Bracken (2005).

1.2. Pregnancy signal phenomenon

Pregnancy symptoms, including aversions to taste and smells, nausea, and vomiting are more common in healthy pregnancies that result in live births and occur less frequently among women whose pregnancies end in spontaneous abortions (Weigel and Weigel, 1989; Weigel et al., 2006). This relationship is attributed to a stronger pregnancy signal produced by higher concentrations of pregnancy hormones in viable pregnancies (Stein and Susser, 1991; Lawson et al., 2002). Caffeine consumption has been shown to decrease with increasing pregnancy signal symptoms during the early weeks of pregnancy (Lawson et al., 2004; Cnattingius et al., 2000). For example, Lawson et al. (2004) reported that mean onset of nausea, vomiting and appetite loss occurred between 5 and 6 weeks from the last menstrual period, accompanied by a 59% decrease in caffeine intake from coffee between weeks 4 and 6. Thus, women experiencing viable pregnancies are more likely to reduce their caffeine intake in response to the pregnancy signal than women who go on to have a spontaneous abortion. As a result, reduced caffeine consumption may be a consequence of pregnancy viability rather than increased consumption causing any reproductive adversity. “Reverse causation” is the term used to describe such errors in causal inference.

Control for confounding by pregnancy signal symptoms is critical for caffeine studies of spontaneous abortion and fetal death, and may have importance for studies of other adverse pregnancy outcomes. This task, however, is complicated by the difficulty of measuring pregnancy signal symptoms. Studies that include only dichotomous indicators for nausea and vomiting fail to capture the severity, frequency and duration of the symptoms. Furthermore, aversions to specific foods or beverages, which may be equally or more relevant to decreased caffeine consumption, are rarely assessed. Studies have revealed that women who decrease their coffee consumption during early pregnancy commonly attributed these changes to an acknowledged aversion to the taste, smell or thought of coffee (Lawson et al., 2004); whereas, nausea reported as number of hours per week was not statistically associated with reduced coffee consumption (Lawson et al., 2002). Thus, separate assessment of coffee aversion has been recommended for studies of caffeine and pregnancy outcomes (Lawson et al., 2002; Lawson and LeMasters, 2006). Efforts to disentangle this complex relationship will require improved, prospective measurement of all relevant dimensions of the pregnancy signal.

1.3. Residual confounding by smoking

Most investigators recognize the importance of controlling for confounding by smoking when evaluating the reproductive effects of caffeine. Smoking and caffeine use are strongly associated, as heavier smokers tend to consume more caffeine than others (Schreiber et al., 1988; Zavela et al., 1990). Furthermore, smoking is considered a risk factor for many adverse reproductive outcomes such as infertility, spontaneous abortion, fetal growth restriction, stillbirth, and preterm birth (Cnattingius, 2004). Controlling for self-reported smoking status, however, may not provide adequate control for confounding when smoking is measured inaccurately. The stigma of smoking during pregnancy may lead to inaccurate reporting of smoking status or under-reporting of the amount smoked per day (Ford et al., 1997; Klebanoff et al., 1998b; Lindqvist et al., 2002). Morrison (1984) described the potential for residual confounding to occur when the more socially acceptable behavior of caffeine consumption is more accurately reported than the less acceptable behavior of smoking tobacco. Because the two behaviors are highly correlated, the more accurately reported caffeine consumption conveys information about tobacco consumption. Furthermore, many investigators control only for smoking status (yes/no) without consideration of amount smoked. Thus, incomplete control for the effects of smoking may explain observed associations commonly attributed to caffeine use. Some authors have attempted to improve upon these measurements by incorporating cotinine measurements as biomarkers of nicotine exposure. It is important, however, to acknowledge that these biochemical markers reflect recent tobacco exposures and may or may not accurately control for actual smoking patterns during the relevant window of exposure.
1.4. Precision of results

Measures of association (e.g., odds ratios and relative risks) and confidence intervals are frequently reported to two decimal places when, in fact, study precision is rarely sufficient for this degree of detail to be meaningful. Thus all results discussed in this review are rounded to one decimal place.

2. Subfecundity

Studies assessing the impact of caffeine on fertility potential have evaluated a variety of outcomes including time to pregnancy, infertility, semen quality and selected endpoints of assisted reproductive technologies.

2.1. Time to pregnancy studies

Time to pregnancy studies identify determinants of fecundability, defined as the probability of conception within a non-concepting menstrual cycle (Baird et al., 1986). Each of the three studies that evaluated the relationship between caffeine/coffee exposure and time to conception, none of which were specifically designed to evaluate caffeine exposures, used a retrospective time to pregnancy design within a population of pregnant women (Hassan and Killick, 2004; Cole et al., 2006). The most prominent limitation of this pregnancy-based approach is that participation is restricted to those who have achieved a pregnancy (Tingen et al., 2004). Thus, sub-fecund couples are underrepresented, and sterile couples are excluded entirely. If exposure is associated with longer wait times or sterility, more highly exposed sub-fecund women would be excluded and associations would be underestimated (Spira, 1998; Joffe et al., 2005). Given the retrospective nature of the data collection, these studies are also vulnerable to recall errors for reports of exposure as well as recollected time to conception. Although recall of time to pregnancy has been demonstrated to be relatively accurate at the group level over several years (Joffe et al., 1993), women with longer time to pregnancies would have to recall their past exposures over a longer time period compared to women with shorter time to pregnancies. Thus, exposure reports may be influenced by the outcome of delayed conception. The retrospective time to pregnancy study design is also criticized for lack of ability to account for timing of intercourse, which may interfere with the ability to accurately identify cycles at risk of conception. Prospective time to pregnancy studies that collect data on ovulation and timing of intercourse as couples attempt to conceive are considered the best available, although not without some limitations, such as pregnancy planning bias, low participation rates and concerns regarding the generalizability of results from volunteer populations (Tingen et al., 2004).

2.2. Fecundability vs. Infertility

Infertility is defined as failure to conceive within 12 months. Few exposures would be anticipated to lead to all or nothing effects on fertility. Thus, a continuous measure of fecundability is more informative than a dichotomous indicator of infertility because it allows for detection of diminished fecundity (Savitz et al., 2002).

2.3. Semen quality and timing of exposure assessment

Semen characteristics, including volume, sperm concentration, motility, morphology, and markers of DNA damage in sperm, have been studied as indicators of male fertility potential. Caffeine studies evaluating semen quality have been mostly cross-sectional; thus, the timing of caffeine assessment does not coincide with the relevant window for spermatogenesis, which occurs over 74 days (Nussey and Whitehead, 2001). However, coffee consumption appears to be relatively stable in some populations (Barone and Roberts, 1996). Thus, caffeine consumption assessed at the time of semen collection might generally reflect exposure throughout spermatogenesis. Patterns of exposure preceding the window for spermatogenesis would be relevant if delayed or permanent effects on the spermatogenic cycle were suspected via the mechanism of stem cell disruption (Jensen et al., 2006).

2.4. Selection bias in studies of semen quality

Participation rates in studies of semen quality are typically low, leading to concerns of selection bias when study volunteers differ from those who refuse (Cohn et al., 2002). If men with fertility problems are more motivated to participate in semen studies and more likely to modify their caffeine intake or other behaviors in response to their concerns, the association between caffeine and semen quality would be distorted toward the null value due to overrepresentation of affected individuals with low exposure.

2.5. Contribution of male exposures

Two studies recognized the importance of including caffeine exposures of male partners when assessing fecundity endpoints beyond semen characteristics (Klonoff-Cohen et al., 2002; Cole et al., 2006). These studies evaluated male and female caffeine consumption separately or the combined monthly caffeine intake for the couple, but the joint effects of caffeine use in both partners has not been fully explored.

2.6. Review of individual studies of subfecundity

2.6.1. Assisted reproductive technology (ART) outcomes


This study evaluated the possible contribution of caffeine in both partners. This prospective cohort study was conducted among 221 couples undergoing in vitro fertilization (IVF) and gamete intra-fallopian transfer (GIFT) in Southern California between 1993 and 1998. Consumption of caffeine in caffeinated or decaffeinated coffee, tea, soft drinks, cocoa drinks and chocolate was assessed in relation to sperm characteristics, number of oocytes retrieved and fertilized, number of embryos transferred, achieving a pregnancy, live birth deliveries, miscarriage, multiple gestations, and gestational age at birth.

For women, caffeine consumption was not associated with number of oocytes retrieved, number of oocytes fertilized, number of embryos transferred or achieving a clinical pregnancy when undergoing IVF or GIFT (measures of association not presented). According to the definition provided by the authors, “not having a live birth’ resulted from either not becoming pregnant or experiencing a miscarriage”. Among females receiving IVF and GIFT, associations between not achieving a live birth and caffeine intake of >50 mg/day compared to 0–2 mg/day during the week before [OR:3.8 (0.9–15.8)] and the week of the procedure [OR:4.0 (0.5–31.1)] were imprecise and not statistically significant. Statistically significant associations were identified for caffeine intake reported for other time periods further removed from the procedure, including usual lifetime intake and intake during the week of the initial clinical visit, (OR:3.9 (1.3–11.6) for >50 mg/day over
lifetime; OR: 3.8 (1.4–10.7) for >50 mg/day during the week of the initial clinic visit).

Male caffeine consumption was not associated with sperm count, motility or morphology or the occurrence of pregnancy (data not shown by authors). On the other hand, caffeine intake among males was associated with an increased probability of multiple gestations (presumably mostly twins) in couples who achieved a pregnancy using IVF and GIFT (for increase of 100 mg/day OR = 2.2 (1.1–4.4) for usual caffeine intake; OR = 3.0 (1.2–7.4) for week of initial clinical visit; OR = 2.2 (0.9–5.0) for week before sperm collection). Only 57 of 71 pregnant couples had complete information on male caffeine intake (usual and week of initial clinical visit) and confounders and only 45 had complete data for the assessment during the week before sperm collection.

Strengths of this study include being the first to focus on endpoints occurring within couples receiving assisted reproductive technology (ART) treatment and the assessment of caffeine intake across time.

The authors acknowledge the major limitation of the study was the small sample size, which resulted in limited statistical power and imprecise measures of association. This study population reported an unusually low level of caffeine exposure, presumably due to fertility concerns. Thus, the study’s capacity to assess the effects of moderate caffeine intake was limited.

2.6.2. Time to pregnancy studies


This retrospective study enrolled 2112 pregnant women from prenatal clinics in the United Kingdom. Several lifestyle factors, including coffee and tea consumption, were evaluated in relation to subfecundity measured as time to pregnancy >12 months (typically referred to as “infertility”) and mean time to pregnancy following cessation of birth control. The study strengths include a high response rate (99%) and large sample size.

No details regarding the measurement of “coffee and/or tea intake” were disclosed other than being reported retrospectively in cups per day (combined). Because a cup of coffee contains substantially more caffeine than a cup of tea and information on soda and energy drinks was lacking, the combined count of servings would potentially more caffeine than a cup of tea and information on soda and energy drinks was lacking, the combined count of servings would potentially misclassify total caffeine exposure. Women who consumed the most coffee and/or tea (>6 cups/day) had a marginally longer average time to pregnancy (10.4 months, 95% CI 8.1–12.8) compared to “mild” (<6 cups/day) users (8.4 months; 95% CI 7.7–9.1) (p = 0.1) and a greater odds of subfecundity [OR:1.7 (1.1–2.7)].

When mean time to pregnancy was compared graphically across five categories of coffee/tea consumption (0, ≤5, 6–10, 11–15, and 16–20 cups/day), those with the most extreme intake (16–20 cups/day) appeared to have a longer time to pregnancy compared to non-consumers (19.7 vs. 9.6 months). The point estimate for the highest intake, however, was imprecise (number of women consuming 16–20 cups/day not reported).

The study limitations, which include potential recall bias and exposure misclassification, hinder interpretation.


This study recruited 41 couples receiving prenatal care during the third trimester of pregnancy with the goal of evaluating effects of persistent organic pollutants on fecundability. Participants were restricted to couples who were not smoking at the time of conception and in which the female partner was ≤ age 35. According to the authors’ description, similar numbers of couples were selected who conceived early (first month) and late (>5 months) as well as “a few” who conceived in between. Thus, subject selection was based on the time to conception outcome. As a result, the cohort design approach to data analysis is questionable and comparisons of the probability of pregnancy in any given month in the exposed and unexposed groups are likely to be invalid. For valid comparisons, the subjects in the cohort would need to be selected independently of their outcome status. The lack of details defining caffeine exposure also raised concerns about the general quality of the retrospective exposure assessment and relevance of the exposure time frame. Given the methodological concerns, this null study offers no useful information regarding caffeine and fecundability.


The retrospective study of subfertility conducted among 2317 pregnant women was not designed to address risk associated with caffeine intake, but rather aimed to identify the most parsimonious models predicting time to pregnancy greater than 12 months and time to pregnancy greater than 24 months. Caffeine intake, defined as coffee and tea intake of 1–6 cups/week and >7 cups/week was included among the lifestyle variables assessed in this study. However, caffeine was not retained in the final models which were limited to statistically significant predictors of subfertility. No measures of association for caffeine were reported.

2.6.3. Ovulatory infertility


Women without a history of infertility in the Nurses Health Study II cohort (n = 18,555) who became pregnant or tried to become pregnant during the 1991–1999 follow-up period were selected for this analysis. Caffeine intake was collected from food frequency questionnaires administered in 1991 and 1995 to assess food and beverage intake during the previous year. Ovulatory disorder was reported as a reason for infertility in questionnaires administered every 2 years. Neither total caffeine intake from all sources nor frequency of coffee, decaffeinated coffee or tea intake were associated with infertility due to ovulatory disorder. Two or more soft drinks per day, however, were positively associated with risk of ovulatory infertility (OR: 1.6 (1.2–2.2)), independent of caffeine intake and total energy intake. Non-caffeinated, sugared and diet soft drinks showed similar associations with ovulatory disorder infertility, suggesting the association may be due to chance, components of soft drinks other than caffeine or sugar, or dietary patterns in which soft drinks are preferentially consumed to the exclusion of nutritious alternatives.

The results offer no evidence to indicate a role for caffeine in the development of ovulatory infertility. The findings, however, are limited by the potential for exposure misclassification. Although the exposure data were collected prospectively, measurement error was possible given the exposure assessment was applied to pregnancies or pregnancy attempts occurring up to 4 years after the food frequency questionnaire was administered.

2.6.4. Sperm quality


This cross-sectional study evaluated correlations between coffee consumption and DNA damage in the semen of 179 men, approximately half of whom had impaired fertility. Men who drank >250 ml of coffee per day did not have higher levels of DNA adducts than “non-drinking or sporadically drinking subjects”. Furthermore, no correlations were observed between amount of coffee consumed and concentrations of DNA adducts or semen parameters.
This study has a number of limitations, including lack of detail about exposure assessment and lack of attention to possible confounding by age or other selection factors. Furthermore, reports of current coffee consumption may not reflect relevant exposures during the period of spermatogenesis.

The crude results presented in this study provide no suggestive evidence of a link between caffeine intake and DNA damage in sperm.


The purpose of this study was to establish reference standards for semen characteristics in Brazil and to examine effects of exposures such as caffeine consumption on semen measurements. Although described as a prospective study, these cross-sectional data were collected from a population of 500 healthy, fertile men age 24–63 scheduled for vasectomies. Semen samples were collected in the hospital before the vasectomy. Coffee use was categorized as 0, 1–3, 4–6 and >6 cups per day, but no details regarding the data collection procedures were provided. Mean values for semen volume, sperm concentration and sperm morphology did not vary meaningfully across the four categories of coffee use. Mean sperm motility, however, was observed to increase slightly with increasing coffee consumption, from 57.1% (sd 16.2) for non-users to 62.4% (sd 16.0) for men consuming >6 cups/day (p = 0.037). Thus, no adverse effects of coffee drinking on sperm quality were observed.

Despite the large study size, the lack of study design details and the absence of control for confounding limit this study’s contribution to resolving the question of what effects coffee and/or caffeine may have on reproduction. By restricting their sample to men seeking a vasectomy (i.e., men who have reason to consider themselves fertile), the authors have eliminated men who might have limited fertility. Thereby, the authors have reduced their ability to identify a coffee effect.


A total of 80 non-smoking men participated in this cross-sectional study evaluating factors associated with DNA damage in sperm. DNA damage was measured using single-cell electrophoresis (sperm Comet) and reported as the average percentage of DNA staining outside the area of the sperm nucleus, referred to as % tail DNA.

Alkaline % tail DNA (indicating single-strand DNA breaks) was not related to caffeine consumption. Under neutral conditions representing double-stranded DNA breaks, men with the highest caffeine consumption (>308 mg/day) had 19% higher mean % tail DNA compared to non-users (39.1 (sd 10.5) vs. 32.8 (sd 6.7), p = 0.005). Neutral % tail DNA did not correlate with semen quality as measured by sperm concentration, total sperm count, motility, and progressive motility.

The results suggest that DNA damage in sperm may be slightly increased in healthy men consuming large quantities of caffeine, but bias due to confounding and exposure misclassification cannot be ruled out. Although the paper’s focus was on the effects of male age, age and factors other than total kilocalorie intake and the history of urinary tract infections were not controlled in sub-analyses of caffeine use.


Young-adult sons (n = 343) of women who were members of a Danish pregnancy cohort were assessed for semen quality and serum hormone concentrations in relation to intrauterine coffee exposure and current caffeine consumption patterns. Average maternal coffee exposure during pregnancy was obtained from questionnaires completed during the 36th week of gestation, which collected categorical responses as 0–3, 4–7 and >8 cups/day. At the time of semen and serum collection, the male participants reported their current daily coffee and cola intake. Categorical responses for coffee and cola were each assigned an estimated caffeine concentration (e.g., 1–4 cups coffee/day = 250 mg; half to one liter of cola per day = 75 mg), which were combined to create categories of low (0–25 mg), medium (50–125 mg) and high (175–1075 mg) caffeine exposure. After adjustment for confounders, including mother’s and son’s smoking, a non-significant trend toward decreasing mean testosterone (19.2, 17.7 and 17.8 nmol/l for 0–3, 4–7, and >8 cups/day, p = 0.06) and inhibin B levels (181, 173, and 162 ng/ml; p = 0.09) was observed with increasing prenatal coffee exposure. Current caffeine consumption was associated with increased adjusted mean testosterone levels (17.9, 19.0, and 20.4 nmol/l for low, medium, and high caffeine; p = 0.007). No effects on sperm concentration, total sperm count, semen volume, morphology or motility were observed in adjusted analyses of either prenatal coffee or current caffeine exposures.

Among mothers with high coffee consumption during pregnancy, a higher proportion of sons drank coffee on a daily basis (25%) compared to sons of mothers with lower intake (16%). Results of sub-analyses for semen volume, sperm concentration, and testosterone levels are reported to be unchanged when also adjusted for the effects of maternal/son’s caffeine consumptions.

The authors acknowledge the third trimester assessment of average exposure during pregnancy may not accurately reflect caffeine intake during the relevant window of testicular development. Furthermore, exposure misclassification was likely given the assignment of a mid-range caffeine concentration to all individuals within a broad category of current coffee or cola intake. Like most studies of semen quality, the participation rate was low (48.5%) introducing the possibility of selection bias. Although this report improves upon previous studies of semen quality, which had limited adjustment for confounders, the dichotomous measurement of current and maternal smoking may have failed to fully control for amount smoked. Overall, the study provides no indication that perinatal coffee consumption or current caffeine intake adversely affects semen quality in young adult males.

3. Spontaneous abortion

A good review of studies that have evaluated the relationship between caffeine consumption and spontaneous abortion has been published by Signorello and McLaughlin (2004).

3.1. Missing early losses

Some women conceive and then miscarry without any recognition of these events other than missing one period (Weinberg et al., 1992; Wilcox et al., 1999). By all definitions, they had a spontaneous abortion, and yet they did not seek medical care and thus are not included in studies of spontaneous abortion. Studies are biased to the extent that they miss these early spontaneous abortions. The best studies seek to improve outcome ascertainment by recruiting women when they first become pregnant or even earlier when trying to conceive, utilizing biomedical advances in early pregnancy detection. An alternative approach is to exclude all early losses before some specified gestational stage, e.g., 8 weeks, in an effort to
create a homogeneous population for study. Because the causes of early losses appear to be distinct from those of later miscarriages, the results of such studies may not be readily extrapolated to populations at risk for early pregnancy loss.

Studies of caffeine and spontaneous abortion vary by the range of gestational ages included for study (unspecified (Wen et al., 2001; Giannelli et al., 2003); 6–12 weeks (Signorello et al., 2001); <13 weeks (Maconochie et al., 2007); 6–16 weeks (Rasch, 2003); ≤20 weeks (Khoury et al., 2004; Weng et al., 2008; Savitz et al., 2008b); <28 weeks (Tolstrup et al., 2003). Consequently, comparability is compromised.

3.6. Late recognition of fetal demise

Some fetuses die in utero weeks before being expelled (Simpson, 1990). Exposures during the time between fetal demise and recognition of the loss are irrelevant. To the extent that this time interval is unrecognized, bias can result. Studies of caffeine and pregnancy loss that attempt to exclude exposures occurring during the time period immediately preceding recognition of the loss (Chattingius et al., 2000; Bech et al., 2005) may improve upon the approximation of the etiologically relevant time period.

3.7. Review of individual studies of spontaneous abortion

3.7.1. Cohort studies


In this prospective study, women who consumed ≥100 mg/day of caffeine during the first trimester were at elevated risk of spontaneous abortion [100–299 mg/day: RR:2.0 (1.0–4.1); ≥300 mg/day: RR:2.5 (1.0–6.4)] compared to those consuming <20 mg/day (n = 584). These increased risks were not apparent when the focus was consumption prior to the onset of nausea (n = 206) or in women who never experienced nausea (n = 73), but were limited to caffeine intake after the onset of nausea (n = 498): RR:1.8 (0.8–3.9), RR:2.4 (0.9–6.2) and RR:5.4 (2.0–14.6) for intakes of 20–99, 100–299 and ≥300 mg/day, respectively. These findings could be explained by the pregnancy signal.

Frequent assessments of caffeine intake throughout pregnancy and evaluation of the interaction between caffeine and nausea are strengths of this study. Limitations include the small number of events in the stratified analyses which resulted in imprecise measures of effect. In addition, control for potential confounders may not have been sufficient, since they were ascertained only at enrollment and were analyzed in broad categories (e.g., smoking at enrollment, yes/no), creating the opportunity for residual confounding. Furthermore, assumptions were made about the temporal association of caffeine consumption and spontaneous abortion, although the authors acknowledge that the exact timing of fetal demise was unknown. Duration of nausea was explored by restricting an analysis to women reporting nausea in at least two monthly questionnaires, but results were imprecise and non-significant.


Miscarriage occurred in 21 of 62 confirmed pregnancies following in vitro fertilization (IVF) and gamete intra-fallopian transfer (GIFT). Unstable but elevated point estimates were reported for caffeine intake [OR:6.2 (0.9–40.8) for ≥50 mg/day] during the week of the initial clinic visit. No associations with first trimester caffeine use were observed. The authors stated, “Because the sample size was small, the CIs were very wide and the magnitude of association for caffeine and miscarriage may be unreliable”. The study controlled for several potential confounders, but certain known confounders such as smoking and pregnancy signal symptoms were not controlled in the analysis. Thus, the results of this study do not provide convincing evidence of a link between caffeine and spontaneous abortion among women receiving assisted reproductive technology (ART) treatment.

This study evaluated 258 spontaneous abortions (≤20 weeks of gestation) occurring among a cohort of 2407 women with clinically recognized pregnancies. Caffeine assessment considered daily consumption in a ‘typical week’ during three time periods – pre-pregnancy, four weeks after last menstrual period (LMP), and at the time of interview, referred to as ‘current consumption’ (i.e., before 16 completed weeks or when still pregnant for those with losses). Overall, the study reported no association between coffee consumption or total caffeine intake before or during pregnancy and risk of spontaneous abortion up to 20 weeks of gestation. Among women interviewed after the miscarriage, current caffeine consumption >144.3 mg/day was associated with an increased risk of spontaneous abortion [OR: 1.9 (1.1–3.5)] compared to non-smokers. In contrast, among women interviewed before their loss, no association with current caffeine intake was observed [OR: 1.1 (0.6–1.8)]. These disparate results could reflect recall bias, increased consumption patterns following fetal demise, true differences in consumption due to absence of a strong pregnancy signal, a relationship between caffeine consumption and later miscarriages only, or chance.

This study has several strengths including a large sample, a prospective design, use of an analytic approach that estimates the probability of having a loss in a given week, conditional on still being pregnant (i.e., at risk of spontaneous abortion) at the beginning of that week, and use of median and 75th percentile cut-points for defining exposure categories, which increase precision when biologically meaningful cut-points are unknown.

The results of this study do not support an association between spontaneous abortion and caffeine intake before or during pregnancy at the levels assessed. The most likely explanation of the associations produced by the sub-analysis of exposure data collected after the event of a loss is recall bias.

3.7.2. Nested case-control studies


This study used an atypical definition of spontaneous abortion as pregnancy loss within the first 28 weeks of pregnancy, thus complicating comparisons with other studies which apply the clinical definition, loss before 20 weeks. This nested case-control study was conducted within a cohort of 11,088 non-pregnant women randomly sampled from the general population of 20–29 year olds living in Copenhagen, Denmark. A baseline interview was conducted between May 1991 and January 1993. A follow-up interview was administered 2 years later to ascertain all pregnancies (n = 1381) and related outcomes (n = 303 spontaneous abortions) occurring during the follow-up interval. The Danish Hospital Discharge Registry was also used to confirm interview reports and to ascertain pregnancy outcomes in women who did not complete the follow-up questionnaire.

The adjusted odds ratio of miscarriage before 28 weeks gestation was significantly increased only for women consuming >900 mg caffeine per day from coffee or tea [OR: 1.7 (1.0–3.0)], after adjustment for maternal age, marital status, cigarette smoking and alcohol intake. At consumption levels similar to those examined by others (e.g., 300 mg/d), average daily pre-pregnancy intake of caffeine was not associated with miscarriage.

This study had a number of methodological features that limit confidence in the results. Because of the time lag between ascertainment of caffeine exposure from the first interview and conception (mean 9.3 ± 6.5 months), caffeine data obtained at baseline may misclassify patterns of consumption more proximal to conception. Pregnancy symptoms were also not assessed and thus were not controlled in the analysis. Furthermore, while it is possi-
ble that the 20% of self-reported miscarriages that were not regis-
try-confirmed represented very early fetal losses among women who did not seek medical care, it is also possible that they were not miscarriages. Test results to confirm pregnancies were not available.

3.7.3. Case-control studies

Giannelli, M., Doyle, P., Roman, E., Pelerin, M., Hermon, C., 2003. The effect of caffeine consumption and nausea on the risk of miscar-

This case-control study was conducted among nulliparous wo-
men seeking care for spontaneous abortion (n = 160 cases) or preg-
nancy (n = 314 controls). Cases were interviewed about 3 weeks after their pregnancy loss on average, whereas controls were inter-
viewed at the first prenatal care visit which typically occurred at a more advanced gestational age.

When compared to women reporting <151 mg/day, women consuming more than 300 mg/day during pregnancy were at in-
creased odds for spontaneous abortion [OR:1.9 (1.0–3.6) for 301–
500 mg/day and OR:2.2 (1.1–4.4) for >500 mg/day]. No associ-
ations were observed for pre-pregnancy caffeine use.

The burden of recalling caffeine exposure was not equivalent for cases and controls. The authors report collecting data on the timing and explanation for variations in typical caffeine consumption pat-
terns before and during pregnancy (but not actual change in amount consumed), although it does not appear that such changes were incorporated into the exposure estimates.

A strength of this study is its attempt to control for severity of nausea. As anticipated, significantly fewer cases than controls re-
ported nausea in this study population (45% of case and 81% of con-
trols interviewed in first trimester) and spontaneous abortion was strongly associated with less severe nausea. Despite these strong associations, controlling for severity of nausea (none, mild, moder-
ate, and severe) had little impact on the magnitude of the reported point estimates and no interaction between nausea and caffeine in-
take was observed.

The limitations of this study include potential recall bias, in-
complete control for smoking (excluded as a potential con-
founder when measured as yes/no) and inclusion of caffeine intake following fetal demise. The 2-fold increased odds observed in this study are similar in magnitude to the association produced in Savitz et al. (2008b) when exposure data were retrospectively reported by cases as compared to prospective reporting. The study also did not consider dietary aversions as an indicator of the preg-
nancy signal phenomenon, as sensitivity to odors and/or food/bev-
 erage aversions may be more closely associated with decreased caffeine consumption than nausea severity.


This case-control study included 303 women with clinically rec-
ognized spontaneous abortions between 6 and 16 weeks of gesta-
tion and 1168 control women pregnant with a live fetus in the same range of gestational age. Women reporting heavy caffeine use since becoming pregnant ( >375 mg/day) had a 2.2 (1.5–3.2) times greater odds of spontaneous abortion compared to women consuming 0–198 mg/day.

The major strengths of this study include the use of control pregnancies of similar gestational ages, which appropriately repre-
sents the source population for the cases, the relatively large sam-
ple size, and the high proportion of heavy caffeine users in the study population (46.6% of cases and 28.9% of controls). Among the study limitations considered by the author are no data to con-
trol for pregnancy symptoms, the possibility of including exposure following fetal demise and the possibility of overestimation due to recall bias given cases reported exposures while being hospitalized for evacuation of the pregnancy. The study author reasons recall bias is an unlikely explanation because concern about caffeine use during pregnancy was not widespread in Denmark during the mid-1990’s study period.

A substantial proportion of the study population was excluded due to missing data on gestational age (23.8% of case respondents and 21.4% of controls). In addition, it is not possible to disentangle the evidence to determine whether the observed associations re-
flect something other than a diminished or absent pregnancy sig-
 nal in pregnancies destined to fail.


Data for this case-control study were derived from the National Women’s Health Study of adult women living in the United King-
dom in 2001. Women with a pregnancy history identified in a two-stage population-based survey were selected as cases if their last pregnancy ended in a first trimester miscarriage (<13 com-
pleted weeks) or if they had a miscarriage in any pregnancy con-
ceived since 1995 (n = 603). This latter group represented about 40% of all cases. Controls were women whose last pregnancy pro-
gressed to 13 weeks gestation or beyond (n = 6116). Eighty-three percent of cases were conceived since 1995, compared to 49% of controls, thus there was potential for differential recall between cases and controls.

Average caffeine intake from beverages >300 mg/day during the first 12 weeks of pregnancy was independently associated with an increased odds of miscarriage compared to no consumption [OR:1.5 (1.1–2.2) for 301–500 mg/d; OR:1.7 (1.2–2.4) for >500 mg/d]. After further adjustment for nausea severity, however, caffeine intake was no longer related to the odds of miscarriage [OR:1.0 (0.7–1.5) for 301–500 mg/d and OR:1.1 (0.8–1.7) for >500 mg/d].

The limitations of this study include the potential misclassifi-
cation of exposure and outcome due to lengthy and differential time frames for exposure recall, self-reported outcomes, and con-
fining caffeine intake to beverages. These data do not support an association between caffeine consumption from beverages and odds of first trimester miscarriage after adjusting for the confound-
ing effect of nausea severity.

3.7.4. Caffeine metabolism


This study is one of three papers (Signorello et al., 2001; Karyp-
dis et al., 2006; George et al., 2006) published using data collected as part of a case-control study of caffeine and miscarriage in Upps-
sala, Sweden (Crattingius et al., 2000). The original publication by Crattingius et al. was previously reviewed by Leviton and Cowan (2002). In the original study, 562 confirmed cases of spontaneous abortions between 6 and 12 weeks of gestation were identified from a university hospital, the sole source of care for women experi-
encing pregnancy loss. Controls (n = 953) were identified from women seeking prenatal care in Uppsala and were frequency matched to cases by completed weeks of gestation and area of res-
idence. This study was well-designed in that controls represented the source population of the cases, i.e., women in their first trimes-
ter of pregnancy. A major strength of this study was karyotyping of cases when fetal tissue could be obtained, although this was available on fewer than half of the cases. Another positive quality was the measurement of caffeine consumption, which although ascer-
tained retrospectively, incorporated multiple sources of exposure, method of preparation, serving size, and captured reports of caf-
eine use week by week. The potential drawback of the exposure
assessment was the likely inclusion of caffeine intake following unrecognized fetal demise.

The 101 chromosomally normal spontaneous abortions were compared to the 953 controls. With the goal of evaluating variability in caffeine metabolism as a risk factor for spontaneous abortions, the authors estimated the activity levels of two enzymes, cytochrome P4501A2 (CYP1A2) and N-acetyltransferase 2 (NAT2), given both are involved in the metabolism or detoxification of caffeine (Campbell et al., 1987a; Nebert et al., 1996; Arnaud, 1994).  Using genomic DNA from whole blood, polymorphisms of the NAT2 gene were determined by polymerase chain reaction (PCR) amplification to identify slow (homozygous mutated alleles) and fast acetylator genotypes (heterozygous or homozygous wild type alleles). CYP1A2 phenotypes were determined using the index described by Campbell et al. (1987b), which calculates a ratio of four urinary metabolites of caffeine as an indicator of caffeine clearance. Low and high CYP1A2 activity were defined as log-transformed CYP1A2 index values below and above the median value identified among controls (median index value = 0.73).

When stratified by CYP1A2 activity, caffeine intake above 100 mg/day was associated with increased odds of spontaneous abortion among women with high CYP1A2 activity [OR:2.4 (1.0–5.8) for 100–299 mg/day and OR:3.2 (1.2–8.2) for ≥300 mg/day compared to 0–99 mg/day], but not among those with low activity. Independent of caffeine intake, smoking status, nausea score, maternal age and week of gestation, high CYP1A2 activity was associated with an elevated odds of spontaneous abortion [OR:2.9 (1.7–5.0)]. NAT2 genotype was not associated with spontaneous abortion among women with high CYP1A2 activity [OR:2.4 (1.0–5.8) for 100–299 mg/day and OR:3.2 (1.2–8.2) for ≥300 mg/day], but not among those with low activity. Independent of caffeine intake, smoking status, nausea score, maternal age and week of gestation, high CYP1A2 activity was associated with an elevated odds of spontaneous abortion [OR:2.9 (1.7–5.0)]. NAT2 genotype was not associated with spontaneous abortion. The authors suggest that prolonged exposure to caffeine metabolites might explain their unexpected findings.

A limitation of using spot urine samples in population-based studies to phenotype CYP1A2 activity (as opposed to the less feasible method of administering a standardized test dose of caffeine) is that recent caffeine consumption is required in order to detect the caffeine metabolites in urine (Nordmark et al., 1999). Thus, women consuming little or no caffeine (approximately 1/3 of cases and controls) were excluded from the analyses. Furthermore, the exclusions resulted in small sample sizes and imprecise estimates, particularly within the stratified analyses.

Because CYP1A2 is involved in the metabolism of numerous drugs in addition to caffeine, the authors recognize that the results may indicate potential links between spontaneous abortion and other unmeasured factors. Cigarette smoke is one compound that has been shown to induce high CYP1A2 activity (Campbell et al., 1987b). Classifying women as either smokers or non-smokers, instead of actual quantity smoked (or concentration of plasma cotinine) might have contributed to residual confounding by smoking. This may also explain why high CYP1A2 activity was associated with spontaneous abortion contrary to expectations that risk would increase with slower caffeine clearance. Thus, caution is advised when drawing inferences from these findings.


The Swedish case-control study was conducted again by Karypis et al. (2006) to evaluate the odds of spontaneous abortion associated with CYP1B1 polymorphisms and a possible interaction with caffeine consumption. CYP1B1 is an enzyme that influences the metabolism of steroid hormones, such as testosterone, progesterone, and estriol, and of caffeine, among other agents. CYP1B1 activity, like CYP1A2, is also induced by smoking (Pipari et al., 2000). Women who were homozygous for the Val allele had an adjusted odds of miscarriage 1.5 times higher than women homozygous for the Leu allele (95% CI = 1.0–2.1), and the association was consistent among non-smokers [OR:1.6 (1.1–2.4)]. The risk increased with increasing caffeine consumption, but almost only among Val/Val. This indicates a significant interaction between homozygosity for Val and caffeine intake.

Since the Leu variant contributes to inactivation of testosterone (Shimada et al., 1999) and higher levels of testosterone have been associated with miscarriage (Okon et al., 1998), Leu/Leu homozygotes may be protected from spontaneous abortion. The authors acknowledge that CYP1B1 is involved in the metabolism of many compounds including steroid hormones and procarcinogens as well as caffeine; thus, the observed associations may not be directly attributed to caffeine metabolism.

3.7.5. Recurrent pregnancy loss


This case-control study of repeated miscarriage was conducted within the Swedish study of spontaneous abortions reported by Cnattingius et al. (2000). Cases included 108 women from the original case group who had two or more consecutive miscarriages. Controls were women with at least two pregnancies (n = 583), of which the last was a normal intrauterine pregnancy, confirmed by vaginal ultrasound.

After adjustment for potential confounders, the odds of repeated miscarriage was not significantly increased in heavy caffeine users [OR:1.8 (0.8–3.9) for ≥300 mg/day]. Caffeine consumption ≥300 mg/day was related to repeated miscarriage in non-smokers [OR:2.7 (1.1–6.2)] but not smokers [OR:0.4 (0.05–4.1)]. The test for interaction was not statistically significant.

As with the original study, the increased odds of repeated miscarriage associated with high caffeine intake only in non-smokers may be a result of lower prevalence of other risk factors for miscarriage in non-smokers, making a relation with caffeine more apparent. It may also be due to the fact that smoking, as the authors report, increases the rate of elimination of caffeine. Lack of control for pregnancy symptoms could provide an alternative explanation for the association between caffeine consumption and repeated spontaneous abortion in non-smokers, as described in Section 3.3.

3.7.6. Recurrent pregnancy loss and caffeine metabolism


This case-control study of recurrent early pregnancy loss evaluated associations with polymorphisms in glutathione S-transferase (GST) and cytochrome P450 genes. The authors reasoned that polymorphisms in these genes may reflect impaired drug metabolism and detoxification, which could increase susceptibility to adverse outcomes resulting from chemical exposures. The study included 187 case women who had at least two unexplained consecutive spontaneous abortions occurring <17 weeks of gestation. The cases were selected from a referral hospital and 109 controls were selected from unrelated acquaintances who had at least one uncomplicated pregnancy and no spontaneous abortions (and were, thus, considered matched by age, socioeconomic status and district). The ratio of less than one control per case is not explained, but suggests differential response rates for cases and controls. Details regarding coffee exposure assessment are also omitted.

Odds ratios for the effects of caffeine consumption were not reported, but our calculations show no observed associations between daily coffee intake and recurrent pregnancy loss [crude OR:0.8 (0.4–1.5) for 1–5 cups and crude OR:1.4 (0.7–2.9) for ≥(and equal to) 7] five cups compared to non-coffee drinkers]. The non-mutually exclusive categories of coffee consumption are those reported by the authors.
GSTP1b-1b genotype (representing lower enzyme activity) was associated with recurrent pregnancy loss [OR:2.9 (1.0–10.1), especially among coffee drinkers [OR:4.1 (1.2–13.3)]. The increased OR among coffee drinkers could be attributable to poorer precision in the smaller subgroup, which is based on only three controls homozygous for the GSTP1b allele. It could also be explained by uncontrolled confounding by smoking.

Although the GSTP1b-1b polymorphism appeared to be more common among women with recurrent early pregnancy loss, the limited data presented in this paper offer little evidence to implicate a specific role for coffee intake via direct effects or interactive effects with GST polymorphisms.


The authors of this small case-control study (58 cases and 147 controls) reported no overall association between caffeine intake ≥300 mg/day and recurrent pregnancy loss [OR:1.8 (0.7–4.6)] when compared to intake of 0–99 mg/day. Among women homozygous for CYP1A2*1F (A/A) alleles, considered to have heightened caffeine metabolism, caffeine intake ≥300 mg/day was associated with recurrent pregnancy loss [OR:5.2 (1.1–25.9)] when compared to limited caffeine use (0–99 mg/day). Effect modification by CYP1A2 genotype was not observed among women with other CYP1A2 genotypes.

The limitations of this study include the small sample size, poor response rates (56.6% for cases and 58.1% for controls), lack of information on the timing of recruitment in relation to the previous pregnancy and implications for accurate exposure recall, no assessment of pregnancy symptoms, and the possibility of residual confounding by smoking which was measured as never, former, current and continuous smoker. Smokers homozygous for the CYP1A2*1F (A/A) allele have higher CYP1A2 activity compared to other CYP1A2 genotypes (A/C and C/C) (Sachse et al., 1999). Thus, associations within the CYP1A2*1F strata may be explained by smoking, particularly if reported caffeine use reflects actual smoking patterns (as described by Morrison, 1984).

The methodological limitations do not allow unambiguous conclusions to be drawn about interactive effects of heavy caffeine use and CYP1A2 genotype on recurrent pregnancy loss.

4. Fetal death

Clinical convention distinguishes fetal death, defined as fetal demise after 20 weeks of gestation, from spontaneous abortion defined as pregnancy loss <20 weeks of gestation. The distinction is typically drawn at the mid-point of pregnancy because it approximates the point of fetal viability, which is generally regarded as occurring close to 23–24 weeks of gestation. Because both outcomes address fetal loss, but at different points along the continuum of pregnancy, many of the methodological considerations identified for studies of spontaneous abortions are also applicable to studies of fetal death.

4.1. Pregnancy signal

Studies of caffeine and fetal death tend to focus on mid-pregnancy exposures and thus may be particularly subject to confounding by the pregnancy signal. Most women decrease their caffeine consumption during the early part of pregnancy and maintain their lower than pre-pregnancy levels of consumption throughout the remainder of their pregnancy (Boylan et al., 2008). Thus, women who are heavy coffee consumers in the last half of pregnancy may not have experienced a strong pregnancy signal early in pregnancy. Only one study of fetal death (Matijasevich et al., 2006) considered nausea and vomiting, but measurement was limited and food/drink aversions were not considered.

4.2. Heterogeneity

Efforts have been made to group fetal deaths into more etiologically homogeneous outcomes according to the time of fetal demise (antepartum vs. intrapartum; early fetal deaths ≤28 weeks vs. stillbirths ≥28 weeks) and cause of death. The evaluation of fetal deaths by likely causes (e.g., congenital infection, malformations, placental abruption) is hindered by the difficulty of attributing deaths to a single cause, the challenge of systematic identification of all contributing causes, and the need for large sample sizes (Leviton, 1987). While a worthwhile goal, the quality of analyses which classify outcomes by cause of fetal death remain questionable.

4.3. Selection of controls

Controls selected from live, healthy births (Matijasevich et al., 2006; Bech et al., 2006) may introduce selection bias. As with studies of spontaneous abortion, controls selected from on-going pregnancies matched by gestational age would provide the most accurate representation of the exposure distribution among the population that generated the cases of fetal deaths.

4.4. Late recognition of fetal demise

The exact timing of death is rarely observed, but can occur weeks before the fetal loss is recognized. Like studies of spontaneous abortion, the inclusion of caffeine intake up to the point of pregnancy termination may inflate associations with fetal deaths if the diminished pregnancy signal following fetal demise leads to increased caffeine consumption (Stein and Susser, 1991).

4.5. Review of individual studies of fetal deaths


This prospective cohort study of 18,478 singleton pregnancies in Denmark reported an increased odds of stillbirth (≥28 completed weeks of gestation) among pregnant women drinking ≥48 cups of coffee per day compared to non-coffee drinkers [OR:2.2 (1.0–4.7)]. The strength of this study was its prospective design, which avoided opportunities for recall bias. The measurement of caffeine/coffee intake, however, was limited to current coffee consumption at 16 weeks of gestation, without reference to a standard cup size. Although other sources of caffeine intake were collected, the authors ignored contributions from tea, cola or chocolate since few women reported high intakes from these sources. Because 3922 women contributed more than one pregnancy to the cohort, sub-analyses addressing the lack of independence between observations were conducted. Results were not presented, but were reported as “comparable”. If women with less viable pregnancies consume more caffeine because they have fewer pregnancy symptoms and aversions, then higher caffeine consumption would be a consequence of an unhealthy pregnancy rather than a cause. Wisborg et al. (2003) did not consider pregnancy signal symptoms in their analyses.

or more cups of coffee per day were at increased risk of death between 20 and 27 weeks of gestation [HR:2.3 (1.3–3.9)], but were not at increased risk of death after 27 weeks [HR:1.3 (0.7–2.4)]. Risk of stillbirth due to placental dysfunction was 2.3 times greater among women consuming ¥4 cups of coffee per day compared to women who consumed no coffee [HR:2.3 (1.2–4.3)]. No associations were observed for other stillbirth subgroups such as unexplained intrauterine deaths, umbilical cord complications, congenital malformations, “other” conditions such as infection and maternal disease, or intrapartum deaths.

To minimize bias that can occur when caffeine consumption is increased as a result of undetected fetal demise, the authors repeated analyses after excluding losses occurring over a range of 2–28 days following the interview. The hazard ratios became attenuated with increasing lag time and non-significant in all exposure categories, suggesting the results could be explained by the pregnancy signal. Although the data are not shown, the authors note the decline in hazard ratios to be particularly strong among fetal deaths ¥20 weeks, but less so for fetal deaths ¥20 weeks. Associations with later fetal losses may be less susceptible to the influence of undetected fetal demise since exposure assessment (between 13 and 19 weeks of gestation) preceded the loss by a longer time period. However, reverse causation remains a possibility if higher coffee intake is a marker of placental dysfunction and thus a consequence of the reduced or absent symptoms that accompany less viable pregnancies, regardless of the timing of fetal demise. The authors acknowledge their inability to assess the impact of pregnancy symptoms on the observed associations.


In this paper, the same research group as above conducted a nested case-control study within the Danish National Birth Cohort to evaluate the interrelationship between caffeine, caffeine metabolism and stillbirth. Cases (n = 142) were defined as stillbirths occurring ¥28 weeks of gestation, excluding intrapartum deaths. Controls (n = 157) were selected from live births, frequency matched by parity. The authors evaluated genotypes either known [cytochrome P4501A2 (CYP1A2) and N-acetyltransferase 2 (NAT2)], or suspected [glutathione S-transferase η [GSTA1]], to be active in caffeine metabolism. CYP1A2 genotypes were grouped into fast (A/A) and slow (A/C and C/C) oxidizers. NAT2 genotypes were grouped into fast (Fast/Fast and Fast/Slow) and slow (Slow/Slow) acetylators. GSTA1 genotypes were classified according to high activity (a/a) and reduced activity (a/b and b/b). Coffee was the only source of caffeine considered in this analysis. The methods used to ascertain coffee intake are not provided, but the limitations are presumed to be the same as described for Bech et al. (2005) (see Section 3.7.1).

When caffeine use was assessed without consideration for metabolic genotype, drinking ¥4 cups of coffee per day was not associated with stillbirth [OR:1.0 (0.5–2.3)]. Women with stillbirths had a 1.9-fold increased odds of having a slow caffeine metabolism as characterized by all three genotypes (slow CYP1A2, slow NAT2 and low GSTA1) compared to controls [OR:1.9 (1.0–3.4)]. However, when genotypes were assessed separately or in paired combinations, no associations with stillbirth were observed. The lack of interaction between genotype and caffeine consumption suggests the associations with these genotypes may not reflect causal pathways specific to caffeine metabolism.


Cases (n = 382) included all antepartum fetal deaths (¥20 weeks of gestational age or weighing >350 g) occurring in the 16 maternity hospitals within the capital city of Uruguay. Controls (n = 792) were healthy, full term, live births without growth restriction, frequency matched by hospital. Participants were interviewed within 24 h following delivery for caffeine intake from maté (herbal tea) and coffee during each trimester. The justification for limiting assessment to coffee and maté was that these are the primary sources of caffeine in South America. However, according to their own report of caffeine consumption within the South American region (Santos et al., 1998), up to 48% of pregnant women reported consumption of other sources such as soft drinks, chocolate bars, and black tea, which accounted for approximately one-fourth of their total caffeine intake during pregnancy. Thus, exposure misclassification is likely.

The authors report that mean caffeine consumption of ¥300 mg/day throughout pregnancy was associated with fetal death [OR:2.3 (1.2–4.4)]. Several maternal characteristics were considered as confounders, although the criteria for confounding relied on p values, which can result in an appreciable loss of information (Dales and Ury, 1978). The crude measurement of smoking (yes/no) and pregnancy symptoms (yes/no for vomiting or nausea in first trimester) and failure to consider alcohol intake may have also contributed to incomplete control of confounding.

As noted by the authors, recall bias could have inflated the association if case mothers reported past caffeine use more accurately than controls. Another limitation of this study was the use of live births as controls, which may not accurately represent the exposure distribution in the population from which the cases arose (Signorello and McLaughlin, 2004).

In light of these limitations, this study does not provide convincing evidence that high caffeine consumption throughout pregnancy is associated with fetal death ¥20 weeks of gestation.

5. Gestational age and preterm birth

5.1. Heterogeneity

Preterm birth includes a heterogeneous group of disorders, suggesting heterogeneous etiologies (Savitz et al., 1991, 2005; Klebanoff and Shiono, 1995; Klebanoff, 1998a; Pennell et al., 2007; Berhman and Butler, 2007; McLelath et al., 2008; Savitz, 2008a). The so-called “spontaneous preterm delivery” group includes preterm labor, pre-labor premature rupture of membranes, placental abruption, and cervical insufficiency, which are associated with intrauterine inflammation. Medically indicated preterm births can be characterized by maternal and fetal origins. The maternal medical indications group is almost exclusively pre-eclampsia, and is attributed to dysfunctional placenta. Fetal indications are heterogeneous and include non-reassuring fetal testing, oligohydramnios, Doppler abnormalities of umbilical cord blood flow, or severe intrauterine growth restriction identified on antenatal ultrasound examination. Only two studies attempted to evaluate relatively homogeneous outcomes (Mikkelsen et al., 2008; Haugen et al., 2008).

It is not yet clear that the processes leading to delivery near the boundary of viability (23–24 weeks) are the same as those that lead to delivery near the upper boundary of prematurity (34–36 weeks). The two studies that acknowledged the possibility that early and late prematurity might be different entities dichotomized premature deliveries at 35 weeks, rather than a considerably earlier week in pregnancy (Mikkelsen et al., 2008; Haugen et al., 2008).

5.2. Accurate estimation of gestational age

Correct classification of preterm birth is dependent on accurate estimates of gestational age. The three most commonly used meth-
Growth. [Discussed also in 7. Fetal birth. Am. J. Epidemiol. 155, 32–37]

Assessed as confounders, but had little impact on the results. These plasma cotinine concentrations. Pregnancy symptoms were also tion. The authors controlled for smoking by using third trimester is unlikely that women with shorter gestations would have been bering intake patterns across previous weeks and months. Since

300–499 or 

ers grouped according to average daily caffeine intakes across the mean length of gestation nor mean birth weight differed for moth-

births <37 weeks of gestation could potentially obscure existing associations with caffeine intake. According to the authors, neither births were not considered separately. Combining all preterm associations with caffeine intake. According to the authors, neither

-3 months at 2562 J.D. Peck et al. / Food and Chemical Toxicology 48 (2010) 2549–2576

ods are based on ultrasound, date of last menstrual period and neo-

natal assessment of physical and neurological maturity at birth (Lynch and Zhang, 2007). No method is perfect, but the use of early ultrasound is considered to provide the most accurate estimation, within 5–10 days when completed at 12–14 weeks of gestation and 9–12 days when completed at 15–20 weeks of gestation (Saltvedt et al., 2004).

Gestational age based on date of last menstrual period can be flawed due to recall errors or delayed ovulation, commonly overes-

timating pregnancy duration (Savitz et al., 2002). In the absence of other information, gestational age is sometimes estimated using neonatal evaluations such as the Dubowitz and Ballard examinations, which score the physical and neuromuscular development of the newborn (Dubowitz et al., 1970; Ballard et al., 1979, 1991). These postnatal estimates are less precise and accurate than the preferred prenatal methods and have a tendency to underesti-

mate gestation for post-term deliveries and to overestimate gesta-

tion by up to 2 weeks for deliveries occurring before 40 weeks (reviewed by Lynch and Zhang, 2007).

Considering the deficiencies in each of these methods, some have recommended a hierarchy of assessments ordered by accu-

racy and availability of the measurements. One example preferred the dates of embryo retrieval or intrauterine insemination or ultra-

sound examination before the 14th week of gestation. If these were not available, the order of preference continued with ultrasound at 14 weeks or later, followed by menstrual dating without ultra-

sound confirmation, and finally gestational age recorded after neo-

natal assessment (McElrath et al., 2008).

5.3. Review of individual studies of preterm birth


In this cohort study from Sweden, 873 pregnant women were interviewed twice, between gestational weeks 6–12 and 32–34, for their recall of caffeine consumption during the previous weeks of pregnancy. Although gestational age was confirmed by ultra-

sound examination, spontaneous and medically indicated preterm births were not considered separately. Combining all preterm births <37 weeks of gestation could potentially obscure existing associations with caffeine intake. According to the authors, neither mean length of gestation nor mean birth weight differed for moth-

ers grouped according to average daily caffeine intakes across the entire pregnancy (4–34 weeks of gestation) of 0–99, 100–299, 300–499 or >500 mg/day. Furthermore, average daily caffeine in-

take in each trimester was not associated with duration of pregnancy.

Retrospective exposure assessment may have resulted in errors in caffeine measurement given the difficulty of accurately remem-

bering intake patterns across previous weeks and months. Since

consumption patterns were assessed before delivery, however, it is unlikely that women with shorter gestations would have been influenced to systematically report more or less caffeine consump-

tion. The authors controlled for smoking by using third trimester plasma cotinine concentrations. Pregnancy symptoms were also assessed as confounders, but had little impact on the results. These data do not support an association between caffeine and preterm birth, however caffeine exposures after 32–34 weeks could not be evaluated.


This study measured paraxanthine, the major metabolite of caf-

feine, in third trimester serum samples banked for 2515 women participating in the Collaborative Perinatal Project (CPP) between 1959 and 1966. The subjects in this study served as the controls in a previous case-control study of spontaneous abortion (Kleba-

noff et al., 1999); thus, all had delivered liveborns >28 weeks of gestation. Serum samples collected after 26 weeks of gestation were stored frozen for over 30 years before caffeine metabolite concentrations were measured. After controlling for maternal ethnicity, paraxanthine concentrations were not associ-

ated with gestational age or preterm birth.

The stability of caffeine metabolites in serum is unknown. In re-

sponse to concerns about measurement error raised by Grosso et al. (2004), the authors responded by demonstrating that de-

tected concentrations of serum paraxanthine following long-term storage were consistent with self-reported intake in another cohort assembled during the same time period (Klebanoff and Longnecker, 2004).

Because the CPP study was conducted in the early 1960s, caf-

feine use during pregnancy was relatively common in the study population, although actual consumption patterns were not di-

rectly assessed. Other strengths of the study include the opportu-

nity to assess a biomarker of caffeine exposure that avoids measurement errors related to inaccurate recall and the difficulty of accounting for all sources. In light of individual differences in caffeine metabolism, paraxanthine levels may reflect biologic dose better than reported caffeine consumption. On the other hand, the paraxanthine biomarker represents recent caffeine intake (half-

life = 10 h in later pregnancy) (Aldridge et al., 1981) and may re-

flect exposure during the relevant window of susceptibility only for those whose intake patterns remain relatively constant over time.

The data do not support an association between third trimester paraxanthine concentrations and pregnancy duration or preterm delivery.


Within this study of couples undergoing IVF and GIFT (described in Section 2.6), the association between caffeine in-

take and gestational age was assessed in 39 live births. No asso-

ciation was observed between caffeine intake among the male partners and gestational age. Maternal caffeine intake >50 mg/ day during the week of the first fertility clinic visit was associ-

ated with a 3.5 week decrease (95% CI = 6.7, –0.3) in gestational age when compared to women reporting 0–2 mg/day. Similar results were reported for usual “lifetime” caffeine consumption, but results for intake during pregnancy were not reported. The authors cautiously report the findings as having “borderline significance” while acknowledging the small sample size and limited precision.

Although the results were reported as adjusted, the specific control variables were not specified. Factors controlled in analyses of other outcomes in this report included smoking, alcohol use, woman’s age, race, years of schooling, parity, type of infertility, type of procedure, and number of ART attempts. However, with only 39 observations, the precision of the results would be ques-

tionable with this many covariates (Feinstein 1996).

Bracken, M.B., Triche, E.W., Belanger, K., Hellenbrand, K., Leaderer, B.P., 2003. Association of maternal caffeine consumption with decre-

ments in fetal growth. Am. J. Epidemiol. 157, 456–466. [Discussed also in 7. Fetal Growth]

This prospective cohort study included 2291 pregnant women enrolled by 24 gestational weeks (14.4 weeks on average). All
women consuming ≥ 150 mg/day during the previous week were invited to participate as well as a random sample of those consuming <150 mg/day. Caffeine exposures were quantified by measuring caffeine concentrations in urine at the baseline interview, and by self-reported consumption during the first and last trimester of pregnancy. A major strength of this study is that it was designed to assess pregnancy outcomes in relation to caffeine use and, thus, incorporated a detailed assessment of caffeinated beverage intake including method of preparation, brand names and more accurate reporting of serving sizes. The omission of caffeine from food and medicinal sources, however, may have underestimated exposure status.

Preterm births were not differentiated according to spontaneous or medically indicated deliveries. The frequencies of preterm birth and IUGR in this cohort were lower than those reported for the general US population within a similar time period suggesting that participants consisted of women who had generally healthier pregnancies compared to the general US population.


This population-based case-control study of 323 preterm deliveries and 664 controls explored numerous demographic, medical and lifestyle characteristics as predictors of preterm delivery. Phone interviews were conducted 4–8 weeks after delivery. Specific details of the methods for caffeine assessment were not provided. Analyses were limited to crude odds ratios assessed separately for coffee, tea and caffeinated soft drink consumption measured as <1 cup per day compared to ≥ 1 cup per day. A crude association between coffee consumption and preterm birth was observed (OR = 1.4, 95% CI 1.0–1.9), but was not maintained in the final multivariable model reported for statistically significant predictors of preterm delivery.


In this study of 1,341 diabetic pregnancies, the monthly assessment of caffeine exposure was limited, measured as the average number of 8 oz cups consumed daily from all caffeinated beverages, giving equal weight to coffee, tea and soft drinks. Analyses of preterm birth focused on caffeine exposure after 20 weeks of gestation. To assess the quality of this measurement, the authors compared the serving counts averaged across the last half of pregnancy to estimates of total caffeine consumption during this time period converted to equivalent cups of coffee per day. The agreement between methods, as measured by the Kappa statistic, was reported to be 0.61, 0.65 and 0.71 for 0, 1–2, and ≥ 3 cups/day. Thus, the analyses of preterm birth are subject to considerable exposure misclassification. The authors elected not to report results using total caffeine consumption.

In this report, no association was observed between caffeine consumption after 20 weeks of gestation and gestational age at delivery after controlling for age, smoking, glycemic control and other indicators of diabetes severity. Without a more accurate measurement of caffeine exposure, the findings offer little insight into associations with preterm birth.


This retrospective cohort study explored consumption of maté, a popular beverage in South America prepared by steeping leaves of Ilex paraguariensis in hot water. It is considered a major source of caffeine intake among women in Southern Brazil. Women (n = 5189) in five local maternity hospitals were interviewed within 24 h following delivery. Maté use during pregnancy was quantified as number of days per week (0, 1–6 and 7 days per week) rather than number of servings. The amount of actual caffeine consumption was not specifically investigated, but according to results from a previous study in the same source population (Santos et al., 1998), women reporting daily consumption of maté averaged approximately 300 mg of caffeine per day.

Gestational age was measured using a clinical estimate at birth (i.e., Dubowitz score), which has been shown to have reasonable, but imperfect, agreement with ultrasound measurements (Vik et al., 1997). In light of these limitations, the authors’ failure to find a relationship between maté consumption and duration of pregnancy has limited significance.

This case-control study compared 520 women who delivered at least three weeks before term to 1966 controls who delivered at term in the same hospitals in Northern Italy. Because of potential etiologic heterogeneity, subgroups of preterm births with and without small for gestational age (SGA) were evaluated separately. It is unclear how the exposure information was originally collected and combined for analyses. For example, it is not known whether consumption patterns were reported for specific weeks or by trimester of pregnancy which were then summed or whether participants reported an overall estimate of average consumption during the entire pregnancy. Caffeine consumption during pregnancy was relatively low in this population, limiting the opportunity to assess associations with high intake levels. Given exposure assessment occurred within the 3 days following delivery, recall bias was a potential concern. Positive associations with caffeinated beverage intake, however, were not observed.

Associations with tea, cola or decaffeinated coffee were not observed for either preterm subgroup. Women who consumed two or more servings of coffee per day were at reduced risk of delivering an SGA newborn before term compared to non-consumers [OR:0.5 (0.3–0.8)]. The reduced risk did not achieve statistical significance for preterm delivery of an appropriate for gestational age infant [OR:0.7 (0.4–1.1)].

The authors attribute this unexpected inverse association to potential increases in coffee consumption among controls that may accompany decreased nausea during the third trimester, in conjunction with decreased coffee consumption among concerned case mothers who may have become aware of restricted fetal growth by the third trimester. Pregnancy symptoms, however, were not evaluated. Given the limitations presented above, this study does not provide convincing evidence either for or against a causal link between caffeine and preterm birth.


This study distinguishes itself from observational studies by using an experimental design to randomly assign 1197 heavy coffee drinkers to caffeinated or decaffeinated instant coffee during the last half of pregnancy. Mean birth weight and gestational age were compared across treatment groups. While random exposure assignment helped reduce selection biases, exposure measurement error remained, since participants in both treatment groups received no restrictions on amount of coffee consumed and were free to consume other sources of coffee or caffeinated beverages. In
addition, based on interview data, more than one-third of the women in the decaffeinated group were daily consumers of decaffeinated coffee (>1 cup/day). This cross-over bias serves to make the caffeine distribution in the two treatment groups more similar, thereby weakening the ability to detect true differences should they exist.

Analysis of the data using the intent to treat approach (i.e., by treatment assignment) found that decaffeinated coffee consumers had a distribution of pregnancy duration that was similar to that of decaffeinated coffee consumers. This approach, however, ignores the individual level exposure data. In the absence of an analysis of actual caffeine intake, the authors do offer analyses stratified by “compliance” which was defined according to frequency of consumption of decaffeinated coffee outside of that provided by the study. The lack of association between caffeine assignment and preterm birth was consistently observed across compliance groups.


These two companion studies were coordinated to assess the effects of a Mediterranean-type diet on preterm birth in two large birth cohorts in Denmark and Norway. Low coffee consumption, defined as ≤2 cups of coffee per day, was evaluated as part of a Mediterranean-type diet. Both studies were conducted within large existing birth cohorts and were restricted to non-smoking women between ages 21 and 38 with a BMI between 19 and 32, pregnant with singletons, with normal calorie intake and no history of ≥3 spontaneous abortions. Preterm deliveries were evaluated in both studies according to early (22–34 weeks) and late (35–36 weeks) preterm births as well as all preterm births combined (<37 weeks of gestation). Both studies reported results specifically for coffee consumption, but the findings for associations with preterm birth were inconsistent between the two studies.

The Danish study (Mikkelsen et al., 2008) reported data from 35,530 non-smoking women recruited from the Danish National Birth Cohort during the 25th week of gestation. Coffee consumption during the previous 4-week period was collected as part of a food frequency questionnaire. Gestational age at birth was primarily obtained from mother’s reported last menstrual period. Coffee intake ≤2 cups per day was associated with a 26% lower odds of early preterm birth [OR:0.7 (0.6–0.9)] compared to women consuming >2 cups/day, after adjustment for other components of the Mediterranean diet and other confounders. No association with late preterm birth was observed [OR:0.9 (0.8, 1.1)].

Because these studies were designed to assess the effects of a Mediterranean diet and not caffeine intake specifically, measurements of all sources of caffeine exposure were not obtained. Thus, the results are specific to coffee consumption and not caffeine. To the extent that (1) coffee is the primary source of caffeine exposure in Danish women and (2) consumption patterns during the fifth month of pregnancy represent either the critical window of exposure or patterns of caffeine use maintained during the critical window, the results could be suggestive of a weak effect of caffeine on early but not late preterm birth.

The study published by Haugen et al. (2008) was conducted among 26,563 women participating in the Norwegian Mother and Child Cohort Study. Food frequency questionnaires were administered during mid-pregnancy (17–24 weeks), but in this study the reference period was the entire pregnancy up to that point, rather than the previous month as reported in Mikkelsen et al. (2008). Thus, coffee exposure was subject to misclassification that may occur when intake patterns are retrospectively reported over many months. Information on gestational age at birth was collected by linking to the Norwegian Medical Birth Registry. In the Norwegian sample, consuming two or less cups of coffee a day was not associated with a reduced risk of delivering before the 35th week [OR:1.11 (0.83, 1.49)] or during the 35th and 36th weeks [OR:1.15 (0.90, 1.46)].

The inconsistent results of these parallel studies by the same group of investigators may be attributed to differences in the quality of exposure and outcome measurements or they may be due to chance. Overall, convincing support for a role of caffeine in the etiology of preterm birth was not demonstrated.

6. Congenital malformations

6.1. Heterogeneity

All malformations are not etiologically identical. Even those studies limited to one organ or related structures (e.g., lip and palate) are likely evaluating heterogeneous entities. Some studies have assessed single malformations (Mongraw-Chaffin et al., 2008; Torfs and Christianson, 2000; Browne et al., 2007; Miller et al., 2009; Slickers et al., 2008) or utilized more refined sub-classifications of observed phenotypes (Browne et al., 2007; Bille et al., 2007; Johansen et al., 2009; Schmidt et al., 2009; Collier et al., 2009) in an attempt to reduce etiologic heterogeneity.

6.2. Biased exposure data

Because congenital malformations are rare, the case-control (case-referent) design is preferred. This design suffers, however, from potential recall bias, which could result in overestimating the contribution of caffeine to the occurrence of congenital malformations. Alternative strategies for control selection, such as the use of controls with other anomalies, have been proposed to assess the contribution of recall bias, but these methods do not remove the bias if it is present (Liefv et al., 1999; Hook, 2000; Schlesselman, 1982).

All studies of caffeine and congenital malformations reviewed in this report selected controls from non-cases or from a random sample of all births in the population.

6.3. Relevance of time of exposure to disturbed development

While many studies define the exposure interval broadly as the first trimester, the relevant window of exposure for most congenital malformations is the period of organogenesis. Exposures after this period are unlikely to be important.

Since early first trimester exposures coincide with the appearance of pregnancy symptoms for many women, reports of caffeine consumption averaged across the entire first trimester (or longer periods) might not reflect actual exposures during the relevant period of fetal development. Furthermore, the retrospective nature of exposure assessment limits measurement precision for narrowly defined periods of gestation. Although the mean timing of symptom onset is reported to occur between 5 and 6 weeks after the last menstrual period (Gadsby et al., 1993; Lawson et al., 2004), over 13% of pregnant women have been reported to experience symptom onset as early as within the 2 weeks following the estimated time of conception (i.e., 4 weeks after last menstrual period) (Gad-
sby et al., 1993). Thus, concern for accurate exposure assessment in the context of symptom-related changes in caffeine consumption...
remains relevant for outcomes such as congenital malformations that result from very early disruptions to fetal development.

Pre-pregnancy caffeine exposure has been used as a surrogate for consumption in early stages of gestation before pregnancy symptoms develop. This approach would result in misclassification of exposure for women who changed their intake patterns either because they planned their pregnancy or experienced early pregnancy symptoms. The direction of the bias produced by these measurement errors is difficult to predict. If measurement errors are equally likely among cases and controls, misclassification would likely underestimate caffeine-malformation associations when binary measures of exposure are assessed.

6.4. Outcome ascertainment

Recognition of congenital malformations requires the fetus to survive until birth, or at least until prenatal diagnosis. Even malformations among fetuses that survive to birth, however, are not always evident at delivery and may go undiagnosed. When studying malformations that are sometimes fatal, selection bias can occur if exposure leads to higher rates of pregnancy loss in malformed fetuses, resulting in lower proportions of exposed cases (Khoury et al., 1989). Failure to identify malformations resulting in spontaneous or elective abortions may lead to under-ascertainment of cases. Since most studies of congenital malformations are conducted in collaboration with birth defect registries, the impact of active vs. passive surveillance systems on the completeness of reporting must also be considered.

6.5. Review of individual studies of congenital malformations


This case-control study included 306 cases of cleft lip, cleft palate, or both matched to 306 controls by “same district during the same time period”. Given the limited information provided, potential for selection bias cannot be disregarded.

The study was not designed specifically to evaluate caffeine as a risk factor; however, coffee consumption was part of an assessment of dietary preferences. Details regarding the definition of the reference periods “before” and “during” pregnancy were omitted. The authors do not offer a statistical comparison between cases and controls beyond assessing the difference in proportions (chi square test) consuming <1 cup of coffee per week. By our calculations, the crude odds ratios for coffee consumption during pregnancy were 0.8 (0.6–1.1) for 1–2 cups/week and 0.9 (0.4–2.3) for 3–6 cups per week, using the <1 cup/week group as the referent. For coffee consumed before pregnancy, the crude odds ratios were 0.7 (0.5–1.0) for 1–2 cups per week and 0.5 (0.3–0.9) for 3–6 cups per week compared to consumers of <1 cup/week. Thus, case mothers were less likely to consume coffee before pregnancy than the unaffected controls. Given the lack of consideration for founders and great potential for exposure misclassification and recall bias, these data do not make a meaningful contribution to the body of evidence regarding caffeine and congenital malformations. Khoury, J.C., Madovnik, M., Buncher, C.R., Kalkwarf, H., McElvy, S., Khoury, P.R., Sibai, B., 2004. Consequences of smoking and caffeine consumption during pregnancy in women with type 1 diabetes. J. Matern. Fetal Neonatal Med. 15, 44–50. [Discussed also in 3. Spontaneous Abortion and 5. Gestational Age and Preterm Birth]

This study of pregnancy complications among 191 pregnant women with type 1 diabetes evaluated associations between first trimester caffeine use and all major malformations combined. Any consumption of caffeine during the first trimester (i.e., none vs. one or more cups of coffee, tea or soft drinks) was not associated with major malformations [crude OR:2.0 (0.4–11.2)]. The number of observed malformations was not described, but was reportedly too small to estimate adjusted odds ratios. This investigation was severely limited by small sample size, potential confounding, the combination of etiologically heterogeneous malformations, and inadequate exposure assessment.


This population-based case-control study included 997 Down syndrome cases from the California Birth Defects Monitoring Program and 1007 liveborn non-malformed controls from the general population, frequency matched to cases by hospital of birth. Women were interviewed approximately 5–6 months following delivery for consumption of coffee, tea and soft drinks “around the time of conception”. The primary analyses focused on coffee consumption, with the reference group being women who consumed 0–3 cups of coffee per day.

A protective association between heavy coffee intake (>4 cups/day compared to ≤3 cups/day) and Down syndrome was observed among non-smokers [OR:0.5 (0.3–0.8)], but not smokers [OR:1.6 (0.8–3.4)]. The authors interpret their results as evidence that non-smoking mothers (defined as not smoking within three months of conception) consuming high levels of caffeine were more likely to miscarry a fetus with Down syndrome, thereby reducing the prevalence of cases recognized at later deliveries among heavy caffeine users. In other words, the authors suggest that the observed protective effect may indicate selection bias inherent in studies of congenital malformations such as Down syndrome which go largely undetected due to early spontaneous abortions (as described by Khoury et al., 1989). The authors speculate that the lack of a similar observed effect among smokers could be attributed to increased metabolism and caffeine clearance associated with smoking.

While the results presented in this report offer no evidence for a role of caffeine in the etiology of Down syndrome, they also do not directly evaluate contributions of caffeine use to the early loss of Down syndrome fetuses.


This study utilized prospectively collected data on coffee, tea and cola consumption in a case-cohort design, which included 134 cases of cleft lip with and without cleft palate and 58 cases with cleft palate only identified within the Danish National Birth Cohort. Controls (n = 828) were randomly selected from the birth cohort. The authors observed no associations with coffee intake for all oral clefts combined or by subtype. Mothers of babies with isolated cleft palate had 2.5 (1.1–5.6) times greater odds of consuming 5 or more cups of tea per day compared to mothers of controls. Weekly cola intake exceeding one liter was marginally associated with cleft lip with or without cleft palate [OR:1.5 (0.9–2.4)].

The major strength of this study is the evaluation of oral clefts by clinically confirmed subtypes (i.e., cleft lip with and without cleft palate and cleft palate only), which may be etiologically distinct.

There are several limitations, however. Analyses by subtype were limited by small numbers and lacked precision. While exposure assessment was reported to take place between gestational weeks 12–27 (for 90%), few details of the data collection are presented. It is not clear whether consumption was assessed as usual consumption since conception or as average consumption during the first trimester or during a specific reference period. There was no attempt to assess caffeine intake from all sources combined
or patterns of caffeine consumption that may fluctuate with pregnancy symptoms. Closure of lip and palate structures occurs around the 8th week of gestation within normal fetal development (Burdi and Faist, 1967; Yoon et al., 2000). Thus the relevant period of exposure for oral clefts coincides with the time in early pregnancy when pregnancy symptoms begin to appear, with average onset between 5 and 6 weeks of gestation and symptoms peaking by week 8 on average (Gadsby et al., 1993; Lawson et al., 2004). Thus, reports of average daily consumption across the entire first trimester may not reflect actual patterns of exposure during the etiologically relevant period of fetal development.

The absence of consistent results by type of beverage is not consistent with an etiologic role for caffeine in the development of cleft lip and/or palate. Although the measurement errors described above may have tended to obscure associations with caffeinated beverages, these errors would not be expected to differ by type of beverage. While the non-statistically significant protective effect of coffee may be interpreted as evidence for caffeine-related difference among malformed fetuses, we caution against this conclusion since oral clefts do not commonly result in early fetal loss and thus are not susceptible to the form of selection bias described by Khoury et al. (1989) that occurs when cases are identified from live births.


This large case-control study from the National Birth Defects Prevention Study identified specific cardiovascular malformations (n = 4196) from the birth defect registries of eight states and 3957 controls randomly selected from hospital records or birth certificates within each state. This population-based study has a number of strengths including a sample size large enough to evaluate specific malformations considered etiologically homogeneous and an assessment of caffeine intake from multiple sources. The authors also evaluated a complete and well justified list of potential confounders and effect modifiers, providing specific details regarding the criteria for assessment. After conducting a thorough analysis, the authors reported no positive associations between pre-pregnancy caffeine intake and cardiovascular malformation subtypes.

The primary weakness of this study involves retrospective exposure assessment far removed in time from the critical window of susceptibility. Interviews were conducted 8–12 months after delivery on average, with some occurring as late as 24 months after delivery dates. While the burden of recall appeared to be similar for cases and controls, the excessive time gap could have led to reporting errors. Although sensitivity analyses conducted by the authors showed no difference in results when subjects interviewed more than 1 year after the estimated date of delivery were eliminated, these findings do not alleviate concerns about exposure misclassification since recall up to 1 year after delivery could be just as flawed.

The rationale provided for evaluating pre-pregnancy exposure rather than first trimester exposure is that it may better depict intake patterns during the susceptible period for fetal heart development, which tends to occur before most pregnancy symptoms develop (Lacroix et al., 2000). The authors acknowledge that exposure misclassification would likely occur for pregnancy planners or those experiencing early pregnancy symptoms who changed their intake patterns during this early period of gestation.

In the authors’ words, the study “does not provide any appreciable evidence of an association between maternal caffeine consumption and risk of [cardiovascular malformations].”


This nested case-control study of cryptorchidism was conducted among children born to mothers enrolled in the Child Health and Development Studies between 1959 and 1967. Cases (n = 84) were boys with an undescended testicle at birth that remained undescended until 2 years of age. Controls (n = 252) were selected from non-cases and matched 3:1 by race/ethnicity and date of birth. The authors report a modest association between cryptorchidism and caffeine use equivalent to 3 cups of coffee per day [OR:1.4 (1.1–1.9)] after controlling for alcohol, smoking, body mass index and child’s birth weight.

The strengths of the study include prospective data collection on health behaviors at a time when there was less stigma associated with the use of tobacco, alcohol and caffeine during pregnancy. Thus, under-reporting of such patterns would be less likely to occur in this study population and exposure reports would not be influenced by knowledge of the birth outcome.

Selection bias cannot be ruled out as an alternative explanation for the weak association observed in this study. A large proportion of cases (33/101 = 33%) and controls (40/252 = 16%) were excluded from analyses because of missing data. If exclusions differed from inclusions with respect to case/control status and factors that correlated with caffeine consumption, the observed association with caffeine could be distorted.

Another issue pertaining to study quality is the potential for exposure misclassification. Caffeine exposure was assessed by interview conducted “during early pregnancy”, but the specific reference period was not described and the assessment did not capture fluctuations that typically occur during pregnancy. Thus, it is questionable whether the recorded data reflects accurate exposures during the relevant period of fetal development. Although the susceptible period for development of cryptorchidism is not well understood, the relevant time window could plausibly include mid to late pregnancy, given normal testicular descent occurs between gestational weeks 25 and 32 (Rotondi et al., 2001).

Potential confounding by gestational diabetes was also not considered. Mild gestational diabetes has been identified previously as a risk factor for cryptorchidism (Virtanen et al., 2006) while coffee consumption during pregnancy has been linked to a reduced risk of gestational diabetes (Adeney et al., 2007). Thus, gestational diabetes may serve as a negative confounder of the association between caffeine and cryptorchidism. Thus, in the presence of a true association, adjusting for the influence of gestational diabetes may potentially strengthen the observed association.

Given the limitations considered, the study results do not provide convincing evidence for an association between early pregnancy caffeine use and persistent cryptorchidism.


Also originating from the National Birth Defects Prevention Study (NBDPS), this multicenter case-control study examined caffeine intake and other maternal characteristics as risk factors for bilateral renal agenesis or renal hypoplasia. The study consisted of 75 cases and 868 controls. Utilizing data on typical daily caffeine intake reported for the year preceding pregnancy, the study shares many of the main strengths and limitations of Browne et al. (2007) and other caffeine studies derived from the NBDPS. However, the authors incorporated additional data on reported changes in coffee, tea or soda consumption during pregnancy (more, same, less or no intake compared to the year before pregnancy) in an effort to more accurately classify “negligible” vs. “nonnegligible” intake during...
pregnancy. Intake was classified as negligible when there was no report of coffee, tea or soda consumption during pregnancy, mean daily caffeine intake was <10 mg in the year before pregnancy and no intake was reported during pregnancy, or mean daily caffeine intake was <30 mg in the year before pregnancy accompanied by decreased consumption of one or more caffeine sources and no increases in the other caffeine sources during pregnancy. In this report, contributions from chocolate or caffeine-containing medications were not included. No associations with nonnegligible caffeine intake were observed (adjusted OR: 1.01 (95% CI 0.58–1.75). The authors expressed concern that exposure misclassification due to reliance on caffeine exposure recalled for the year before pregnancy may have obscured modest associations.


Using data from the National Birth Defects Prevention Study, this case-control study analyzed 464 infants with anorectal atresia and 4940 controls with no major birth defects. Mothers were interviewed by telephone 6–24 months after the estimated date of delivery (mean 228 days). Caffeine consumption was measured as total caffeine derived from usual intake of beverages and chocolate reported for the year before pregnancy.

Modest borderline significant associations were observed for all categories of caffeine intake [OR: 1.4 (1.0–1.9) for 10–99 mg; OR: 1.3 (1.0–1.8) for 100–299 mg; OR: 1.5 (1.0–2.2) for >300 mg compared to <10 mg]. It is notable that the point estimates were strengthened (but less stable) when caffeine exposure was refined according to reported changes in caffeine intake during pregnancy (i.e., restricted to those in reference group reporting same or less caffeine during pregnancy and those in the exposed groups reporting same consumption or more during pregnancy) [OR: 2.6 (1.2–5.6) for 10–99 mg; OR: 2.1 (1.0–4.4) for 100–299 mg; OR: 2.6 (1.2–6.0) for >300 mg]. All findings are reported as unadjusted because none of the factors evaluated met the criterion for confounding (i.e., 10% change in caffeine estimate), including smoking. However, “any smoking” during the periconceptional period was found to be associated with anorectal atresia in these data, which raises the question of residual confounding by smoking due to measurement error or variable specification in the multivariate model. Recall bias and exposure misclassification resulting from the need to collapse reporting or from poor representation of true periconceptional caffeine exposures are other considerations for the observed associations.


Cases of cleft lip with or without cleft palate (n = 377) and cleft palate only (n = 196) were identified from two surgical centers in Norway. Controls (n = 763) were randomly selected from the national birth registry. Mothers were interviewed 14–15 weeks after delivery for coffee, tea and soft drink consumption during the first three months of pregnancy. No associations were observed for total caffeine intake from all sources and risk of cleft lip with or without cleft palate [OR: 1.2 (0.7–2.0) for >500 mg compared to 0–100 mg] or cleft palate only [OR: 1.1 (0.5–2.2) for >500 mg compared to 0–100 mg]. Coffee intake, however, was weakly associated with cleft lip with or without cleft palate [OR: 1.6 (1.1–2.4) for ≥3 cups/day], but not cleft palate only. In contrast, tea consumption appeared to protect against risk of both subtypes.

The study controlled for known or suspected confounders, including smoking and nausea. The primary limitation, however, was the possibility of recall bias. As noted for Bille et al. (2007), the lack of association with total caffeine intake and inconsistent results by type of beverage is not supportive of an etiologic role for caffeine in the development of cleft lip and/or palate.


Due to the large size of the National Birth Defects Prevention Study, this case-control study was able to separately assess associations with specific types of neural tube defects including spina bifida (n = 459), anencephaly (n = 218) and encephalocele (n = 91) as compared to 4143 non-malformed controls. Because total average daily caffeine intake from coffee, tea, soda and chocolate was assessed during the year prior to pregnancy, the use of caffeine-containing medications during the periconceptional period (one month before pregnancy through the first three months of pregnancy) was assessed separately. Caffeine exposure was evaluated as total mg/day and by source as cups per day. Modest associations with spina bifida were observed for any consumption of caffeine (> 10 mg/day; OR = 1.4; 95% CI 1.1–1.9), any caffeinated coffee (≥1 cup/month; OR = 1.3; 95% CI 1.0–1.6), and any caffeinated soda (>0/day; OR = 1.2; 95% CI 1.0–1.6). When stratified by smoking, alcohol and maternal age, the associations between spina bifida and any caffeine intake were only observed among women without the high risk characteristics (i.e., among non-smokers, non-alcohol users, younger aged women). Any consumption of caffeinated tea was found to be protective for spina bifida (OR = 0.7; 95% CI 0.6–0.9). When examined across increasing categories of consumption, associations were limited to the groups with lower levels of consumption; thus, no evidence of a dose–response with increasing caffeine intake was observed. Similarly, associations with encephalocele were observed for coffee and tea, but only for categories of 1 cup/day of coffee and not greater levels of consumption. No associations with anencephaly were observed.

As with other NBDFS studies, the authors acknowledge the potential for recall bias (e.g., interviews conducted an average of 9.7 and 8.0 months after delivery for cases and controls), measurement error (e.g., exposure reported for year before pregnancy, and used only the implied serving size of “a cup”) and possible residual confounding (e.g., imprecise measurement of some covariates such as smoking (yes/no)). Although the lack of a dose–response detracts from the strength of evidence for a causal association, the authors suggest tolerance effects that develop among regular users may diminish dose effects. For higher levels of consumption (≥200 mg/day), the authors suggest tolerance effects that develop among regular users may diminish dose effects.


The National Birth Defects Prevention Study was also the source for this case-control study of orofacial clefts. This study included 1531 infants with cleft lip with or without cleft palate, 813 infants with cleft palate only and 5711 controls with no major birth defects. Isolated and multiple malformations were also assessed separately. The NBDFS details concerning caffeine measurement and other study considerations have been described above. For total caffeine intake from coffee, tea, soda and chocolate, odds ratios were modestly elevated for limited amounts of caffeine intake (10–199 mg/day) relative to <10 mg/day for most outcomes (e.g., isolated cleft lip with or without cleft palate: OR = 1.2; 95% CI 1.0–1.5 for 100–<200 mg/day), but no associations were observed for higher levels of caffeine intake (200 – <300 mg/day and 300 + mg/day). When intake was examined by source, three or more cups of coffee per day was protective against cleft palate only with multiple unrelated malformations (OR = 0.3; 95% CI 0.1–0.9) but an increased odds ratio was observed for similar tea intake (OR = 2.4; 95% CI 1.3–4.6). Medication containing 100 + mg of caf-
feine per dose was associated with isolated cleft lip with or without cleft palate (OR = 2.3; 95% CI 1.3–4.0) relative to no use of caffeine-containing medication. The authors interpret their findings as failing to provide support for an overall association between maternal caffeine intake and orofacial clefts, noting that effects with caffeine-containing medications should be further explored for the role played by other substances, confounding by indication and the possibility that users represent those with higher daily caffeine intake.

7. Fetal growth restriction

As a perinatal outcome of interest, fetal growth is considered a marker of healthy intrauterine development and a predictor of postnatal morbidity and mortality (Savitz et al., 2002). Most studies of caffeine and fetal growth have assessed intrauterine growth restriction (IUGR) (also referred to as SGA) defined as birth weight <10th centile for gestational age according to a standard growth curve from a selected reference population appropriate for the infant (by sex and race). Other measures of fetal growth explored in relation to caffeine use include birth weight, relative birth weight (Z-scores), low birth weight (<2500 g), high birth weight (>4000 g), birth length, ponderal index (birth weight (g)/birth length (cm) × 100), head circumference, abdominal circumference, placental weight, and placental diameter.

7.1. Defining growth restriction

The external standards of birth weight for gestational age used to define IUGR vary among studies. While it is agreed that a single standard is not appropriate for use in all populations and that the standard used should be population-specific, no population-specific standards have been adopted (Ott, 2006). Furthermore, the birth weight standards in use do not stratify the growth curves by the same population characteristics, so they may be inconsistently specified by any combination of sex, race and/or parity.

Because it is difficult to distinguish constitutionally small babies from babies who are genuinely growth restricted, births defined as IUGR using a population standard (such as the 10th centile) will capture heterogeneous outcomes. Thus, the inclusion of genetically small but otherwise normal babies as IUGR would attenuate associations of potential risk factors with fetal growth restriction. Alternative methods have been proposed for identifying infants who fail to obtain their inherent growth potential. These methods compare birth weight to a customized fetal growth curve, which predicts weight for gestational age according to maternal height and weight, sex, race/ethnicity and parity (Gardosi, 1997, 2006; Zhang et al., 2007). Customized growth curves have not been widely used, however, in studies of IUGR etiology.

7.2. Accurate estimation of gestational age

The issues addressed in Section 5.2 concerning accurate estimation of gestational age and preterm birth are also relevant to studies of IUGR. While ultrasound-based pregnancy dating is often preferred, this method is also derived from measurements of fetal growth (e.g., the bi-parietal diameter of the skull), which can be influenced by fetal growth restriction. Thus, IUGR infants may escape identification if this circular argument causes gestational age to be underestimated by the use of ultrasound measurements.

7.3. Relevant window of susceptibility

The timing of exposure assessment is important for studying the etiology of fetal growth restriction, but the exact window of susceptibility is unknown. Although fetal size was previously believed to be determined during the third trimester of pregnancy when weight gain is most rapid, recent evidence suggests that fetal growth restriction may be determined by conditions occurring early during the first trimester of pregnancy (Smith et al., 1998; Smith, 2004; Bukowsky et al., 2007). This uncertainty underscores the importance of assessing caffeine exposure throughout the course of pregnancy when investigating possible associations with fetal growth.

7.4. Pregnancy signal

Although the role of the pregnancy signal is well acknowledged in studies of caffeine and spontaneous abortion, confounding by pregnancy symptoms has been considered less often in studies of IUGR. Yet, the pregnancy signal might be related to placental size. Fetal growth restriction is often associated with a small placenta (Naeye, 1987; Redline and Patterson, 1994; Thame et al., 2004). Still unknown is whether the process that limits fetal growth also limits placental growth, or whether a small placenta reduces fetal growth by synthesizing inadequate amounts of proteins that promote growth. Either way, the small placenta can be expected to synthesize less of the hormones needed for growth, some of which at high levels may produce the pregnancy signal (Lawson et al., 2002).

7.5. Review of individual studies of fetal growth restriction


Gestational age was estimated by administering the Ballard examination within the first day of life (Ballard et al., 1979), which may have contributed to nondifferential misclassification of IUGR. Although the study population was large, the study was limited by the low percentage of women consuming more than moderate amounts of caffeine (>300 mg/day) during the two time periods assessed (5% in month 1 and 2% in month 7). This limited the power to detect associations with caffeine use >300 mg/day. On the other hand, the authors acknowledge that recall bias was a possibility for month seven caffeine consumption, which was reported after delivery. In addition, pregnancy symptoms were not considered as a potential confounder.

The data presented in this study provide no evidence to support a link between caffeine use in the first or seventh month of pregnancy and fetal growth restriction.
of gestation onward was obtained from the third trimester interview (conducted between weeks 32–34). The long recall period associated with the retrospective reports of consumption occurring up to 7 months prior may have produced nondifferential misclassification. Furthermore, averaging intake across large spans of time such as trimesters or throughout pregnancy may misrepresent peak exposures during the relevant window of susceptibility.

The authors reported no differences in adjusted mean birth weight or Z-scores across caffeine intake categories defined as 0–99, 100–299, 300–499 or ≥500 mg/day during the first, second or third trimesters or for average consumption throughout pregnancy. The authors controlled for confounding by third trimester smoking (yes/no using cotinine >15 ng/ml) and pregnancy symptoms, but this had little impact on the results. Furthermore, no effect modification by smoking or pregnancy symptoms was observed.


This study evaluated third trimester serum paraxanthine concentrations in archived samples from Collaborative Perinatal Project participants. Caffeine metabolites might measure biologic dose better than reported caffeine consumption, but reflect only recent exposures (Aldridge et al., 1981). Because the serum samples were stored for more than 30 years before being analyzed, the stability of the caffeine metabolite in the available specimens is also questioned.

The authors reported that risk of delivering an SGA infant increased with rising third trimester serum paraxanthine concentrations, but only among smokers. The increased risk among smokers was modest (displayed graphically as ORs ≈ 2.0 and lower) and only present for categories of paraxanthine concentrations exceeding the 65th percentile (>715 ng/ml). These effects were observed after controlling for self-reported number of cigarettes smoked per day within the stratum of smokers. No associations with serum caffeine concentrations were observed. The authors acknowledge that residual confounding due to under-reporting of number of cigarettes smoked could have exaggerated observed associations for paraxanthine. Furthermore, pregnancy symptoms were not evaluated. Because the modest associations observed in this study could be influenced in an unpredictable manner by sample desiccation and confounding, cautious interpretation is advised.


To evaluate the effect of caffeine intake on newborn and placental characteristics, the authors recruited a group of women who smoked <10 cigarettes per day (n= 60) and a group of non-smokers (n= 63) who delivered at term (37–41 weeks). The reference period for the reported caffeine intake from coffee and tea was not specified. The authors reported lower mean birth weights and placental weights for women reporting average daily consumption of caffeinated beverages. No associations with serum caffeine concentrations were observed. The authors acknowledged that residual confounding due to under-reporting of number of cigarettes smoked could have exaggerated observed associations for paraxanthine. Furthermore, pregnancy symptoms were not evaluated. Because the modest associations observed in this study could be influenced in an unpredictable manner by sample desiccation and confounding, cautious interpretation is advised.

Thus, the results do not offer convincing support for an effect of caffeine on fetal growth or placental development.


This prospective cohort study of 2291 pregnant women ≤24 gestational weeks evaluated urinary caffeine concentrations and self-reported caffeine exposures during early and late pregnancy in relation to IUGR, low birth weight and preterm birth. A major strength of this study is that it was designed to assess pregnancy outcomes in relation to caffeine consumption and, thus, incorporated a very detailed assessment of caffeine exposure from beverage sources.

First and third trimester caffeine consumption was not associated with increased risk of IUGR or low birth weight. Increased concentrations of urinary caffeine (mg/g creatinine) were also not associated with IUGR [OR:1.0 (0.8–1.1)] but appeared to be protective for low birth weight [OR:0.7 (0.5–1.0)]. When birth weight and caffeine were assessed as continuous variables, each 100 mg of caffeine consumed during the first trimester was associated with a birth weight reduction of 28 g (95% CI 10–46 g). No such associations were observed with low birth weight [OR:1.00 (0.98–1.00)]. The authors conclude that moderate caffeine consumption during the first trimester may have a modest effect on birth weight that may not be clinically important. No associations with third trimester caffeine consumption were reported. Ultimately, the authors reasoned that urinary caffeine may not be a useful biomarker since less than 2.0% of caffeine is excreted in this form.

This study provides no evidence to suggest that caffeine consumption during early or late pregnancy is related to growth restriction as measured by IUGR and low birth weight. Only modest reductions in birth weight were observed with increasing caffeine use.


This study of risk factors for high birth weight (>4000 g) evaluated a large cohort of women without diabetes who gave birth in Denmark (1990–1999). Women seeking prenatal care (n= 24,083) completed a questionnaire at approximately 16 weeks of gestation reporting average daily consumption of caffeinated beverages. The reference period for the self-reported caffeine intake was not described.

Consuming more than 200 mg/day was associated with a decreased odds of giving birth to a high birth weight infant compared to consuming <200 mg/day [OR:0.9 (0.8–1.0) for 200–399 mg/day and OR:0.9 (0.8–1.0) for >400 mg/day]. The main strengths of this study were the large sample size and control for number of cigarettes smoked per day (e.g., non-smoker, 1–4, 5–9, 10–14, 15+ cigarettes/day), alcohol intake, gestational age, and other confounders. Misclassification of caffeine, however, was possible given the single assessment at 16 weeks of gestation would not capture changing patterns of consumption during pregnancy. The modest protective odds ratio may also overestimate the relative risk given the outcome was relatively common (19%) in this study population.


This study population included subjects (n= 858) from the Norwegian site of a multi-site Scandinavian study of SGA. This study is given use of a single measurement of caffeine intake, which did not capture sources other than tea and coffee or specify cup size. Thus, the results do not offer convincing support for an effect of caffeine on fetal growth or placental development.

This study provides no evidence to suggest that caffeine consumption during early or late pregnancy is related to growth restriction as measured by IUGR and low birth weight. Only modest reductions in birth weight were observed with increasing caffeine use.

First and third trimester caffeine consumption was not associated with increased risk of IUGR or low birth weight. Increased concentrations of urinary caffeine (mg/g creatinine) were also not associated with IUGR [OR:1.0 (0.8–1.1)] but appeared to be protective for low birth weight [OR:0.7 (0.5–1.0)]. When birth weight and caffeine were assessed as continuous variables, each 100 mg of caffeine consumed during the first trimester was associated with a birth weight reduction of 28 g (95% CI 10–46 g). No such associations were observed with low birth weight [OR:1.00 (0.98–1.00)]. The authors conclude that moderate caffeine consumption during the first trimester may have a modest effect on birth weight that may not be clinically important. No associations with third trimester caffeine consumption were reported. Ultimately, the authors reasoned that urinary caffeine may not be a useful biomarker since less than 2.0% of caffeine is excreted in this form.

This study provides no evidence to suggest that caffeine consumption during early or late pregnancy is related to growth restriction as measured by IUGR and low birth weight. Only modest reductions in birth weight were observed with increasing caffeine use.

This study of risk factors for high birth weight (>4000 g) evaluated a large cohort of women without diabetes who gave birth in Denmark (1990–1999). Women seeking prenatal care (n= 24,083) completed a questionnaire at approximately 16 weeks of gestation reporting average daily consumption of caffeinated beverages. The reference period for the self-reported caffeine intake was not described.

Consuming more than 200 mg/day was associated with a decreased odds of giving birth to a high birth weight infant compared to consuming <200 mg/day [OR:0.9 (0.8–1.0) for 200–399 mg/day and OR:0.9 (0.8–1.0) for >400 mg/day]. The main strengths of this study were the large sample size and control for number of cigarettes smoked per day (e.g., non-smoker, 1–4, 5–9, 10–14, 15+ cigarettes/day), alcohol intake, gestational age, and other confounders. Misclassification of caffeine, however, was possible given the single assessment at 16 weeks of gestation would not capture changing patterns of consumption during pregnancy. The modest protective odds ratio may also overestimate the relative risk given the outcome was relatively common (19%) in this study population.


This study population included subjects (n= 858) from the Norwegian site of a multi-site Scandinavian study of SGA. This study is given use of a single measurement of caffeine intake, which did not capture sources other than tea and coffee or specify cup size. Thus, the results do not offer convincing support for an effect of caffeine on fetal growth or placental development.
one of few to prospectively collect caffeine exposure data through the use of food diaries. Diaries were completed across 3 weekdays in the second (17–20 weeks) and third trimesters (33 weeks). While likely to capture current intake during the two specified time points with fewer recall errors, food diaries would not necessarily reveal intake patterns that may fluctuate from week to week, month to month, or even weekday to weekend. For analyses, caffeine was dichotomized to represent intake above and below the mean value (232 mg/day at 17 weeks; 205 mg/day at 33 weeks).

No association was observed between “high” caffeine intake at 17 weeks and birth of an SGA infant [OR: 1.1 (0.6–2.1)], but high consumption at 33 weeks was associated with an increased odds of SGA [OR: 1.6 (1.0–2.5)]. The association for third trimester caffeine consumption was modified by infant sex [OR: 2.8 (1.4–5.5) for males; OR: 1.0 (0.5–2.0) for females]. These estimates were adjusted for smoking at conception (yes/no), pregnancy weight, education and previous SGA birth, but not for maternal age. Although the findings were consistent among smokers and non-smokers, residual confounding by amount smoked could remain if reported caffeine consumption reflected actual frequency of smoking (among smokers and inaccurately reported non-smokers alike) (Morrison, 1984).

The sex-specific effects of caffeine on SGA are difficult to explain. Fetal sex might be a marker of more severe pregnancy symptoms. For example, having a female fetus has been strongly associated with hyperemesis gravidarum (Tan et al., 2006). We do not know of any sex differences for less severe nausea, but if similar patterns exist, women with male fetuses may have had less nausea, and therefore consumed more coffee. The possibility of sex-specific effects of caffeine on SGA is intriguing, but consideration of all potential confounders including nausea and aversions would be necessary before a causal link could be legitimately considered.


This case-control study of term singletons born in Italy selected 555 SGA babies and 1966 controls. The methods for estimating gestational age for the SGA definition were not described. Information on coffee, tea, and cola was collected after delivery, measured as number of cups per day before pregnancy and during each trimester. Total caffeine intake from all beverage sources was not assessed.

The authors observed no associations between SGA and intake of three or more cups of coffee during the first, second or third trimester of pregnancy. Likewise, no associations were observed for heavy coffee consumption (> 4 cups/day) before pregnancy [OR: 1.3 (0.9–1.9)]. Because the control inclusion criterion for full term deliveries was not applied equally to the selection of cases, the authors repeated their analyses after restricting cases to births delivered after 37 weeks of gestation. This reduced the odds ratios for the heaviest coffee consumption categories to exactly 1.0 for all time periods assessed (i.e., before pregnancy and during each trimester). When tea, cola and decaffeinated coffee were each evaluated separately, no associations were observed.


In addition to evaluating preterm birth, this retrospective cohort study assessed SGA births in relation to exposure to a popular caffeinated beverage consumed in South America called maté. All women (n = 5189) giving birth to singletons in the five local maternity hospitals were interviewed within the 24 h following delivery. Frequency of maté use during pregnancy was assessed as number of days the drink was consumed per week (0, 1–6 and 7 days per week). The authors equated daily maté consumption with a daily average caffeine intake of 300 mg (Santos et al., 1998). Gestational age was estimated using the Dubowitz score.

After controlling for maternal age, education, parity, cigarette smoking during the third trimester, previous abortion and previous low birth weight infant, the prevalence of SGA births did not differ among women consuming maté 0, 1–6 or 7 days per week. The primary limitation of this study was the non-specific measure of caffeinated beverage consumption in days per week rather than servings per day. Other sources of caffeine intake were not considered. Recall bias was also possible given women were interviewed after delivery. Confounding by alcohol and nausea was not considered in the analyses. Because of its limitations, this study should be viewed as weak evidence that caffeine does not influence the risk of fetal growth restriction.


This study was conducted within the prospective cohort described by Bracken et al. (2003) who were selected on the basis of caffeine consumption > or < 150 mg/day. Of the 2291 participants, 1606 had cord blood samples available for analysis of serum caffeine, paraxanthine, theophylline and theobromine concentrations.

No associations were observed for the highest quartile of serum caffeine concentrations [OR: 0.5 (0.1–2.0)]. Caffeine metabolites were not associated with IUGR when evaluated independently, but infants born to women with the highest concentrations of paraxanthine (fourth quartile) had a 3-fold increased risk of IUGR [OR: 3.3 (1.2–9.2)], but only when also controlling for serum caffeine concentrations. This led the authors to suspect that metabolic activity rather than absolute concentrations of caffeine and its metabolites may have more relevance for fetal growth, so the remaining analyses assessed the ratio of paraxanthine to caffeine as a marker of CYP1A2 enzymatic activity. The adjusted odds ratio for a one standard deviation increase in the ratio of paraxanthine to caffeine was 1.2 (1.1–1.4). Thus, fast metabolizers experienced a higher risk of IUGR than slow metabolizers.

The major strength of this study was the use of biomarkers in cord blood measurements as indicators of biologic dose entering the fetal circulation. Given the short half-life of caffeine and its metabolites, concentrations observed at delivery may not accurately characterize exposure throughout pregnancy unless caffeine consumption habits were fairly consistent over time.

Only 55% of the population had gestational age confirmed by ultrasound. As with all studies of IUGR, errors in gestational age based on inaccurate recall of the date of the last menstrual period can lead to misclassification of IUGR. Residual confounding by smoking could have overestimated the association between caffeine metabolism and IUGR. Urinary cotinine levels (before 25 weeks of gestation) were available for the cohort and reported in a previous paper by Bracken et al. (2003), but only self-reported smoking (yes/no) during the third trimester was utilized in these analyses. This choice likely reflects the preference for third trimester smoking measurements more proximate to the timing of the cord blood measurements.

As the authors acknowledge, CYP1A2 activity may be a marker for other compounds such as tobacco smoke that induce metabolic activity and alter fetal growth (Campbell et al., 1987b). The observed effect of metabolic activity, however, was similar in self-reported smokers and non-smokers. Confounding by nausea was not evaluated, but it is unknown if pregnancy symptoms would be related to metabolic activity.

These findings are suggestive of a possible modest relationship between high metabolic activity, as measured by the ratio of para-
xanthine to caffeine concentrations in cord serum, and risk of IUGR. Better control for smoking would have enhanced confidence in the results.


This study did not directly assess the effects of caffeine on fetal growth, but measured the effects of a one-cup dose of coffee on maternal and fetal blood flow during the third trimester. A group of 10 non-smoking women in their third trimester of pregnancy underwent Doppler examinations before and after coffee consumption (100 mg caffeine). All participants typically consumed 1–3 cups of coffee per day. Resistance index values were calibrated to measure blood flow in the maternal uterine artery, umbilical artery and fetal middle cerebral artery 30 min after coffee intake. Coffee had no effect on maternal or fetal blood flow. When the effects of coffee on stress levels were assessed by measuring salivary cortisol and chromogranin A (CgA), coffee intake reduced salivary cortisol levels in the 10 pregnant women but not in a comparison group of 14 women who were not pregnant. CgA concentrations, which were considered an indication of physiological stress, increased following coffee consumption in non-pregnant women, but significant increases were not detectable in pregnant women. The small study size and limited statistical power restricts confidence in the absence of associations.


Women who regularly drank at least three cups of coffee per day (n = 1197) were randomly assigned to caffeinated or decaffeinated instant coffee during the last half of pregnancy. The pregnancies were followed to evaluate differences in gestational age and mean birth weight. Although participants were provided unlimited amounts of coffee, either caffeinated or decaffeinated as assigned, they were also free to consume other sources of coffee and caffeinated beverages. According to self-reports, more than one-third of those assigned to decaffeinated coffee consumed >1 cup of caffeinated coffee on a daily basis.

Using the intent to treat approach to analysis, no difference in birth weight was observed when comparing women assigned to caffeinated vs. decaffeinated coffee. This approach, however, would missclassify true exposure status given poor compliance with assigned coffee treatment. When analyses were restricted to subgroups defined as women reporting no consumption of other caffeinated coffee (n = 283) or women reporting <1 cup of other caffeinated coffee per day (n = 266), the results were unchanged. Birth weight remained similar across caffeine assignment groups within non-smokers and within women smoking 1–10 cigarettes per day. However, among women smoking >10 cigarettes per day, those randomized to caffeinated coffee had a lower mean birth weight than the decaffeinated group (mean difference: 263 g [97–430 g]), adjusted for parity, pre-pregnancy BMI and length of gestation. The possible interaction between smoking and caffeine consumption is unconvincing without presentation of the results by compliance or, preferably, by actual caffeine consumption.


In this study, 750 pregnant women between 20 and 28 weeks gestation were recruited from a prenatal clinic to study depression, anxiety and substance use. Birth outcomes including birth weight and “pregnancy complications” were collected from medical charts on a sub-sample of 452 participants. Pregnancy complications were not defined. Caffeine consumption was collected from interviews conducted at enrolment and described as caffeinated drinks per day during pregnancy, but the data collection procedures were not described. It would appear, however, that all caffeinated beverages were weighted equally. The range of exposure was reported as 0–6 caffeinated drinks per day, with 38% reporting no caffeine consumption. Weak negative correlations were observed between number of caffeinated drinks and birth weight (r = −0.11, p < 0.05). In hierarchical linear regression analyses restricted to women who reported no smoking or alcohol use, caffeine intake explained 8% of the variability in birth weight when controlling for anxiety and depression. In light of the study limitations – which include questionable exposure assessment and lack of control for other important confounders such as maternal age and body mass – this study provides limited information.


This hospital-based, case-control study of SGA births identified 451 cases matched to an equal number of controls by gestational age, sex and race. Interviews were generally conducted within two days of delivery. CYP1A2 and CYP2E1 polymorphisms were genotyped using peripheral blood samples from mothers and newborns. Genotypes were dichotomized as those with one or two copies of the variant allele vs. those with the wild type.

The authors observed no association between caffeine consumption and SGA when using either continuous or dichotomous (<300 vs. ≥300 mg/day) measures of caffeine intake during the month before pregnancy or during the first, second, or third trimester of pregnancy. Adjustment for smoking (none vs. any) and nausea had little impact on the observed lack of associations, although stratification by smoking status revealed a 22% increased odds of SGA among non-smokers for every 100 mg/day consumed during the first trimester [OR:1.2 (1.0–1.5)]. The effect of first trimester caffeine consumption on SGA was not modified by maternal or newborn genetic polymorphisms. Birth weight was reduced by −31 (95% CI −61, −1) and −38 g (95% CI −68, −8) for every 100 mg of caffeine consumed during the second and third trimester, respectively. The effects of caffeine on birth weight were also restricted to non-smokers.

Although the study improved upon most previous studies by including measurements of nausea by trimester (presence vs. absence), residual confounding would persist if severity or aversions were misclassified true exposure status given poor compliance with assigned coffee treatment. When analyses were restricted to subgroups defined as women reporting no consumption of other caffeinated coffee (n = 283) or women reporting <1 cup of other caffeinated coffee per day (n = 266), the results were unchanged. Birth weight remained similar across caffeine assignment groups within non-smokers and within women smoking 1–10 cigarettes per day. However, among women smoking >10 cigarettes per day, those randomized to caffeinated coffee had a lower mean birth weight than the decaffeinated group (mean difference: 263 g [97–430 g]), adjusted for parity, pre-pregnancy BMI and length of gestation. The possible interaction between smoking and caffeine consumption is unconvincing without presentation of the results by compliance or, preferably, by actual caffeine consumption.


This cross-sectional study was conducted among the Nurses’ Mothers’ Cohort. Mothers of the Nurses’ Health Study participants (n = 34,063) were sent questionnaires to collect information on daughter’s birth weight as well as behaviors and conditions during the pregnancy. Mothers were 60–80 years old when completing the questionnaire about events that occurred approximately 40–60 years earlier. Thus, the long recall period is the major limitation of this study. Coffee consumption was measured as intake “during pregnancy” in cups/day. Daughter’s birth weight was also self-reported, although a subset were validated against birth certificates (r = 0.85).

Birth weight was negatively associated with coffee consumption during pregnancy, decreasing by 15, 34 and 54 g for consump-
tion of 1–2, 3–4 and ≥5 cups of coffee per day. The odds of IUGR were modestly increased in a dose–response fashion with increasing coffee consumption, with the strongest association observed among women reporting ≥5 cups of coffee per day [OR: 1.6 (1.3–2.1)]. Although many important confounders were considered, pregnancy symptoms were not accounted for. The weak associations observed in this study could potentially be attributed to measurement error and confounding.


This prospective study from the United Kingdom evaluated a cohort of 2635 women recruited early in pregnancy (8–12 weeks of gestation). A major strength of the study was its thorough assessment of caffeine exposure. Three questionnaires were administered to capture recall of caffeine consumption for each trimester (5–12, 13–28, and 29–40 weeks of pregnancy). The questionnaire considered all beverage, food, and over-the-counter medication sources, brands, portion sizes, and methods of preparation. Caffeine half-life was measured in saliva samples as an indicator of fast or slow caffeine clearance, collected one and five months following a 63.5 mg caffeine challenge (500 ml diet soda over 20 min) after fasting.

This study also strived to improve upon IUGR classification by applying customized fetal growth curves (i.e., identifying birth weight <10th percentile for gestational age according to maternal height, weight, ethnicity, parity and sex) in an effort to avoid misclassifying constitutionally small infants as growth restricted. Furthermore, gestational age was confirmed by ultrasound in all pregnancies. Another positive feature was the use of salivary cotinine concentrations to identify current smokers, non-smokers and those exposed to second-hand smoke. However, these measurements were taken during the first trimester recruitment visit and may not accurately reflect tobacco exposure throughout pregnancy. Caffeine consumption averaged over the entire pregnancy was modestly associated with IUGR OR:1.2 (0.9–1.6) for 100–199 mg/day; OR:1.5 (1.1–2.1) for 200–299 mg/day; OR:1.4 (1.0–2.0) for ≥300 mg/day compared to ≤100 mg/day). Similar associations were observed for caffeine exposure in each trimester, with slightly larger odds ratios for the 2nd and 3rd trimester. Associations between consumption >200 mg/day and reduced birth weight in the range of 60–70 g were also observed across all time periods. When the data were stratified by caffeine clearance, the association with IUGR appeared to remain only among the fast metabolizers; although, the confidence intervals in each strata largely overlapped with the exception of the 200–299 mg/day category (test for interaction p = 0.06).

The major limitation of this study is the potential for confounding by pregnancy symptoms and aversions. The authors mention an assessment of the effects of adjusting for nausea, but these results were not presented and no description of the nature of the nausea data was provided. A related concern is the extremely low participation rate (20%). The authors dismiss the likelihood of selection bias, but the higher prevalence of IUGR in the study population (13%) compared to the general population (10%) suggests that women with a history of fetal growth restriction may have been more motivated to participate in the study. If pregnancies destined to be growth restricted produced a weaker pregnancy signal, selection into the study would be related to both the outcome (IUGR) and the exposure (higher caffeine intake due to fewer symptoms and aversions). Thus, the more highly exposed, growth restricted group would be over-represented. Because pregnancy symptoms and aversions were not controlled in these analyses, selection bias remains a plausible explanation for the modest associations observed in this study.

The authors of the study considered that, for the first time among similar studies, the quantification of caffeine from all known sources reflected “a true picture of total caffeine intake by women during pregnancy”. However, when the validation study compared the caffeine questionnaire to a 3-day food diary and repeated salivary caffeine and paraxanthine concentrations, only fair to moderate levels of agreement (intraclass correlation for food diary = 0.5; Kappa for biomarkers 0.33–0.65) were observed (Bollan et al., 2008). Although considerable steps toward improving the assessment of caffeine exposure were taken, the data collection instrument does not succeed in eliminating all concerns about caffeine measurement error. Potential for recall bias specific to 2nd and 3rd trimester exposure reports may also exist, as women became aware of restricted fetal growth during routine mid- or late pregnancy ultrasounds. This could explain the slightly stronger associations observed for caffeine consumption during 13–28 and 29–40 weeks of gestation.

8. Discussion/conclusions

8.1. Subfecundity

Of the nine publications since 2002, one evaluated multiple outcomes associated with fertility treatment, one considered self-reported ovulatory infertility, three addressed time to conception, and most (4) assessed the relationship between caffeine and semen parameters.

The only study to assess the effect of caffeine on endpoints of assisted reproductive technology reported no influence of previous or current caffeine intake on oocyte retrieval, fertilization, embryo transfer or the occurrence of a clinical pregnancy. The effect of limited caffeine use on failure to achieve a live birth was inconsistent for exposures reported for different time periods that reflected usual and recent exposures. Caffeine use around the week of IVF or GIFT procedures was not associated with failure to achieve a live birth, while associations with usual lifetime use and use reported during first clinic visit were observed. Replication of results in larger populations undergoing ART is needed to address concerns about statistical power, precision, residual confounding and caffeine exposures >50 mg/day.

Exposure measurement errors are a primary concern for the few recent studies addressing time to conception and ovulatory infertility. Potential recall bias and exposure misclassification may explain the modest association reported for coffee and tea consumption and increased time to pregnancy. No support for an association with infertility due to ovulation disorders was provided, but exposure measurement error was likely introduced as a result of the timing of exposure assessments.

Evaluations of semen quality have consistently failed to observe adverse effects associated with caffeine intake. Studies of DNA damage, however, have been more limited but inconsistent. Most of the studies of male reproductive outcomes have suffered from lack of detailed reporting of caffeine exposure assessment, potential exposure misclassification for the relevant etiologic window, no or limited control for confounders, potential selection bias, or restriction to fertile men, which limited the ability to detect caffeine-related abnormalities.

In summary, consistent relationships between caffeine intake and measures of subfecundity have not been observed.

8.2. Spontaneous abortion

The current evidence remains insufficient to permit conclusions regarding the potential role of caffeine in spontaneous abortion.
Studies of caffeine and spontaneous abortion are complicated by the challenge of separating cause and effect. Studies have not successfully addressed the complex interrelationship between viability, pregnancy signal symptoms and caffeine consumption patterns. Of the 15 studies that have evaluated caffeine and spontaneous abortion since the Leviton and Cowan (2002) review, 10 did not attempt to control for pregnancy signal symptoms. Although positive associations were consistently reported by these 10 studies, these consistent findings may very well be attributed to bias that persists across all studies. As a marker of pregnancy viability and a correlate of exposure, confounding by pregnancy signal symptoms may explain observed associations with caffeine use. Women with pregnancies that go to term experience more frequent and severe nausea early in pregnancy compared to women whose pregnancies end in spontaneous abortion (Weigel and Weigel, 1989). Lawson et al. (2002, 2004) demonstrated that weekly duration of nausea (in hours) and appetite loss (in days) is positively related to human chorionic gonadotropin (hCG) levels during pregnancy, whereas hCG levels are also negatively related to coffee consumption. Of those women who decrease coffee consumption during the first trimester of pregnancy, 65% report a physical aversion to coffee (Lawson et al., 2004). Thus, women experiencing viable pregnancies tend to experience a stronger pregnancy signal that ultimately drives caffeine intake downward. The pregnancy signal is, therefore, a crucial confounder of the association between caffeine and pregnancy viability.

Results from studies that have attempted to control for nausea and vomiting during pregnancy have been less consistent. Improved assessments of relevant symptom characteristics, such as aversions to taste and smell, in addition to symptom severity, duration, frequency and timing are needed to improve study validity. The study by Wen et al. (2001) provides perhaps the best evidence for the pregnancy signal phenomenon to date, whereby increased risk of spontaneous abortion was only observed for caffeine consumed after nausea onset, but not for caffeine consumed before nausea onset or among those without nausea. Other persistent problems with the validity of studies of caffeine and spontaneous abortion include confounding by smoking and potential recall bias.

8.3. Fetal death

Three of the four studies evaluating caffeine and fetal death reported moderately positive associations of similar magnitude. Three of the four were conducted by members of the same research group using similar methodologies and similar study populations. None, however, sufficiently address concerns regarding confounding by pregnancy symptoms. Only one study attempted to control for pregnancy symptoms, but the limited assessment of the pregnancy signal defined as presence or absence of nausea or vomiting during the first trimester was insufficient to avoid residual confounding. However, Bech et al. (2005) provided a useful demonstration of how observed associations can be inflated by undetected fetal demise. As with studies of spontaneous abortion, the interpretation of this body of work, which has consistently reported modest associations across studies, needs to consider that these studies may also share common sources of bias which may explain the observed relationship with caffeine use.

8.4. Preterm birth

Larger studies considering total caffeine exposure consistently reported no increased risk of delivery before 37 weeks of gestation. No studies since 2000, however, distinguished spontaneous from medically indicated preterm deliveries. Two studies of Mediterranean-type diets (Mikkelsen et al., 2008; Haugen et al., 2008) separately evaluated early and late preterm births, with inconsistent results between studies. Coffee intake limited to ≤2 cups/day was linked to a lower odds of preterm delivery ≤34 weeks of gestation, but not late preterm delivery (35–36 weeks) in the Danish National Birth Cohort (Mikkelsen et al., 2008). A similar study conducted within the Norwegian Mother and Child Cohort observed no relationship between coffee intake and early or later preterm delivery (Haugen et al., 2008). Combining etiologically distinct outcomes could obscure associations within clinical subtypes of preterm birth.

8.5. Congenital malformations

With a few exceptions, recent studies have not reported an increased risk of malformations with greater caffeine consumption. However, the body of evidence for any single malformation or subgroup is limited. The reports of modest associations between coffee intake and cryptorchidism and total caffeine intake and anorectal atresia could not confidently rule out potential sources of bias such as selection bias due to missing data, exposure misclassification and confounding.

8.6. Fetal growth

Studies of caffeine and fetal growth restriction are equivocal, with approximately half of the studies in this review reporting weak associations with intrauterine growth restriction or reduced birth weight and half observing no effects. The strength of the evidence for a potential effect of caffeine on fetal growth restriction is diminished by the inability to rule out alternative, credible explanations for the observed associations, namely confounding by pregnancy symptoms and aversions.

8.7. Summary

In conclusion, the weight of evidence does not support a positive relationship between caffeine consumption and adverse reproductive or perinatal outcomes. On the whole, associations with subfecundity, preterm delivery and congenital malformations are not routinely observed. Studies of pregnancy loss and fetal growth have generated more interest due to the frequency with which adverse effects are reported in connection with caffeine use. Our review identifies significant methodological weaknesses common to studies of spontaneous abortion, fetal death and fetal growth restriction, which limit confidence in causal interpretation. Consistent with the conclusion of the previous review (Leviton and Cowan, 2002), the studies available from January 2000 through December 2009 do not provide convincing evidence that caffeine consumption increases risk of any reproductive adversity. Future studies addressing the methodological limitations of current research may alter this conclusion. In particular, quantitative methods are available for adjustment for measurement error in the absence of a gold standard (Joseph et al. 1995) and would be especially useful for estimating the impact of errors in the assessment of caffeine exposure.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Acknowledgements

This work was supported by the Caffeine Working Group of the North American Branch of the International Life Sciences Institute (ILSI). ILSI North America is a public, non-profit foundation that
provides a forum to advance understanding of scientific issues related to the nutritional quality and safety of the food supply by sponsoring research programs, educational seminars and workshops, and publications. ILSI North America receives support primarily from its industry membership. Dr. Peck received a grant from the organization for her work reviewing, analyzing, and summarizing the information contained in this article. ILSI North America also received funding for this project from the National Coffee Association. The opinions expressed herein are those of the authors and do not necessarily represent the views of either funding organization.

References


Cnattingius, S., 2004. The epidemiology of smoking during pregnancy, smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine Tob. Res. 6 (Suppl. 2), S121–S140.


Greenland, S., Gustafson, P., 2006. Accounting for independent nondifferential misclassification does not increase certainty that an observed association is in the correct direction. Am. J. Epidemiol. 164, 63–68.


Lacroix, R., Eason, E., Melzack, R., 2000. Nausea and vomiting during pregnancy: A


Lawson, C.C., LeMasters, G.K., 2006. Regarding “Caffeine metabolism, genetics and


Emergency Department Visits Involving Energy Drinks and Limitations of the Drug Abuse Warning Network (DAWN)

Prepared for the American Beverage Association by PinneyAssociates

July 25, 2013
Table of Contents
1 Executive Summary ........................................................................................................3
2 Drug Abuse Warning Network (DAWN) ........................................................................3
3 Data Analysis Approach.................................................................................................4
4 Increasing Number of Energy Drink-Related ED Visits: Real Phenomenon or Artifact? ..................................................................................................................4
  4.1 Limitations of DAWN ............................................................................................9
    4.1.1 Representativeness of the Sample and Validity of Projected Rates for the U.S. 9
    4.1.2 Reliability of Self-Reported Data ..................................................................10
    4.1.3 Inability to Determine Causation ..................................................................10
5 Potential Issues ............................................................................................................11
6 Conclusion ..................................................................................................................13
8 Appendix ....................................................................................................................14
1 Executive Summary

The Substance Abuse and Mental Health Services Administration (SAMHSA) released a report in January 2013, based on data from the Drug Abuse Warning Network (DAWN), suggesting an increase in the number of emergency department (ED) visits involving energy drinks and concluding that the consumption of energy drinks is a “rising public health problem”. At the request of the American Beverage Association, Pinney Associates (PA) was asked to conduct a review of the DAWN report and its findings.

Overall, reports of energy drink-related ED visits need to be viewed in a broader context, as an analysis of DAWN public use data indicates that drug-related ED visits have also increased (both by a similar proportion and absolute magnitude as compared to energy drinks) for a number of other products, including infant formula, vitamins, and laxatives. Furthermore, the vast majority of energy drink-related ED visits appear to have been occasioned by non-serious medical conditions: 84.4% of visits related to caffeine/multivitamins resulted in discharge home, rather than admission to a treatment facility. In comparison, only 75.5% of alternative medicine-related ED visits resulted in home discharge. Given that there are a number of other products demonstrating comparable increases in ED visits, and that these products appear to be associated with a less benign profile than that associated with energy drinks, it is unclear why energy drinks have been singled out by SAMHSA as a public health concern. The DAWN public use data do not support the public health concern flagged by SAMSHA.

2 Drug Abuse Warning Network (DAWN)

DAWN is a public health surveillance system that monitors “drug-related” visits to hospital EDs. Each year DAWN produces estimates of such visits for the nation as a whole and for selected metropolitan areas. To be a DAWN case, the ED visit must involve a drug, either as the direct cause of the visit or as a contributing factor. Such a visit is referred to as a “drug related visit.” The reason a patient used a drug is not part of the criteria for considering a visit to be drug-related. Drugs include: alcohol1; illegal drugs, such as cocaine, heroin, and marijuana; pharmaceuticals (e.g., over-the-counter medicines and prescription medications); and nutraceuticals, such as nutritional supplements, vitamins, and caffeine-containing products. DAWN cases are identified by the systematic review of ED medical records in participating hospitals. DAWN cases broadly encompass all types of drug-related events, including accidental ingestion and adverse reactions, as well as explicit drug abuse. SAMHSA noted in its report on energy drinks that although energy drinks are not treated as drugs by the FDA, ED visits involving energy drinks were classified as adverse reactions if the chart documented them as such.2

---

1 Alcohol is considered a reportable drug when consumed by patients aged 20 or younger. For patients aged 21 and older, alcohol is reported only when it is used in conjunction with other drugs.

2 Within DAWN, an ED visit is categorized as an adverse reaction when the chart documents that a prescription or over-the-counter pharmaceutical, taken as prescribed or directed, produced an adverse drug reaction, side effect, drug-drug interaction, or drug-alcohol interaction.

Page 3 of 18
PinneyAssociates, Inc.
The exact DAWN survey methodology has been adjusted over time in order to, according to SAMHSA, “improve the quality, reliability, and generalizability of the information produced by DAWN” (Source: DAWN 2010 Codebook). The current approach, which was developed based on recommendations from a 1997 panel of experts and a 2-year SAMHSA evaluation of design alternatives, was introduced in 2003, but not fully implemented until the 2004 data collection year.

3 Data Analysis Approach
In order to put the SAMHSA findings on energy drinks into perspective, PA conducted a number of additional analyses using the DAWN public-use dataset. However, there is an important caveat to these analyses that must be acknowledged; namely, information on the use of energy drinks per se is not currently available in the public-use data file. Rather, the public-use data file only contains information on the larger category of “caffeine/multivitamins,” of which the “energy drinks” category is a subset. As this larger category appears to be mostly comprised of energy drink-related visits (about 80% overall, from 2005-2011) information pertaining to caffeine/multivitamin-related ED visits are used as a proxy for energy drink-related visits in all reported analyses. Outreach to SAMHSA revealed that the agency has received several requests for the specific energy drink data, but thus far has declined to make these data public.

4 Increasing Number of Energy Drink-Related ED Visits: Real Phenomenon or Artifact?
According to the SAMHSA report, the number of ED visits involving energy drinks doubled from 10,068 visits in 2007 to 20,783 visits in 2011.³ Notably, however, an analysis of DAWN public-use data indicates that the total number of overall drug-related ED visits (regardless of the specific drug/s involved) also increased between 2007 and 2011, rising from 3.9 million visits to 5.1 million visits. Therefore, the increase in energy drink-related visits should be understood in the context of an increase in overall drug-related ED visits. It is not known whether this reflects a real increase in the utilization of EDs, or an artifact perhaps resulting from change in the data collection or case identification methodology. In 2007, energy drink-related visits comprised 0.25% of all drug-related ED visits. In 2011, energy drink-related visits comprised 0.41% of all drug-related ED visits.

Furthermore, as shown in Table 1 below, estimated drug-related ED visits appear to have increased not only for energy drinks, but for a number of other drugs/products, including infant formula, alternative medications, and other miscellaneous products such as dermatological agents (e.g., Vick’s, hand lotion), gastrointestinal agents (e.g., laxatives), isopropyl (rubbing) alcohol, and ophthalmic preparations (e.g., eye drops, contact solution). Not only have drug-related ED visits increased for these other products by similar proportions as for energy drinks, for many, their absolute magnitude is similar, too (see Figure 1 below). In addition, energy drink-related ED visits appear to

³ It is important to note that these are not raw numbers of visits, but estimates projected to a national sample. The limitations of the weighting system used to derive these projected estimated are discussed in Section 4.1.1 below.
be more likely to be associated with non-serious complaints that do not require further medical follow-up, compared to ED visits related to other product/medications. Yet, increasing ED visits associated with these other products have not been identified as a public health concern.

Figure 1 Number of ED Visits Related to Specific Products

It is unclear whether these data reflect an increase in the levels of accidental and/or intentional exposure to substances and drugs in general, including energy drinks, or if there are methodological and statistical processes that may give the appearance of notable increases in drug-related ED visits. It is possible, for example, that the observed increases in some categories could be due to increased awareness by health professionals of certain substances, or increased perception of certain categories as problematic. This could lead to either increased detection of such substances (e.g., if the medical interviewer asks about them more than previously) or increased attribution of ED visits to the substance (e.g., if the medical interviewer is more likely to record the substance or to name it as a factor in the ED visit).
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total drug-related ED visits</td>
<td>3,998,228</td>
<td>4,383,494</td>
<td>4,595,263</td>
<td>4,916,328</td>
<td>5,067,374</td>
<td>26.74%</td>
</tr>
<tr>
<td>Total drug reports</td>
<td>6,248,023</td>
<td>6,957,634</td>
<td>7,270,914</td>
<td>7,808,492</td>
<td>8,046,258</td>
<td>28.78%</td>
</tr>
<tr>
<td>Caffeine/multivitamin</td>
<td>12,750</td>
<td>18,970</td>
<td>14,415</td>
<td>18,734</td>
<td>29,379</td>
<td>130.42%</td>
</tr>
<tr>
<td>Energy drinks</td>
<td>10,068</td>
<td>16,059</td>
<td>13,119</td>
<td>15,219</td>
<td>20,783</td>
<td>106.43%</td>
</tr>
<tr>
<td>Nutritional products</td>
<td>59,389</td>
<td>74,437</td>
<td>80,724</td>
<td>93,749</td>
<td>95,089</td>
<td>60.11%</td>
</tr>
<tr>
<td>Iron products</td>
<td>7,800</td>
<td>8,885</td>
<td>11,020</td>
<td>12,982</td>
<td>12,711</td>
<td>62.96%</td>
</tr>
<tr>
<td>Minerals and electrolytes</td>
<td>11,140</td>
<td>16,364</td>
<td>15,088</td>
<td>16,094</td>
<td>14,946</td>
<td>34.17%</td>
</tr>
<tr>
<td>Electrolyte replacement solutions, orala</td>
<td>673</td>
<td>689</td>
<td>855</td>
<td>1,282</td>
<td>1,824</td>
<td>171.03%</td>
</tr>
<tr>
<td>Oral nutritional supplements</td>
<td>15,388</td>
<td>15,919</td>
<td>20,835</td>
<td>26,014</td>
<td>33,855</td>
<td>120.01%</td>
</tr>
<tr>
<td>Infant formula</td>
<td>12,764</td>
<td>12,019</td>
<td>16,582</td>
<td>22,242</td>
<td>28,212</td>
<td>121.03%</td>
</tr>
<tr>
<td>Vitamin and mineral combinations</td>
<td>9,499</td>
<td>13,566</td>
<td>13,847</td>
<td>16,369</td>
<td>14,834</td>
<td>56.16%</td>
</tr>
<tr>
<td>Vitamins</td>
<td>18,915</td>
<td>26,905</td>
<td>28,857</td>
<td>29,381</td>
<td>29,672</td>
<td>56.87%</td>
</tr>
<tr>
<td>Alternative medicines</td>
<td>13,320</td>
<td>15,892</td>
<td>15,951</td>
<td>20,806</td>
<td>24,222</td>
<td>81.85%</td>
</tr>
<tr>
<td>Herbal products</td>
<td>8,603</td>
<td>6,661</td>
<td>8,864</td>
<td>11,915</td>
<td>12,508</td>
<td>45.39%</td>
</tr>
<tr>
<td>Nutraceutical products</td>
<td>4,385</td>
<td>8,975</td>
<td>7,356</td>
<td>8,600</td>
<td>10,087</td>
<td>130.03%</td>
</tr>
<tr>
<td>Probiotics</td>
<td>330</td>
<td>485</td>
<td>128</td>
<td>752</td>
<td>1,760</td>
<td>433.33%</td>
</tr>
<tr>
<td>Gastrointestinal agents</td>
<td>78,826</td>
<td>94,468</td>
<td>104,390</td>
<td>101,940</td>
<td>103,358</td>
<td>31.12%</td>
</tr>
<tr>
<td>Antidiarrheals</td>
<td>6,947</td>
<td>8,462</td>
<td>8,526</td>
<td>12,113</td>
<td>10,859</td>
<td>56.31%</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Laxatives</td>
<td>19,424</td>
<td>28,053</td>
<td>27,621</td>
<td>29,668</td>
<td>33,861</td>
<td>74.33%</td>
</tr>
<tr>
<td>Dermatological agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical emollients</td>
<td>2,832</td>
<td>2,937</td>
<td>2,972</td>
<td>5,622</td>
<td>4,836</td>
<td>70.76%</td>
</tr>
<tr>
<td>Hydrocortisone, topical</td>
<td>2,019</td>
<td>2,817</td>
<td>4,206</td>
<td>4,284</td>
<td>3,997</td>
<td>97.97%</td>
</tr>
<tr>
<td>Camphor</td>
<td>460</td>
<td>1,402</td>
<td>238</td>
<td>1,032</td>
<td>2,204</td>
<td>379.13%</td>
</tr>
<tr>
<td>Hydrogen peroxide, topical</td>
<td>593</td>
<td>471</td>
<td>957</td>
<td>2,361</td>
<td>1,503</td>
<td>153.46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS Stimulants</td>
<td>48,732</td>
<td>53,169</td>
<td>53,652</td>
<td>66,888</td>
<td>93,457</td>
<td>91.78%</td>
</tr>
<tr>
<td>Caffeine</td>
<td>6,434</td>
<td>5,930</td>
<td>7,293</td>
<td>8,633</td>
<td>8,936</td>
<td>38.89%</td>
</tr>
<tr>
<td>Isopropyl alcohol, topical</td>
<td>2,252</td>
<td>4,504</td>
<td>2,473</td>
<td>2,779</td>
<td>3,219</td>
<td>42.94%</td>
</tr>
<tr>
<td>Ophthalmic preparations</td>
<td>9,137</td>
<td>9,125</td>
<td>11,828</td>
<td>13,653</td>
<td>14,506</td>
<td>58.76%</td>
</tr>
</tbody>
</table>

*a* Electrolyte replacement solutions include products such as Gatorade, Powerade, Pedialyte, etc.

*b* Camphor includes products such as Vick’s, Biofreeze, etc.

*c* Caffeine includes coffee, as well as other caffeine-containing products, including caffeine pills and diet pills.

*d* Ophthalmic preparations include contact solution, eye drops, etc.
An important consideration in the assessment of drug-related ED visits is the health outcomes or consequences associated with such visits. While DAWN does not capture information on the nature of the complaint or symptom severity that prompted the ED visit, there is information available on the disposition or discharge status of ED visits that can serve as a proxy for measuring clinical severity and acuity. Table 2 below shows the results of an analysis of the 2011 DAWN public-use data that was conducted to determine the percentage of visits resulting in discharge home for all drug-related ED visits, caffeine/multivitamin-related visits, and for three groups of selected comparator products (nutritional products, which includes iron products, minerals and electrolytes, oral nutritional supplements, vitamins; alternative medicines, which includes herbal products, nutraceutical products, probiotics; and CNS stimulants) (see Appendix Table 5 for additional information on the visit and demographic characteristics associated with caffeine/multivitamin-related ED visits, as well as the three selected comparator products).

Of the overall caffeine/multivitamin-related ED visits in 2011, 84.4% resulted in discharge home. Considering ED visits related to caffeine/multivitamin use only (i.e., no other drug involvement), the percentage of visits resulting in discharge without any further follow-up was even higher (88.3%), demonstrating that the vast majority of energy drink-related ED visits are for non-serious complaints that do not require further medical care. Notably, home discharge rates for caffeine/multivitamin-related ED visits are substantially higher than those for drug-related ED visits overall (63.8%). These findings are consistent with information from the American Association of Poison Control Centers’ (AAPCC) National Poison Data System which indicates that in cases involving energy drink exposure where medical outcome was assessed, the vast majority of cases were considered to be not serious (83% of cases with medical outcomes classified as “none” or “minor”).4 This suggests that ED visits associated with consumption of energy drinks are not as serious as those associated with other drugs.

Table 2 Home discharge rates for selected ED visit types

<table>
<thead>
<tr>
<th>Visit Type</th>
<th>% of Visits Resulting in Discharge Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>All drug-related ED visits</td>
<td>63.8%</td>
</tr>
<tr>
<td>CNS stimulants-related visits</td>
<td>74.2%</td>
</tr>
<tr>
<td>Alternative medicines-related visits</td>
<td>75.5%</td>
</tr>
<tr>
<td>Nutritional products-related visits</td>
<td>80.3%</td>
</tr>
<tr>
<td>Caffeine/multivitamin-related visits</td>
<td>84.4%</td>
</tr>
</tbody>
</table>

4 Bronstein AC, et al. 2011 Annual Report of the American Association of Poison Control Centers’ National Poison Data System (NPDS): 29th Annual Report. Clinical Toxicology 2012;50:911-1164. Note: Energy drinks were added as a generic code to NPDS in 2010. Because only partial year data is available for 2010, it is not yet possible to assess trends related to energy drinks with these data.
4.1 Limitations of DAWN

Though not directly addressing the reported rise in energy drink-related ED visits, there are a number of limitations of DAWN that are worth noting.

4.1.1 Representativeness of the Sample and Validity of Projected Rates for the U.S.

DAWN uses a sample of hospital EDs to estimate national ED visit rates, including 13 major metropolitan areas and a supplementary sample to cover the remainder of the U.S. In 2002, prior to the most recent DAWN re-design, there were 21 metropolitan areas included in the sample. The DAWN redesign methodology report called for an expansion to 48 metropolitan areas in order to provide better national coverage and to increase the reliability and stability of their estimates. However, in 2004 (the first complete year of the redesigned DAWN) only 15 metropolitan areas had sufficient participation to warrant separate, stand-alone estimates. As of 2011 (the latest year for which public use data are available), the number of metropolitan areas with sufficient participation was further reduced to 13. Thus, although the expert panel that evaluated DAWN recommended more participating hospitals to increase reliability, in fact there are now fewer participating hospitals.

It is important to understand that DAWN’s reporting is not based on a straightforward enumeration of cases. DAWN projects to a national estimate of cases based on combining results from two sources: approximately 183 hospitals in 13 major metropolitan areas, and approximately 50 supplementary hospitals in 2011. Although the metropolitan hospitals actually report more cases, the supplementary hospitals actually exert greater influence on the projected national estimate. On average, one case in the supplementary sample represents 135 weighted cases, whereas one case in any of the 13 main metropolitan areas represents, on average, fewer than 5 weighted cases (see Appendix Table 4). Therefore, a single case from a supplementary hospital can count 27 times more than a case from one of the metropolitan hospitals that report data to DAWN. This can distort the estimate. For example, a small ‘outbreak’ at a community hospital could potentially skew the national statistics; a single case of energy drink use presenting to a hospital in the supplementary sample could be counted as though it were 863 cases (the maximum weight for a single case in 2011), possibly seriously skewing the national statistics and resulting in misleading trend data.

In 2011, the vast majority (85.6%) of weighted caffeine/multivitamin-related ED visits were derived from the supplementary sample. This does not appear to be unique to caffeine/multivitamins, however, as an analysis of selected comparator products (i.e., nutritional products, alternative medicines, and CNS stimulants) revealed that for these three other drug classes/product categories the bulk of the weighted reporting is also coming from the supplementary sample: 83.7% for nutritional products, 83.4% for alternative medicines, and 87.3% for CNS stimulants.

Using the publicly available DAWN data, we examined trends in caffeine/multivitamin-related ED visits by individual metropolitan area and observed a variable pattern. Among the 11 metropolitan areas with available data between 2007-2011, two areas experienced a decrease in caffeine/multivitamin-related ED visits during this time period.
(Denver, Phoenix); four areas experienced an increase between 50-100% (Boston, Chicago, Houston, Minneapolis-St. Paul); and five areas (Dade County (Miami), Detroit, New York City, San Francisco, and Seattle) experienced an increase greater than 100%. This may imply that there are regional variations in trends in ED visits related to energy drinks or that there are regional variations in the characterization of ED visits, possibly from a greater local awareness in the higher reporting areas. An analysis of selected comparator products also revealed regional variation in ED visits. For the category of CNS stimulants, for example, one metropolitan area experienced a decrease in ED-related visits between 2007 and 2011; one area experienced an increase of less than 50%; five areas experienced an increase between 50-100% and two areas experienced an increase greater than 100%.

4.1.2 Reliability of Self-Reported Data
The reliability of DAWN data is dependent on information listed by the provider on the ED medical chart, which is typically based on patient self-report taken by the triage nurse. Therefore, the drugs actually involved in ED visits might not all be identified and documented. As noted in the SAMHSA report, of the 20,783 ED visits involving energy drinks in 2011, more than half (58%) were reported to involve energy drinks only. However, it is possible that while some patients presenting to the ED may have readily reported use of an energy drink (a legal product, and thus more likely to be considered socially acceptable), they may have been reluctant to report any other drug use that may have occurred in conjunction with their use of an energy drink (e.g., use of illegal drugs, drugs for which there was no valid prescription or use of alcohol by those under legal age). Further, as described above, the salience of certain drugs/substances and the perception of the drug/substance as a problem could also affect reporting by the provider.

4.1.3 Inability to Determine Causation
Many drug-related ED visits involve multiple drugs. As noted in the SAMHSA report, of the 20,783 ED visits involving energy drinks in 2011, 42% reportedly involved other drugs. Use of pharmaceuticals was most commonly reported in conjunction with energy drink use (27%), with 9% of visits involving energy drinks and central nervous stimulants. About 13% of visits involved energy drinks and alcohol and 10% of visits involved energy drinks and illicit drugs, with 5% involving energy drinks and marijuana. In these instances, it may be difficult or impossible to determine whether a single drug or product is responsible for the visit or if the visit was the result of the interaction between the drugs. Furthermore, important information that could aid in assessing causation is not captured (e.g., nature of the complaint/symptoms that brought the patient to the ED, overall health of the patient, amount used/exposure information). Importantly, there is no specific information on consumption of other caffeine-containing products (e.g., coffee – which is included in the larger caffeine category by DAWN, but not listed as a specific product). This is particularly important given the wide variability in caffeine content of popular brands of coffee. According to an analysis prepared for
the Food and Drug Administration (FDA) on caffeine consumption in the U.S.\textsuperscript{5}, the mean amount of caffeine consumed by the U.S. population has remained relatively stable between 2003 and 2008 at approximately 300 milligrams per person per day despite the entry of energy drinks into the marketplace. Furthermore, according to the same analysis, energy drinks contribute a small portion of the caffeine consumed, with major sources of caffeine being coffee, soft drinks and tea.

5 Potential Issues

The estimates provided in the SAMHSA report are based solely on number of ED visits, and do not account for the availability of the product (i.e., sales). As shown in Table 3 (which includes data for the years 2007-2011, since as noted by SAMHSA, statistical tests were not used until 2007 when the number of ED visits involving energy drinks exceeded 10,000) and Figure 2 (which displays data for the years 2005-2011, consistent with the figure presented in the SAMHSA report), the increase in energy drink-related ED visits was accompanied by an increase in the number of cases of energy drinks sold. However, ED visits still appear to be increasing at a higher rate than sales.

Table 3 Energy drink-related ED visits and number of cases of energy drinks sold (2007-2011)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of energy</td>
<td>10,068</td>
<td>16,059</td>
<td>13,119</td>
<td>15,219</td>
<td>20,783</td>
<td>106.4%</td>
</tr>
<tr>
<td>drink-related visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases sold (millions)</td>
<td>234.1</td>
<td>244.5</td>
<td>240.1</td>
<td>261.5</td>
<td>305.0</td>
<td>30.3%</td>
</tr>
<tr>
<td>Number of energy</td>
<td>43.0</td>
<td>65.7</td>
<td>54.6</td>
<td>58.2</td>
<td>68.1</td>
<td>58.4%</td>
</tr>
<tr>
<td>drink-related visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per 1 million cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{5} Source: Beverage Digest Fact Book

Figure 2 Energy drink-related ED visits and cases of energy drinks sold (in millions), 2005-2011

Energy Drink ED Visits and Cases Sold (in millions), 2005-2011

- ED Visits
- Cases Sold (millions)
6 Conclusion
Although the DAWN report has attracted a lot of attention, careful analysis of the report and the public data underlying it, do not appear to be consistent with a signal of substantial medical harm. The vast majority of caffeine/multivitamin-related ED visits appear to be associated with non-serious complaints that do not require further medical follow-up, as 84.4% of visits related to these products resulted in discharge home, a higher rate than observed for other products. The reported rate of ED visits related to caffeine/multivitamins remains quite small, representing a tiny fraction of the overall visits to EDs each year. Finally, the limitations of the DAWN system suggest caution in basing public health policy on the results relative to energy drinks.
# Appendix

## Table 4 DAWN weighting by metro area (2011)

<table>
<thead>
<tr>
<th>Metro Area Description</th>
<th>Number of Cases, Unweighted</th>
<th>% of Unweighted Cases</th>
<th>Average Weight</th>
<th>Minimum Weight</th>
<th>Maximum Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston-Cambridge-Quincy, MA-NHMSA:(1)</td>
<td>24,889</td>
<td>10.86%</td>
<td>3.86</td>
<td>1.60</td>
<td>8.54</td>
</tr>
<tr>
<td>New York City - 5 Boroughs (Part of New York-Newark-Edison, NY-NJ-PA MSA):(2)</td>
<td>39,776</td>
<td>17.35%</td>
<td>3.13</td>
<td>0.94</td>
<td>22.84</td>
</tr>
<tr>
<td>Chicago-Naperville-Joliet, IL-IN-WI MSA:(3)</td>
<td>21,918</td>
<td>9.56%</td>
<td>6.68</td>
<td>1.42</td>
<td>28.77</td>
</tr>
<tr>
<td>Detroit-Warren-Livonia, MI MSA:(4)</td>
<td>22,502</td>
<td>9.82%</td>
<td>4.20</td>
<td>1.23</td>
<td>11.62</td>
</tr>
<tr>
<td>Minneapolis-St. Paul-Bloomington, MN-WI MSA:(5)</td>
<td>12,049</td>
<td>5.26%</td>
<td>4.50</td>
<td>1.33</td>
<td>8.04</td>
</tr>
<tr>
<td>Fort Lauderdale Division of Miami-Fort Lauderdale, FL MSA:(6)</td>
<td>5,352</td>
<td>2.33%</td>
<td>6.15</td>
<td>2.59</td>
<td>14.30</td>
</tr>
<tr>
<td>Dade County Division of Miami-Fort Lauderdale, FL MSA:(7)</td>
<td>7,101</td>
<td>3.10%</td>
<td>4.46</td>
<td>2.57</td>
<td>8.57</td>
</tr>
<tr>
<td>Houston-Baytown-Sugar Land, TX MSA:(8)</td>
<td>9,115</td>
<td>3.98%</td>
<td>10.31</td>
<td>3.32</td>
<td>27.90</td>
</tr>
<tr>
<td>Denver-Aurora, CO MSA:(9)</td>
<td>12,112</td>
<td>5.28%</td>
<td>3.01</td>
<td>1.10</td>
<td>7.34</td>
</tr>
<tr>
<td>Phoenix-Mesa-Scottsdale, AZ MSA:(10)</td>
<td>13,166</td>
<td>5.74%</td>
<td>4.76</td>
<td>1.05</td>
<td>15.87</td>
</tr>
<tr>
<td>Oakland Division of San Francisco-Oakland-Fremont, CA MSA:(11)</td>
<td>2,462</td>
<td>1.07%</td>
<td>13.29</td>
<td>9.22</td>
<td>18.18</td>
</tr>
<tr>
<td>Location</td>
<td>Count</td>
<td>Percentage</td>
<td>Average</td>
<td>Median</td>
<td>IQR</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------</td>
<td>------------</td>
<td>---------</td>
<td>--------</td>
<td>-----</td>
</tr>
<tr>
<td>SAN FRANCISCO DIVISION OF SAN FRANCISCO-OAKLAND-FREMONT, CA MSA:(12)</td>
<td>8,936</td>
<td>3.90%</td>
<td>4.09</td>
<td>1.14</td>
<td>10.06</td>
</tr>
<tr>
<td>SEATTLE-TACOMA-BELLEVUE, WA MSA:(13)</td>
<td>18,973</td>
<td>8.28%</td>
<td>2.86</td>
<td>1.03</td>
<td>7.74</td>
</tr>
<tr>
<td>ALL OTHER LOCATIONS:(14) (a.k.a. &quot;supplementary sample&quot;)</td>
<td>30,860</td>
<td>13.46%</td>
<td>135.13</td>
<td>2.01</td>
<td>862.82</td>
</tr>
</tbody>
</table>
Table 5 Visit characteristics and demographics for caffeine/multivitamin-related ED visits, nutritional products-related ED visits, alternative medicine-related ED visits and CNS stimulant-related ED visits (2011)

<table>
<thead>
<tr>
<th></th>
<th>Caffeine/Multivitamin Products</th>
<th>Nutritional Products</th>
<th>Alternative Medicines</th>
<th>CNS Stimulants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total ED Visits</strong></td>
<td>29,379</td>
<td>95,089</td>
<td>24,222</td>
<td>93,457</td>
</tr>
<tr>
<td><strong>Combinations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Only</td>
<td>14,393 (48.99%)</td>
<td>63,780 (67.07%)</td>
<td>11,374 (46.96%)</td>
<td>45,951 (49.17%)</td>
</tr>
<tr>
<td>Product, Any</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td>11,952 (40.68%)</td>
<td>11,090 (11.66%)</td>
<td>4,497 (18.57%)</td>
<td>40,648 (43.49%)</td>
</tr>
<tr>
<td>Combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product, Any Alcohol</td>
<td>8,615 (29.32%)</td>
<td>1,644 (1.73%)</td>
<td>1,523 (6.29%)</td>
<td>17,118 (18.32%)</td>
</tr>
<tr>
<td>Combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product, Any Illicit</td>
<td>3,701 (12.60%)</td>
<td>201 (0.21%)</td>
<td>1,653 (6.82%)</td>
<td>12,914 (13.82%)</td>
</tr>
<tr>
<td>Drug Combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product, 2+</td>
<td>3,503 (11.92%)</td>
<td>23,735 (24.96%)</td>
<td>8,870 (36.62%)</td>
<td>14,974 (16.02%)</td>
</tr>
<tr>
<td>Substances, Not</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misuse/Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visit Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quarter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Quarter</td>
<td>5,580 (18.99%)</td>
<td>25,279 (26.59%)</td>
<td>9,059 (37.40%)</td>
<td>20,909 (22.37%)</td>
</tr>
<tr>
<td>Second Quarter</td>
<td>7,764 (26.43%)</td>
<td>26,784 (28.17%)</td>
<td>5,738 (23.69%)</td>
<td>25,739 (27.54%)</td>
</tr>
<tr>
<td>Third Quarter</td>
<td>8,503 (28.94%)</td>
<td>22,483 (23.64%)</td>
<td>5,485 (22.64%)</td>
<td>26,334 (28.18%)</td>
</tr>
<tr>
<td>Fourth Quarter</td>
<td>7,532 (25.64%)</td>
<td>20,542 (21.60%)</td>
<td>3,939 (16.26%)</td>
<td>20,475 (21.91%)</td>
</tr>
<tr>
<td><strong>Part of the Day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early morning</td>
<td>6,367 (21.67%)</td>
<td>14,965 (15.74%)</td>
<td>3,605 (14.88%)</td>
<td>16,914 (18.10%)</td>
</tr>
<tr>
<td>(12:00-5:59 AM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>5,044 (17.17%)</td>
<td>18,738 (19.71%)</td>
<td>4,274 (17.64%)</td>
<td>18,896 (20.22%)</td>
</tr>
<tr>
<td>(6:00-11:59 AM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afternoon</td>
<td>8,236 (28.03%)</td>
<td>29,750 (31.29%)</td>
<td>9,610 (39.68%)</td>
<td>27,655 (29.59%)</td>
</tr>
<tr>
<td>(12:00-5:59 PM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evening/Night</td>
<td>9,733 (33.13%)</td>
<td>31,637 (33.27%)</td>
<td>6,734 (27.80%)</td>
<td>29,993 (32.09%)</td>
</tr>
<tr>
<td>(6:00-11:59 PM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of Substances</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>14,393 (48.99%)</td>
<td>63,780 (67.07%)</td>
<td>11,374 (46.96%)</td>
<td>45,951 (49.17%)</td>
</tr>
<tr>
<td>Case Type</td>
<td>Caffeine/Multivitamin Products</td>
<td>Nutritional Products</td>
<td>Alternative Medicines</td>
<td>CNS Stimulants</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Two or more</td>
<td>14,986 (51.01%)</td>
<td>31,308 (32.93%)</td>
<td>12,848 (53.04%)</td>
<td>47,506 (50.83%)</td>
</tr>
<tr>
<td><strong>Case Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide Attempt</td>
<td>917 (3.12%)</td>
<td>1,473 (1.55%)</td>
<td>1,363 (5.63%)</td>
<td>4,715 (5.05%)</td>
</tr>
<tr>
<td>Seeking Detox</td>
<td>364 (1.24%)</td>
<td>5 (0.01%)</td>
<td>14 (0.06%)</td>
<td>2,272 (2.43%)</td>
</tr>
<tr>
<td>Alcohol Only (Age&lt;21)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>15,914 (54.17%)</td>
<td>79,638 (83.75%)</td>
<td>16,656 (68.76%)</td>
<td>41,311 (44.20%)</td>
</tr>
<tr>
<td><strong>Product Only</strong></td>
<td>13,061 (44.46%)</td>
<td>57,447 (60.41%)</td>
<td>8,528 (35.21%)</td>
<td>28,970 (31.00%)</td>
</tr>
<tr>
<td><strong>Product, Any Pharmaceutical Combination</strong></td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td><strong>Product, Any Alcohol Combination</strong></td>
<td>0 (0.00%)</td>
<td>820 (0.86%)</td>
<td>659 (2.72%)</td>
<td>1,594 (1.71%)</td>
</tr>
<tr>
<td><strong>Product, Any Illicit Drug Combination</strong></td>
<td>5 (0.02%)</td>
<td>5 (0.00%)</td>
<td>0 (0.00%)</td>
<td>5 (0.00%)</td>
</tr>
<tr>
<td><strong>Product, 2+ Substances, Not Misuse/Abuse</strong></td>
<td>2,849 (9.70%)</td>
<td>21,366 (22.47%)</td>
<td>7,469 (30.84%)</td>
<td>10,743 (11.49%)</td>
</tr>
<tr>
<td>Overmedication</td>
<td>1,247 (4.25%)</td>
<td>9,240 (9.72%)</td>
<td>1,769 (7.30%)</td>
<td>10,959 (11.73%)</td>
</tr>
<tr>
<td>Malicious Poisoning</td>
<td>30 (0.10%)</td>
<td>293 (0.31%)</td>
<td>0 (0.00%)</td>
<td>94 (0.10%)</td>
</tr>
<tr>
<td>Accidental Ingestion</td>
<td>232 (0.79%)</td>
<td>2,883 (3.03%)</td>
<td>1,693 (6.99%)</td>
<td>4,510 (4.83%)</td>
</tr>
<tr>
<td>Other</td>
<td>10,675 (36.34%)</td>
<td>1,557 (1.64%)</td>
<td>2,729 (11.27%)</td>
<td>29,596 (31.67%)</td>
</tr>
<tr>
<td><strong>Disposition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged Home</td>
<td>24,798 (84.41%)</td>
<td>76,326 (80.27%)</td>
<td>18,295 (75.53%)</td>
<td>69,379 (74.24%)</td>
</tr>
<tr>
<td><strong>Product Only</strong></td>
<td>12,714 (43.28%)</td>
<td>58,968 (62.01%)</td>
<td>9,470 (39.09%)</td>
<td>39,000 (41.73%)</td>
</tr>
<tr>
<td><strong>Product, Any Pharmaceutical Combination</strong></td>
<td>9,722 (33.09%)</td>
<td>6,949 (7.31%)</td>
<td>2,613 (10.79%)</td>
<td>27,820 (29.77%)</td>
</tr>
<tr>
<td><strong>Product, Any Alcohol Combination</strong></td>
<td>6,416 (21.84%)</td>
<td>461 (0.48%)</td>
<td>1,060 (4.37%)</td>
<td>11,016 (11.79%)</td>
</tr>
<tr>
<td><strong>Product, Any Illicit Drug Combination</strong></td>
<td>3,103 (10.56%)</td>
<td>101 (0.11%)</td>
<td>767 (3.17%)</td>
<td>7,032 (7.52%)</td>
</tr>
<tr>
<td><strong>Product, 2+ Substances, Not Misuse/Abuse</strong></td>
<td>3,431 (11.68%)</td>
<td>14,007 (14.73%)</td>
<td>6,545 (27.02%)</td>
<td>10,506 (11.24%)</td>
</tr>
<tr>
<td>Released to Police/Jail</td>
<td>15 (0.05%)</td>
<td>100 (0.11%)</td>
<td>8 (0.03%)</td>
<td>260 (0.28%)</td>
</tr>
<tr>
<td>Referred to Detox/Treatment</td>
<td>363 (1.24%)</td>
<td>430 (0.45%)</td>
<td>32 (0.13%)</td>
<td>2,134 (2.28%)</td>
</tr>
<tr>
<td>ICU/Critical Care</td>
<td>367 (1.25%)</td>
<td>1,133 (1.19%)</td>
<td>288 (1.19%)</td>
<td>2,074 (2.22%)</td>
</tr>
<tr>
<td>Category</td>
<td>Caffeine/Multivitamin Products</td>
<td>Nutritional Products</td>
<td>Alternative Medicines</td>
<td>CNS Stimulants</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Surgery</td>
<td>5 (0.02%)</td>
<td>387 (0.41%)</td>
<td>0 (0.00%)</td>
<td>5 (0.01%)</td>
</tr>
<tr>
<td>Chemical Dependency/Detox, Psychiatric Unit</td>
<td>50 (0.17%)</td>
<td>189 (0.20%)</td>
<td>1,056 (4.36%)</td>
<td>2,973 (3.18%)</td>
</tr>
<tr>
<td>Other Inpatient</td>
<td>1,804 (6.14%)</td>
<td>13,263 (13.95%)</td>
<td>3,653 (15.08%)</td>
<td>5,608 (6.00%)</td>
</tr>
<tr>
<td>Transferred</td>
<td>972 (3.31%)</td>
<td>2,244 (2.36%)</td>
<td>697 (2.88%)</td>
<td>9,401 (10.06%)</td>
</tr>
<tr>
<td>Left Against Medical Advice</td>
<td>326 (1.11%)</td>
<td>90 (0.09%)</td>
<td>60 (0.25%)</td>
<td>718 (0.77%)</td>
</tr>
<tr>
<td>Died</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Other</td>
<td>672 (2.29%)</td>
<td>222 (0.23%)</td>
<td>108 (0.45%)</td>
<td>823 (0.88%)</td>
</tr>
<tr>
<td>Not Documented</td>
<td>7 (0.02%)</td>
<td>703 (0.74%)</td>
<td>25 (0.10%)</td>
<td>81 (0.09%)</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>20,502 (69.78%)</td>
<td>40,796 (42.90%)</td>
<td>10,684 (44.11%)</td>
<td>54,926 (58.77%)</td>
</tr>
<tr>
<td>Age Category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-11</td>
<td>668 (2.27%)</td>
<td>32,032 (33.69%)</td>
<td>2,762 (11.40%)</td>
<td>10,926 (11.69%)</td>
</tr>
<tr>
<td>12-17</td>
<td>3,082 (10.49%)</td>
<td>2,345 (2.47%)</td>
<td>1,145 (4.73%)</td>
<td>13,859 (14.83%)</td>
</tr>
<tr>
<td>18-24</td>
<td>9,260 (31.52%)</td>
<td>2,627 (2.76%)</td>
<td>3,494 (14.43%)</td>
<td>23,543 (25.19%)</td>
</tr>
<tr>
<td>25-34</td>
<td>7,038 (23.96%)</td>
<td>6,510 (6.85%)</td>
<td>4,148 (17.13%)</td>
<td>21,486 (22.99%)</td>
</tr>
<tr>
<td>35+</td>
<td>9,332 (31.76%)</td>
<td>51,575 (54.24%)</td>
<td>12,673 (52.32%)</td>
<td>23,643 (25.30%)</td>
</tr>
</tbody>
</table>

Race/Ethnicity

<table>
<thead>
<tr>
<th>Category</th>
<th>Male</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Only</td>
<td>18,293 (62.26%)</td>
<td>60,953 (64.10%)</td>
</tr>
<tr>
<td>African American Only</td>
<td>3,475 (11.83%)</td>
<td>14,800 (15.56%)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>7,055 (24.02%)</td>
<td>16,528 (17.38%)</td>
</tr>
<tr>
<td>All Other Races</td>
<td>556 (1.89%)</td>
<td>2,807 (2.95%)</td>
</tr>
</tbody>
</table>
Abstract  Energy drinks are emerging as a public health threat and are increasingly consumed by youth internationally. Energy drinks contain high levels of caffeine, sugar, and novel ingredients, and are often marketed through youth-oriented media and venues. We review these practices and the current inconsistent state of labeling. We also examine international support for regulation of these products, including a survey showing that 85 per cent of United States parents agreed that regulations requiring caffeine content disclosure and warning labels on energy drinks are warranted. We then examine the regulatory structure for energy drinks in the United States, analyzing legal and self-regulatory strategies to protect consumers, especially youth, from these potentially dangerous products. Recommended government interventions include revised labeling requirements, addressing problematic ingredients, and enacting retail restrictions. We conclude by identifying areas for future research.

Introduction

The consumption of sugary beverages is an established public health concern, with energy drinks emerging as a unique and independent risk for youth. Sales of energy drinks are rising at a steady pace. In 2011, they increased by 12.5 per cent overall, and by 15–30 per cent for the category leaders, Red Bull and Rockstar. In a study of 600 nationally advertised beverage products in the United States, the sale of energy drinks surpassed that of either sports or fruit drinks.
The products in this category typically have the word 'energy' in the product name and contain high levels of caffeine plus additional ingredients not found in sodas and juice drinks. (Energy drinks differ from sports drinks which are marketed to accompany physical activity and contain electrolytes.) The energy drink category includes two types of products: drinks and shots. Drinks are sold in 8–32 oz. containers. Many are available in large, non-resealable cans that produce one serving, despite the number of servings listed on the container. Shots come in 2–2.5 oz. single serving containers. Because there are few data on youth consumption of energy shots, this article focuses primarily on energy drinks.

A recent study of US high school students revealed that energy drinks represented 8.8 per cent of sugar-sweetened beverages they consumed, and more than 10 per cent of drinks consumed by males and Hispanic students. Another US study indicated that 31 per cent of 12–17 year olds regularly consume energy drinks. Similarly, a study of German adolescents found that 53 per cent tried energy drinks and 26 per cent of adolescents consumed them regularly. Internationally, Thailand was reported to be the highest per capita consumers of energy drinks in 2007, with the United States, Austria, Ireland, New Zealand, Slovenia, and Kuwait rounding out the top seven countries.

Energy drink consumption is a potential health hazard for the general population and especially alarming for youth due to high levels of caffeine and novel ingredients not normally found in the food supply. The American Academy of Pediatrics (AAP) stated that 'energy drinks have no place in the diet of children and adolescents' due to their 'stimulant content', but energy drink manufacturers continue to advertise directly to adolescents in media also viewed by children. A study by the US Department of Health and Human Services revealed that emergency room (ER) visits involving energy drinks (alone or mixed with other substances) increased tenfold from 2005 to 2009.

The mixing of energy drinks with alcohol is an obvious public health concern, but adolescent consumption of energy drinks alone also poses considerable health risks. Eleven per cent of total ER visits related to energy drink consumption involved youth aged 12–17 years and 75 per cent of those visits were due to energy drink intake alone. Similarly, calls to the Australian poison information center revealed increasing reports of caffeine toxicity from energy drink consumption among adolescents. The median age of callers was 17 years and more than half of all calls were due solely to energy drink consumption.
The first part of this article builds on previous research about negative health effects of energy drink consumption among youth,\textsuperscript{7,9} by discussing the potential health effects of problematic ingredients, inconsistent labeling practices, and the marketing of energy drinks to adolescents. Then it describes international support for increased regulation of energy drinks; we also report on a survey of US parents that indicates such support to protect youth. We review current regulatory structure for energy drinks and analyze legal strategies to protect consumers, especially youth, from these potentially dangerous products. We conclude by identifying areas for future research, in particular the need for more information about energy shot consumption and its effects.

**Inconsistent Labeling**

US Food and Drug Administration (FDA) regulations contain certain requirements for beverage labels but not all manufacturers of energy drinks designate their products as ‘beverages’, thus labels are inconsistent across companies. Manufacturers that label energy drinks as beverages comply with the Nutrition Labeling and Education Act of 1990 (NLEA). Others mislabel their products as dietary supplements and comply with labeling required by the Dietary Supplement Health and Education Act of 1994 (DSHEA). However, DSHEA has significantly more lax requirements and manufacturers can list ingredients on *supplement facts panels* that would not be permitted under the NLEA.\textsuperscript{16} If there are no macronutrients in a product, manufacturers of dietary supplements can eliminate disclosure of the macronutrient list on the supplements fact panel, unlike beverage manufacturers who must list the amount as zero.\textsuperscript{17}

The Food, Drug, and Cosmetic Act (FDCA) does not require caffeine disclosure for beverages or supplements. American Beverage Association (ABA) member companies and some independent ones disclose caffeine voluntarily,\textsuperscript{18} but as many manufacturers do not, consumers would have to call these companies directly to obtain information about the caffeine content.

**Ingredients and Health Risks**

Energy drinks are generally composed of sugar and/or artificial sweeteners, caffeine, and additional ingredients, many of them in high
quantities or novel for beverages, such as guarana and taurine. Under the FDCA, ingredients added to beverages are considered food additives, and must be pre-approved by the FDA if they have not already gained status as GRAS (Generally Regarded as Safe). If a food additive is not proven safe by the entity seeking to introduce it into the food supply, beverages containing such additives are considered ‘adulterated’ and may be condemned by the FDA. Conversely, manufacturers of dietary supplements are responsible for determining their products’ safety without any DSHEA requirement to obtain pre-approval for an ingredient unless it is new. Thus, ingredients not designated GRAS are found in some energy drinks labeled as dietary supplements.

Owing to these labeling issues, it is difficult to determine amounts of many ingredients contained in energy drinks. Table 1 summarizes calorie, sugar, caffeine, and sodium content of prominent, nationally advertised sugar-sweetened energy drinks identified in a 2010 study. On the basis of the labels of these products, the most common additional ingredients are sodium compounds, guarana, panax ginseng, and taurine.

Sugar and sugar substitutes

A comprehensive study of energy beverages reported that the median sugar content of sugar-sweetened energy drinks was 27 g per 8 oz. serving, comparable to sodas and fruit drinks, and higher than sports drinks and flavored water. With one exception, all energy drinks in this analysis were available in large, non-resealable containers, providing excessive sugar and calories in a single serving. Sixty-nine per cent of energy products also contained artificial sweeteners in lieu of or in addition to sugar. More than half of these were not labeled as diet products; diet labels would normally alert consumers to the presence of artificial sweeteners.

Consumption of sugary beverages is associated with increased risk for dental caries, weight gain, overweight, obesity, diabetes, and heart disease. In 2008, sugary beverages made up 31 per cent of added sugar in the diet of 6–11 year olds and 44 per cent of the added sugar consumed by 12–17 year olds in the United States. Although added sugar intake derived from sugary beverages in total, such as soda, has decreased since 1999, added sugar intake from energy drinks has increased. Consistent with sales data, youth may be substituting energy drinks for other sugary beverages.
### Table 1: Caffeine, calorie, sugar, and sodium content of common sugar-sweetened energy drinks

<table>
<thead>
<tr>
<th>Productb</th>
<th>Additional varietiesc</th>
<th>Manufacturer</th>
<th>ABA member company</th>
<th>Can size (oz.)</th>
<th>Caffeine per can (mg)</th>
<th>Calories per can (kcal)</th>
<th>Sugar per can (g)</th>
<th>Sodium per can (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amp Energy</td>
<td>4</td>
<td>PepsiCo</td>
<td>X</td>
<td>16</td>
<td>142</td>
<td>220</td>
<td>58</td>
<td>140</td>
</tr>
<tr>
<td>AZ Energy</td>
<td>3</td>
<td>Arizona</td>
<td>-</td>
<td>15</td>
<td>188</td>
<td>188</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>Full Throttle (Red Berry)</td>
<td>2</td>
<td>Coca-Cola</td>
<td>X</td>
<td>16</td>
<td>160</td>
<td>230</td>
<td>58</td>
<td>160</td>
</tr>
<tr>
<td>Monster Energy</td>
<td>24</td>
<td>Hansen Beverage Company</td>
<td>-</td>
<td>16</td>
<td>160</td>
<td>200</td>
<td>54</td>
<td>180</td>
</tr>
<tr>
<td>Monster Energy</td>
<td>24</td>
<td>Hansen Beverage Company</td>
<td>-</td>
<td>24</td>
<td>240</td>
<td>300</td>
<td>81</td>
<td>270</td>
</tr>
<tr>
<td>Monster Energy</td>
<td>24</td>
<td>Hansen Beverage Company</td>
<td>-</td>
<td>32</td>
<td>320</td>
<td>400</td>
<td>108</td>
<td>360</td>
</tr>
<tr>
<td>NOS</td>
<td>4</td>
<td>Coca-Cola</td>
<td>X</td>
<td>16</td>
<td>160</td>
<td>210</td>
<td>54</td>
<td>410</td>
</tr>
<tr>
<td>Red Bull</td>
<td>0</td>
<td>Red Bull</td>
<td>X</td>
<td>8.4</td>
<td>80</td>
<td>110</td>
<td>27</td>
<td>99</td>
</tr>
<tr>
<td>Red Bull</td>
<td>0</td>
<td>Red Bull</td>
<td>X</td>
<td>12</td>
<td>114</td>
<td>160</td>
<td>39</td>
<td>142</td>
</tr>
<tr>
<td>Red Bull</td>
<td>0</td>
<td>Red Bull</td>
<td>X</td>
<td>16</td>
<td>154</td>
<td>220</td>
<td>54</td>
<td>189</td>
</tr>
<tr>
<td>Red Bull</td>
<td>0</td>
<td>Red Bull</td>
<td>X</td>
<td>20</td>
<td>192</td>
<td>275</td>
<td>68</td>
<td>237</td>
</tr>
<tr>
<td>Rockstar</td>
<td>11</td>
<td>Rockstar</td>
<td>-</td>
<td>8</td>
<td>80</td>
<td>140</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>Rockstar</td>
<td>11</td>
<td>Rockstar</td>
<td>-</td>
<td>16</td>
<td>160</td>
<td>280</td>
<td>62</td>
<td>80</td>
</tr>
<tr>
<td>Rockstar</td>
<td>11</td>
<td>Rockstar</td>
<td>-</td>
<td>34</td>
<td>240</td>
<td>420</td>
<td>93</td>
<td>120</td>
</tr>
<tr>
<td>Venom Energy (Black Mamba)</td>
<td>3</td>
<td>Dr. Pepper Snapple</td>
<td>X</td>
<td>16.9</td>
<td>170</td>
<td>250</td>
<td>57</td>
<td>320</td>
</tr>
</tbody>
</table>

*aNutrition information as of September 2012 for each available can size for nationally advertised energy drink brands identified in the 2011 Sugary Drink FACTS report from the Rudd Center for Food Policy & Obesity.

bInformation given for original variety of drink brand. For those brands that do not have an original variety, the flavor is specified.

cNumber includes additional sugar-sweetened unique flavor varieties within each listed brand, not including multiple can sizes.
Regulating energy drinks

Caffeine

Energy drinks are touted for high caffeine content, but manufacturers do not always report the amount in each container. In the 2010 study of sugary drinks, 54 per cent of 83 total energy drink products reported their caffeine content with a median of 80 mg per 8 oz. serving or shot, more than double the median caffeine in 8 oz. of soda. Two products contained extreme levels and were available in 20 oz. containers, providing 245 mg and 325 mg of caffeine. Another study found that energy drinks may contain up to 505 mg of caffeine per container.

Caffeine toxicity is a concern for youth. In 2007, there were 54,448 caffeine overdoses reported in the United States and a striking 46 per cent of them occurred in persons younger than 19 years. The AAP raised additional concerns for children because of caffeine's effect on developing neurological and cardiovascular systems, plus a risk of physical dependence and addiction. Caffeine binds to cell membranes in place of adenosine, an inhibitory neurotransmitter, causing changes in normal physiological processes. Specific effects of caffeine consumption include disturbed sleep, increased body temperature and gastric secretions, increased blood pressure and heart rate, as well as a risk of physical dependence and addiction. This is especially problematic for youth because they are still growing. The AAP specifically cautioned that dietary intake of caffeine can produce harmful adverse effects in youth and should be 'discouraged for all children'.

Sodium and other ingredients

Energy drinks contain surprisingly high levels of sodium. In the 2010 study, the median sodium level was 123 mg per 8 oz. serving or shot, more than three times the amount in soda. Several energy drinks had even more extreme levels, with one containing 340 mg per 8 oz. serving. Diets high in sodium can result in high blood pressure and increased risk for heart disease and stroke.

Energy drinks often contain specialty ingredients with purported health benefits, but that can have negative effects on young people. Table 2 provides information on three of the most common ingredients: guarana, taurine, and panax ginseng. Many of the same novelty ingredients found in energy drinks are also ingredients in over-the-counter diet drugs. As consumption of energy drinks increases, these ingredients raise...
Table 2: Common energy drink ingredients

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Intended effects</th>
<th>Generally recognized as safe (GRAS)</th>
<th>Comments from the American Academy of Pediatrics clinical report</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guarana</td>
<td>Stimulant (caffeine-containing)</td>
<td>Yes</td>
<td>Guarana is concerning for youth because it increases the total amount of caffeine in the product</td>
<td>Contains 40 milligrams of caffeine per gram</td>
</tr>
<tr>
<td>Taurine</td>
<td>Amino acid believed to assist with cell metabolism, thought to improve athletic performance</td>
<td>No</td>
<td>Amino acids in energy drinks should be discouraged in children</td>
<td>Mayo Clinic study found no evidence that it produces advertised benefit</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>Thought to improve athletic performance</td>
<td>No</td>
<td>Not Available</td>
<td>Potential negative side effects include insomnia, menstrual problems, increased heart rate, and blood pressure disturbances</td>
</tr>
</tbody>
</table>

significant concerns because it is unclear what combined health impact they may have on consumers, especially youth.

Marketing

A comprehensive analysis of marketing practices and youth exposure to this marketing in the United States confirmed that several energy drink manufacturers market their products using media and techniques aimed at adolescents. In 2010, US adolescents saw on average 124 television ads for energy drinks and shots, which is the equivalent of one ad every 3 days. This is similar to adolescents' viewing of regular soda ads (122), and more ads for energy drinks and shots than seen by adults. Adolescents viewed 9–16 per cent more ads than adults for three energy drink brands. The majority of energy drink ads viewed by adolescents appeared on youth-targeted cable networks including Adult Swim (80–90 per cent more adolescent than adult viewers), MTV and MTV2 (88–199 per cent more adolescent viewers), and Comedy Central (20–30 per cent more adolescent viewers).
Energy drink brands also sponsor extreme sports competitions and are prominent in digital media that disproportionately appeals to adolescents. Adolescents were approximately twice as likely to visit the Monster and Rockstar energy drink websites compared to adults, and youth under age 18 often visited Facebook pages of popular energy drinks, comprising 11 per cent of unique visitors for Red Bull and 38 per cent to Monster’s page. Although it does not appear that energy drink companies directly market to children less than 12 years of age, many children view the same media as adolescents. As a result, children in the United States saw on average 62 energy drink and shot ads in 2010, which is on par with the number of ads they saw for the children’s drinks Capri Sun and Kool-Aid.

Support for Regulation

In 2008, scientists and physicians wrote to the FDA requesting increased regulation of energy drinks because their high caffeine content puts youth at risk for caffeine intoxication and alcohol-related injuries. France, Denmark, and Norway attempted to ban Red Bull because of concerns about excessive caffeine and other novel ingredients in the product, but the European Court of Justice found it to be an improper trade restriction.

In 2011, Canada officially designated energy drinks as subject to regulation as food; they established specific criteria, including composition restrictions and labeling requirements. Canada determined the maximum amount of caffeine permitted per single-serve container to be 180 mg and designated all non-resealable containers one serving. Canada also requires labels to disclose the amount of caffeine per serving and to include warnings for use by children and certain sensitive adults.

The Rudd Center for Food Policy & Obesity conducted a nationally representative online survey of 985 US parents of 2–17 year olds in 2011, seeking to understand attitudes about energy drinks, beliefs about appropriateness of these drinks for their children, feelings regarding caffeine and other common ingredients, and attitudes toward energy drink labeling and regulation. They found that 67 per cent of parents were concerned about the caffeine content of beverages for their children, 78 per cent agreed that energy drinks should not be marketed to children and adolescents, and 74 per cent agreed these drinks should not be sold to children or adolescents. In addition, 85 per cent of parents...
agreed that regulations requiring reporting of caffeine and warning labels were warranted for energy drinks.

In 2012, US Senators Durbin and Blumenthal asked the FDA for increased regulation of energy drinks, including clarifying labeling requirements, directly regulating the amount of caffeine permitted in products, and an FDA determination of the safety of other additives and ingredients.\(^\text{35}\)

**Regulatory Recommendations**

The FDA has primary authority over the safety, labeling, and ingredients of energy drinks.\(^\text{36}\) Federal law preempts state and local governments from addressing issues in the FDA's domain. State and local governments (collectively states), via their legislatures and agencies, can, however, exercise authority over public health and safety to regulate the sale of these products and protect consumers.\(^\text{37}\) If a government entity determines that increased regulation of energy drinks is warranted, several options are available, summarized in Table 3 and discussed below.

**Designation as beverages**

The FDA issued a non-binding draft guidance document in 2009 distinguishing beverages from liquid dietary supplements,\(^\text{16}\) and the agency is currently finalizing the guidance document.\(^\text{35}\) The FDA has explained that even if a manufacturer characterizes a product as a dietary supplement, it may be a beverage for regulatory purposes. Beverages can be distinguished by packaging, volume, advertising, name, and similarity to other beverages (for example, soda),\(^\text{16}\) whereas a dietary supplement is defined as 'a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet'.\(^\text{16}\) According to the FDA, energy drinks labeled as supplements are mislabeled.

**Ingredients**

The FDA expressed concern that energy drinks contain some GRAS ingredients 'at levels in excess of their traditional use levels', which 'raises questions regarding whether these higher levels and other new conditions of use are safe'.\(^\text{16}\) The FDA granted GRAS status to added sugar\(^\text{38}\) and caffeine (at levels of 0.02 per cent of the product) in the
Table 3: Potential interventions to reduce underage consumption of liquid energy products

<table>
<thead>
<tr>
<th>Topic</th>
<th>Intervention</th>
<th>Actor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredients</td>
<td>• Reconsider GRAS status for problematic ingredients (including caffeine, sugar, and guarana), especially in large quantities</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>• Add limitations to permissible amounts of GRAS ingredients</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>• Take enforcement action against manufacturers that add unapproved ingredients</td>
<td>FDA, AGs</td>
</tr>
<tr>
<td>Labeling</td>
<td>• Require caffeine disclosures on all products regulated by FDA</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>• Establish Daily Reference Value (DRVs) for caffeine and added sugar</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>• Require warning labels for liquid energy products</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>• Require liquid energy products comply with the NLEA</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>• Take enforcement actions against products mislabeled as dietary supplements</td>
<td>FDA, AGs</td>
</tr>
<tr>
<td></td>
<td>• Take enforcement action against the marketing of mislabeled products or products with false or deceptive claims</td>
<td>FTC, AGs</td>
</tr>
<tr>
<td>Retail</td>
<td>• Require age limits for purchase</td>
<td>Congress, State, Local</td>
</tr>
<tr>
<td></td>
<td>• Establish location restrictions in retail establishments</td>
<td>State, Local</td>
</tr>
<tr>
<td></td>
<td>• Prohibit the sale of the most problematic products</td>
<td>State, Local, AGs</td>
</tr>
<tr>
<td></td>
<td>• Establish excise taxes on highly sugared products</td>
<td>Congress, State, Local</td>
</tr>
<tr>
<td>Marking</td>
<td>• Stop marketing to adolescents, including on programming and in events that appeal to them</td>
<td>ABA, Manufacturers</td>
</tr>
<tr>
<td>Research</td>
<td>• Measure population caffeine consumption and youth consumption of energy drinks and shots</td>
<td>Public Health Community</td>
</tr>
<tr>
<td></td>
<td>• Identify best practices to reduce sales to underage consumers</td>
<td>Policy Advocates</td>
</tr>
</tbody>
</table>

During the approval process, the Select Committee on GRAS substances recognized potential health hazards associated with consuming added sugar at levels higher than at that time and caffeine in doses larger than used in cola-type beverages.\(^{39,40}\) Energy drinks contribute to high \textit{added sugar} consumption, which exceeds the levels at the time of GRAS approval, and they contain far more caffeine than cola-type beverages.\(^{22}\) Further, although the stimulant guarana is GRAS up to a specified amount, it is unclear exactly how much guarana is in energy drinks and how much would be considered safe when it is added to an already highly caffeinated product.
The FDA has the authority to revise GRAS status for sugar, caffeine, and guarana and to regulate the amount of each ingredient permitted to be added to beverages. The agency can mandate maximum levels of these ingredients in single-serving containers.

The FDA also expressed concern that other ingredients in energy drinks are not GRAS and are not being used in accord with existing food additive regulations. Taurine and panax ginseng, among other potential ingredients, are not approved for use in beverages. The FDA has the authority to designate these products as adulterated and unsafe for the food supply. The agency can reprimand manufacturers or condemn the products outright.

Labeling

The US government has several labeling options that should be considered to protect and inform consumers about the ingredients and risks associated with energy drinks. Congress can amend the FDCA and the FDA can issue binding regulations that energy drinks must be labeled as beverages and that caffeine content must be disclosed on all products under the FDA's purview.

Some or all energy drinks should contain warnings about caffeine toxicity and the introduction of ingredients not normally found in the food supply. Today, when caffeine is added to stimulant drug products, the package must bear a specific warning label stating that the product is for 'occasional use only' and not intended for children under 12 years of age. US law requires a warning when 'foreseeable risks of harm posed by the product could have been reduced or avoided by the provision of reasonable instructions or warnings' and the omission of such a warning 'renders the product not reasonably safe'. ER data from visits involving energy drinks, show these products may be regarded as not reasonably safe without warnings.

Consumer protection actions

The Federal Trade Commission (FTC) and state attorneys general (AGs) have authority to institute consumer protection actions to address labeling and ingredient violations identified above. The FTC can bring an action against manufacturers for unfair and deceptive marketing practices. The state AGs have similar authority over questionable marketing and
labeling and can additionally bring actions to protect citizens from particularly problematic products. In 2012, for example, New York's Attorney General started an investigation into whether energy drink manufacturers were misleading consumers about caffeine content and potential health risks.

**Retail restrictions**

State governments in the United States may enact retail regulations. Seventy-nine per cent of energy drinks are sold from convenience stores, and thus subject to a variety of potential regulations. States can, for example, restrict the sale of energy drinks to youth under a certain age; an option supported by parents. In 2010, a New York county legislator proposed a ban on the sale of energy drinks to minors younger than 19 years. Lawmakers can determine which age is appropriate. Implementation would be straightforward, because retail outlets are already legally required to verify the age of customers purchasing alcohol and tobacco.

Another option would be to regulate the location of problematic products in the retail environment, akin to state requirements that tobacco be sold from behind the counter. Energy drinks are generally offered in a refrigerator case near alcoholic or other sugary beverages. This placement may imply that they are similar to sugary beverages and/or encourage consumers to mix them with alcohol. Research might help determine how revised placement of drinks could have a positive impact on public health by discouraging purchases and the mixing with alcohol. Research can answer the question whether the top shelf of coolers or aisles, the back of the store, or behind the counter would help protect consumers.

Another retail restriction would ban the sale of certain energy drinks, such as those in large non-resealable containers or with the highest caffeine content. A bill proposed in Oregon sought to ban sale of 'high-calorie' beverages in single-serving containers larger than 12 oz. The same type of restriction could be placed on the sale of highly caffeinated products in large containers.

Finally, it is noteworthy that an excise tax placed on sugary beverages would surely apply to sugary energy drinks. The underlying rationale and potential benefits of such a tax have been discussed elsewhere; the goal is to decrease consumption. Both federal and state governments can institute excise taxes. Local jurisdictions can sometimes also enact...
taxes or fees – to the extent permitted by the state’s laws governing localities.21

Marketing restrictions

Tighter regulations on the marketing of energy drinks to adolescents are warranted, but in the United States a substantial barrier exists to government enacting such regulations. The Supreme Court has interpreted the First Amendment of the Constitution to protect marketing, or commercial speech, from government interference. Thus, the United States has focused on self-regulation, hoping to maintain some control over marketing directed at youth.

The ABA established guidelines for the sale and marketing of energy drinks, under which member companies agree to refrain from marketing products to children (ages 2–11) and selling them in schools (grade levels K–12).18 The guidelines also state that energy drinks should not be promoted as sports drinks or in connection with alcohol consumption. In response to criticism of marketing that promotes energy drinks to youth, both Red Bull48 and the ABA,49 as a spokes-organization for its member companies, reiterated that they do not market energy drinks to children under age 12. But these self-regulatory pledges do not prohibit marketing targeted directly to adolescents and, as noted, despite these restrictions, children and adolescents continue to be exposed to large numbers of advertisements for energy drinks.

Self-regulation of alcohol marketing to minors (20 years and younger) provides a potential blueprint for reducing energy drink marketing to youth. The FTC has recommended a self-regulatory approach to reduce underage exposure to alcohol marketing. Major alcohol suppliers agreed that they would not advertise in media with an audience comprising more than 30 per cent minors and have largely complied.50 The National Research Council (NRC), Institute of Medicine (IOM),51 and 19 state AGs52 recommended tighter self-regulatory standards, including no alcohol advertising in media with an underage audience share of 15 per cent (approximately their share of the US population) and restrictions on marketing practices with substantial underage appeal. The NRC and IOM also recommended establishment of an independent review board to monitor alcohol marketing practices. A similar protocol would work well for energy drinks.

Companies that belong to the ABA currently comply with their self-regulatory commitments, but this program has limitations. Several of the highest selling energy drink brands do not belong to the ABA. At a minimum, these companies should agree to abide by ABA guidelines. However, to address the majority of youth-targeted marketing of energy drinks, all energy drink manufacturers should also agree to discontinue their marketing practices that disproportionately appeal to adolescents, including advertising on television programming with a higher-than-average proportion of youth in the audience and the use of social media and sponsored events.

Discussion and Conclusion

Existing evidence points to significant public health issues arising from youth consumption of energy drinks, but further research and analysis are needed:

- More comprehensive measurement of youth consumption of caffeine and energy drinks, separate from other sugary beverages. Because energy drinks are relatively new products in the American marketplace, ongoing dietary measurement panels do not adequately monitor and report on these products.
- Research to determine consumer understanding of ingredients and claims on energy drink labels would help us understand the extent to which current practices mislead or deceive.
- Studies of energy shots are also warranted. We know little about energy shot consumption by youth; but 82 per cent of the energy product ads viewed by children and adolescents promoted one shot: 5-Hour Energy. Of all products examined in the 2010 study, a 2.5 oz. shot had the highest per-serving caffeine content overall, 200 mg. Manufacturers designate energy shots as dietary supplements so they are located with other dietary supplements in pharmacies, which may send an unwarranted health message to consumers. In other retail outlets, shots are often located in free-standing displays at the check-out further encouraging purchase. The FDA should pay particular attention to categorization and labeling of shots because companies market them in media viewed by youth and they contain extreme levels of caffeine that could be dangerous for children and adolescents.
To identify best policies, research might help local jurisdictions determine the best location in retail establishments to require problematic products to be placed to discourage purchase by youth. Alternatively, locales can experiment with product placement restrictions to determine which locations work best.

Consumption of energy drinks is a public health concern especially for young people. Increased regulation is warranted to inform and protect consumers by addressing problematic ingredients, clarifying labeling requirements, and restricting youth access. At a minimum, increased self-regulatory efforts should be instituted to protect youth from marketing. Energy drinks are a unique beverage and should be regulated accordingly.

About the Authors

Jennifer L. Pomeranz (JD, MPH) is the Director of Legal Initiatives at the Yale Rudd Center for Food Policy & Obesity at Yale University. Ms. Pomeranz speaks and publishes on subjects including: sugar labeling, weight discrimination, food marketing to children, the First Amendment, preemption, regulating sugary beverages, and innovative legal solutions to obesity. She earned her Juris Doctorate from Cornell Law School, and her Master of Public Health from the Harvard School of Public Health.

Christina R. Munsell (MS) is a Research Associate and Registered Dietitian at the Rudd Center for Food Policy & Obesity at Yale University. She completed a dietetic internship and Master's degree in Health Care Policy and Management at Stony Brook University after earning a Bachelor's degree in Nutrition from Texas Christian University. Munsell works with the marketing team at the Rudd Center, developing and executing projects that analyze food marketing to youth as well as providing nutrition expertise for other Rudd Center projects and research.

Jennifer L. Harris (MBA, PhD) is Director of Marketing Initiatives at the Rudd Center for Food Policy & Obesity at Yale University. She is responsible for identifying and coordinating research initiatives to understand and communicate the extent and impact of children's exposure to food advertising. Dr Harris received her BA in Political Science from...
Northwestern University, her MBA in Marketing from The Wharton School at the University of Pennsylvania, and her PhD in Social Psychology from Yale University. Before returning to graduate school, she worked for 18 years as a Vice President in marketing at American Express and ran a marketing consulting firm specializing in marketing strategy and new product and market development. Dr Harris has written on the psychological and behavioral effects of advertising to children and adolescents and conducted research to quantify the amount and types of food marketing seen by young people and its impact on their health and diet.

References and Notes
Pomeranz et al.


17. 21 U.S.C. 343(g)(5)(F).


19. 21 U.S.C. 321(s).


29. comScore. Site Detail Report. Average of monthly unique visitors from October to December, 2011.


Regulating energy drinks

36. 21 U.S.C. §301 et seq.
38. 21 C.F.R. §84.1854 et seq.
39. 21 C.F.R. §82.180.
41. 62 Federal Register 49816 (23 September 1997).
42. 21 C.F.R. §340.50.
47. OR HB 3222 (2010).
Energy Drinks: An Assessment of the Potential Health Risks in the Canadian Context

Regular Paper

Joel Rotstein¹, Jennifer Barber¹, Carl Strowbridge¹, Stephen Hayward¹, Rong Huang¹ and Samuel Benrejeb Godefroy¹.

¹ Food Directorate, Health Products and Food Branch, Health Canada, Canada
* Corresponding author E-mail: samuel.godefroy@hc-sc.gc.ca

Received 12 February 2013; Accepted 3 June 2013

DOI: 10.5772/56723

© 2013 Rotstein et al.; licensee InTech. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract The purpose of this document is to develop a health risk assessment on energy drinks, based on health hazard and exposure assessments when consumed as a food in Canada. In this document, a typical energy drink is exemplified by the product known as Red Bull™, where a single can serving of 250 ml contains 80 mg of caffeine, 1000 mg of taurine, 600 mg of glucuronolactone and several B vitamins.

Health hazard data on energy drinks were found to be limited and therefore the hazard assessment was based on individual ingredients. Caffeine was identified as the ingredient with the greatest potential for intakes of possible health concern. On this basis, excess consumption of energy drinks would be expected to result in health consequences similar to those from excess exposure to caffeine. The more mild and transient health consequences could include anxiety, headache and insomnia and these health consequences can become chronic conditions. More severe health consequences may include irregular heartbeat, heart attack and, very rarely, death. Currently, the potential for taurine and glucuronolactone to interact with caffeine is unknown and therefore they may or may not exacerbate the effects of caffeine. In addition, the health effects of excessive intake of taurine and glucuronolactone are also unknown. The health hazard assessment concluded that the general adult population could safely consume 2 servings of a typical energy drink per day, with no health consequences. This conclusion was based on the safety of the non-caffeine ingredients of energy drinks at this level of consumption, and the fact that caffeine from other dietary sources in addition to that in 2 servings of energy drinks would not pose a health hazard to the general adult population. The consumption of energy drinks by subpopulations, such as children, adolescents, and pregnant women, should be limited to their respective recommended maximum daily intakes of caffeine, as recommended by Health Canada.

Using exposure modelling, the potential health risk posed by energy drink consumption was examined. However, no Canadian intake data for energy drinks were available. Therefore, for the purpose of modelling intake, it was assumed that energy drinks are consumed in a manner similar to that of caffeinated carbonated soft drinks. In the worst case modelling exposure scenario, energy drinks were substituted for caffeinated carbonated soft drinks on a volume basis.
The energy drink caffeine concentration was set to 320 ppm (80 mg of caffeine/250 ml serving) for modelling purposes. In the most conservative scenario, all caffeinated carbonated soft drinks were replaced by a typical energy drink for consumers who drink these beverages (eaters only). The results of this conservative estimate showed that slightly less than 30% of male and female adults, about 15% of pregnant woman and more than 50% of the children and adolescents, amongst consumers who drank caffeinated carbonated soft drinks, were above Health Canada’s recommended maximum daily caffeine intake.

This extreme scenario only applies to that subset of the population that consumes caffeinated carbonated soft drinks, which does not exceed 8% of young children (1-8 years old), 22% of older children (9-14 years old), 32% of adolescents, 20% of the adult population and 13% of pregnant females.

In critically reviewing the outcomes of this exposure modelling, it appeared that the corresponding health concerns for children and adults would be limited to remote, based on this scenario, in view of the parental control that should exist and would limit access of these products to children, as well as the ability of adults and pregnant women to monitor their own caffeine intake. This hypothetical scenario and its outcomes could not be as easily excluded for adolescents, given that energy drinks tend to be marketed to this subset of the population, which is less likely to adhere to consumption recommendations than adults. The existence of larger volume containers (e.g., 710 ml) increases the likelihood of exceeding caffeine recommended intakes in one consumption setting.

Specific risk management measures to address potentially high caffeine levels in larger volume energy drink products would therefore be desirable. It is acknowledged that various data gaps would need to be addressed to improve the exposure assessment and the overall risk characterization. In particular, data related to the evolving consumption patterns of these products by the various subsets of the population, in Canada, needs to be gathered.

Health Canada’s proposed risk management approach for energy drinks, announced in October 2011 and updated in 2012, limits the concentration and total amount of caffeine in these products and requires that caffeine and nutrition information be displayed on product labels. These measures support the mitigation of risks related to overconsumption of caffeine from this type of product that are within the possible areas of intervention available to a federal food regulator. A more concerted approach (e.g., education, awareness and regulation) and more research would be needed to ascertain the effectiveness of the various measures taken by regulators and other stakeholders.

Keywords Energy drink, Caffeine, Taurine, Glucuronolactone, Inositol, B vitamin

Disclaimer:

This document was developed as a review of the scientific information available pertaining to the safety of ingredients that may be part of the composition of the beverages known as Caffeinated Energy Drinks (Energy Drinks). The document was developed during a period spanning from 2010 to late 2011. A number of references and new studies have been made available since then and are not referenced in the present document. An update of the present Health Risk Assessment is envisaged in 2014-15, upon review of information currently being collected by Health Canada’s Food Directorate since the regulatory decision made in October 2011, to regulate Energy Drinks as beverages (i.e. food) as opposed to their former classification as Natural Health Products.

1. Introduction

1.1 Purpose

The purpose of this document is to provide a health risk assessment of energy drink products based on their consumption as beverages in Canada. The document attempts to provide a scientific analysis based on the information available to date, which could then be used to support the development of suitable risk management measures for these products when consumed as foods.

2. Defining a typical energy drink

2.1 Defining products known as energy drinks

For the purpose of this document, a typical energy drink is characterised by the ingredients and ingredient levels shown in Table 1. Ingredients include caffeine, taurine, glucuronolactone, inositol and a variety of B vitamins. The basis for this characterisation is the formulation of the most commonly sold products of this category of beverages, such as the product known as Red Bull™, which was the first energy drink approved for the market in Canada. Based on 2009 market data of the global marketing research firm ACNielsen, Red Bull™ comprised approximately 37% of the sales of energy drinks in Canada and, as such, had the largest market share. This is consistent with a more recent report (AAFC, 2011) that states that Red Bull™ constitutes 43% of the sales of energy drinks in North America.

Although Health Canada does not have a definition or standard for products known as energy drinks, other food regulators have reached a decision on this aspect of these products. For example, Australia and New Zealand categorizes energy drinks as ‘formulated caffeinated beverages’ which are defined under the Australia New Zealand Food Standards Code as “a non-alcoholic water-based flavoured beverage which contains caffeine and...
may contain carbohydrates, amino acids, vitamins and other substances, including other foods, for the purpose of enhancing mental performance”.

In Europe, the Ireland Food Safety Promotion Board (FSBP) established a committee consisting of external experts to research the health effects of ‘stimulant drinks’ (energy drinks). The committee noted in its final report that there is no agreed definition in the regulatory framework for products referred to as energy drinks or ‘stimulant drinks’. For the purposes of the report, the term ‘stimulant drinks’ was adopted. The committee defined stimulant drinks as “beverages, which typically contain caffeine, taurine and vitamin(s), and may contain an energy source (e.g. carbohydrate), and/or other substance(s), marketed for the specific purpose of providing real or perceived enhanced physiological and/or performance effects” (FSBP, 2003).

2.2 Major components of energy drink products

During the preparation of this manuscript, energy drinks were marketed in Canada under the Natural Health Products (NHP) Regulations. At the time, it was estimated that over 300 energy drink product submissions were before Health Canada for consideration as NHPs. Only twelve were assessed and received a license. Approximately half of the 300 product submissions were either refused a license or withdrawn by the petitioner. A number of products were also on the Canadian market under the provisions of the Unprocessed Product Licensing Regulations. Table 1 below lists the major ingredients and levels typically found in the products that were in the queue for consideration to be licensed as an NHP. For comparison purposes, Table 1 also provides the levels of major ingredients that are typically found in a standard energy drink product.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Formulation of products known as Energy Drinks that have been either licensed or in queue with Health Canada for consideration as NHPs. (mg per serving*)</th>
<th>Typical energy drink (mg per 250 ml serving)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>50 – 200</td>
<td>80</td>
</tr>
<tr>
<td>Taurine</td>
<td>10 – 2000</td>
<td>1000</td>
</tr>
<tr>
<td>Glucuronolactone</td>
<td>600 – 1200</td>
<td>600</td>
</tr>
<tr>
<td>niacin</td>
<td>10 – 40</td>
<td>18*</td>
</tr>
<tr>
<td>vitamin B6</td>
<td>5 – 10</td>
<td>2</td>
</tr>
<tr>
<td>vitamin B12</td>
<td>0.002 - 0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>pantothenic acid</td>
<td>5 – 10</td>
<td>6</td>
</tr>
<tr>
<td>thiamine</td>
<td>0.5 – 5</td>
<td>2</td>
</tr>
<tr>
<td>riboflavin</td>
<td>0.5 – 5</td>
<td>1.65</td>
</tr>
<tr>
<td>Inositol</td>
<td>50-200</td>
<td>50</td>
</tr>
</tbody>
</table>

* Serving size is typically 250-473 ml.

Of the energy drink products that were in the NHP submission queue, approximately 13% fell within the ‘typical description’ for energy drinks. Based on market share data from AC Nielsen (2009), Red Bull™ was ranked the highest, comprising approximately 37% of the market. Energy drinks such as Monster™ and Rockstar™, which contain levels of ingredients higher than the standard and/or contain other ingredients that are not part of the standard, were ranked next but well below Red Bull™ with 5.5% and 4.4% of the market respectively. This market share data has been evolving over the years and may not be reflective of the current market situation.

A wide range of energy drink products is available internationally and in the Canadian marketplace. Ingredients and ingredient levels vary from product to product. While the major ingredients typically found in energy drinks in Canada are listed in Table 1, many other ingredients can be found in these products, particularly various herbs and extracts such as ginseng, ginkgo biloba and green tea extract.

2.3 Energy drink market growth in Canada

According to a 2008 report on the Canadian energy drink market published by Agriculture and Agri-Food Canada (AAFC), in 2006 the “functional beverage category” was valued at 7% of the total soft drink market. Energy drinks are included in the functional beverage category along with sport and nutraceutical drinks. Energy drinks accounted for 65% of the functional beverage sector and 4.6% of the value of the soft drink market. In a more recent report by AAFC (2011), it was noted that there are more than 210 different energy drink brands in North America. It also reported that the energy drink market grew 60.2% from 2007 to 2010 and 5.1% from 2009 to 2010.

3. Health Effects of Energy Drinks

3.1 Introduction

The research on energy drinks is largely limited to a small number of clinical studies (about 12 studies) and case reports. The clinical studies tended to have small numbers of participants (less than 100 subjects) and focused on very specific health effects. These studies mostly examined the effect of energy drink consumption on behaviour and physical activity; therefore, the parameters examined were limited and not necessarily significant from a health and safety perspective. Other studies assessed the consequences of consuming the combination of energy drinks and alcohol.

3.2 Health effects of energy drinks

3.2.1 Acute physiological effects of energy drinks

There is concern that some individuals, who may have increased sensitivity to the ingredients in energy drinks,
may have an acute physiological response, specifically an increase in heart rate and blood pressure. Table 2 summarizes the limited studies on the acute physiological effects of energy drinks. Rashid et al. (2009) investigated 10 healthy women, mean age 20 years. Subjects consumed 140 ml of an energy drink or a placebo. Average systolic blood pressure\(^1\) was significantly higher for the energy drink group compared to placebo. No differences were seen in heart rate, diastolic blood pressure or profile of mood states at any time point. American Heart Association (2007) reported on a study concerning the cardiovascular effects of energy drinks. Fifteen subjects (8 women, 7 men, mean age 26 years) were given 500 ml of an energy drink. The researchers noted an increase in systolic blood pressure and an increase in heart rate in the four hours after consumption of the beverage (cited in BIR 2008). However, across the various studies, changes in blood pressure did not reach hypertensive levels with the consumption of energy drinks. These effects were similar to the effects on blood pressure demonstrated with the consumption of coffee (Riksen et al. 2009).

3.2.2 Behavioural/performance effects of energy drinks

A limited number of studies have assessed the behavioural effects following consumption of energy drinks containing both glucose and caffeine, along with other potentially active agents (see Table 3 below). These studies have identified improvements in performance of attention and/or reaction time tasks and various indices of alertness. For example, Alford et al. (2001) examined the effects of Red Bull Energy Drink over 3 studies in 36 volunteers. Significant improvements in mental performance including choice reaction time, concentration and memory were observed with Red Bull compared to the control drinks. Scholey and Kennedy (2004) investigated the effects of glucose alone, caffeine alone, ginseng and ginkgo at flavouring levels, an energy drink or a placebo in 20 students. Compared to placebo, the energy drink resulted in significantly improved performance on secondary memory and speed of attention factors. Some of the studies attributed the demonstrated effects to the combination of ingredients in energy drinks, rather than caffeine only (Alford et al. 2001; Reyner & Horne 2002; Scholey & Kennedy 2004).

3.2.3 Calories

Except for sugar-free versions, energy drinks, like many beverages, contain sugars in the form of sucrose, glucose, and/or high-fructose corn syrup. The sugar content varies among energy drinks but ranges from 21 to 34 grams per 237 ml can (Clauson et al. 2008). This sugar content is similar to that of carbonated caffeinated soft drinks. It constitutes the vast majority of calories in these products. A 250 ml serving of a typical energy drink contains 110 calories, which is similar to the 86-130 calories in the same volume of a carbonated caffeinated soft drink (USDA Nutrient Database, 2011).

3.3 Health Effects of Energy Drinks and Sports Activity

Energy drinks are frequently marketed to individuals interested in athletics and an active lifestyle. The main ingredients in energy drinks purported to enhance sport performance are caffeine and carbohydrates. The term “energy drink” itself implies that its consumption might enhance physical activity.

Energy drinks should not be confused with ‘sports drinks’. Sports drinks are typically a mixture of carbohydrates and electrolytes formulated to enhance athletic performance and prevent dehydration, and, unlike energy drinks, they do not contain caffeine. Conversely, energy drinks contain caffeine which is a stimulant and therefore they are not considered suitable to re-establish normal body function after exercise (e.g. normal heart rate).

The effects of energy drinks on exercise have been investigated in a small number of studies (see Table 4 below). Studies investigating the use of energy drinks have generally found an improvement in endurance performance. Ivy et al. (2009) found that the consumption of 500 ml of a Red Bull energy drink 40 minutes before a simulated cycling time trial in 12 trained cyclists significantly improved endurance performance compared to a non-caffeinated, sugar-free placebo. Forbes et al. (2007) found that the consumption of Red Bull energy drink significantly increased upper body muscle endurance but had no effect on anaerobic peak or average power during repeated Wingate cycling tests in healthy young adults, when compared to a non-caffeinated, isoenergetic, control beverage. Lockwood et al. (2009) found that pre-workout energy drink consumption, significantly improved some physiological adaptations to combined aerobic and resistance training, when compared to a non-caffeinated, sugar-free control drink. Lastly, a study investigating the use of a sugar-free energy drink (Red Bull) found that there was no difference in run time-to-exhaustion or perceived exertion in young adults when compared to non-caffeinated sugar-free placebo (Candow et al. 2009). Overall the studies’ result suggest that the consumption of energy drinks may enhance physical ability but it is not clear whether the effect is due to the presence of caffeine, sugar or both of these constituents in the energy drink.

\(^1\) During each heartbeat, blood pressure varies between a maximum (systolic) and a minimum (diastolic) pressure.
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Test Material (composition)</th>
<th>Methods</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind, placebo-controlled</td>
<td>Red Bull Energy Drink (32 mg/dL caffeine, 240 mg/dL glucuronolactone, 400 mg/dL taurine) Low Calorie Red Bull Energy Drink (32 mg/dL caffeine, 240 mg/dL glucuronolactone, 400 mg/dL taurine) High Calorie Placebo (carbonated water, tap water and dextrose) Low Calorie Placebo (carbonated water, tap water and dextrose) NB: Banana flavouring and green colouring were added to all test materials</td>
<td>Study 1: 69 subjects (48 women, 21 males, mean age 20 y) consumed 250 ml Red Bull™, Low Calorie Red Bull™, high calorie placebo, or low calorie placebo. Study 2: 21 subjects (9 men, 12 women, mean age 22 y) consumed 250 ml Red Bull™ pre and post cold pressor test.</td>
<td>Study 1: No changes noted in overall cardiovascular function or blood glucose over 2 hour test period. Study 2: A significant increase in diastolic blood pressure in the males immediately after submersion of the hand in cold water (5°C). No significant change noted in females.</td>
<td>Ragsdale et al. 2010</td>
</tr>
<tr>
<td>Randomized, double-blind, crossover, placebo-controlled</td>
<td>Meltdown RTD (140 ml contains: 230 mg caffeine, unknown amounts of methyltetradecylthioacetic acid, yerba mate extract, methyl-sympathrine, methylphenylethylene, 11-hydroxy yohimbine, yohimbine HCL, alphayohimbine, and methyl-hordenine HCl) Placebo (described as similar in appearance and taste to Meltdown RTD but only contained inert substances)</td>
<td>10 subjects (mean age 20 y) received 140 ml of Meltdown RTD energy drink or a placebo.</td>
<td>Mean systolic blood pressure was significantly higher for the energy drink group compared to placebo. No differences noted in heart rate, diastolic blood pressure, or profile of mood states.</td>
<td>Rashti et al. 2009</td>
</tr>
<tr>
<td>Prospective</td>
<td>Unspecified energy drink (250 ml contains: 1000 mg taurine, 100 mg caffeine, unstated amounts of vitamins B5, B6, B12, glucuronolactone, niacinamide)</td>
<td>15 subjects (7 men, 8 women, mean age 26 y) consumed 500 ml (2 cans) of an energy drink daily for the next 5 days.</td>
<td>Within 4 hours of energy drink consumption, mean systolic blood pressure and heart rate significantly increased. Diastolic blood pressure significantly increased within 2 hours of energy drink consumption.</td>
<td>Steinke et al. 2009</td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td>Unspecified energy drink (250 ml contains: 1000 mg taurine, 80 mg caffeine, 600 mg glucuronolactone, unstated amounts of vitamins B2, B5, B6 and B12, sugar-free sweetener and thickeners) Placebo (carbonated water)</td>
<td>50 subjects (34 men, 16 women, mean age 22 y) consumed either a 250 ml sugar-free energy drink or 250 ml of carbonated water (control)</td>
<td>Compared with baseline values, there was a significant increase in platelet aggregation following energy drink consumption; no change was observed with control. Mean arterial pressure significantly increased following energy drink consumption compared with control.</td>
<td>Worthley et al. 2010</td>
</tr>
</tbody>
</table>

1 Test material composition is listed as it is described in the published report.  

Table 2. Studies investigating the acute physiological effects of energy drinks
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Test material (composition)1</th>
<th>Methods</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind</td>
<td>Red Bull Energy Drink (250 ml contains: carbonated water, 21.5 g sucrose, 5.25 glucose, 1 g taurine, 600 mg glucuronolactone, 80 mg caffeine, 50 mg inositol, and unstated amounts of niacin, panthenol, B6, B12, riboflavin, flavours, colours) Carbonated water Dummy energy drink (unstated amounts of low calorie quinine flavoured carbonated water with lime, apple and blackcurrant concentrates)</td>
<td>36 subjects (19 men, 17 women, age range 18-30 y) in 3 studies received no drink, 250 ml of carbonated water, Red Bull energy drink, or “dummy” energy drink.</td>
<td>Compared to control drinks, Red Bull energy drink significantly improved mental performance including choice reaction time, concentration, and memory.</td>
<td>Alford et al. 2001</td>
</tr>
<tr>
<td>Double-blind</td>
<td>Red Bull Energy Drink (250 ml contains: 21 g sucrose, 5 g glucose, 1 g taurine, 600 mg glucuronolactone, 80 mg caffeine, 50 mg inositol, and unstated amounts of vitamin B complex) Placebo (250 ml contains: 21 g sucrose, 5 g glucose, 50 mg inositol, and unstated amounts of vitamin B complex)</td>
<td>11 subjects (male and female, mean age 24 y) received 500 ml of an energy drink or a control drink prior to car simulator test. Control drink consisted of identical drink minus the caffeine, taurine and glucuronolactone.</td>
<td>The energy drink significantly reduced lane drifting and improved reaction time, particularly for the 1st hour.</td>
<td>Horner &amp; Reyner 2001</td>
</tr>
<tr>
<td>Double-blind</td>
<td>Red Bull Energy Drink (250 ml contains: 21 g sucrose, 5 g glucose, 1 g taurine, 600 mg glucuronolactone, 80 mg caffeine, 50 mg inositol, and unstated amounts of vitamin B complex) Placebo (250 ml contains: 21 g sucrose, 5 g glucose, 50 mg inositol, and unstated amounts of vitamin B complex)</td>
<td>12 subjects (7 men, 5 women, mean age 24 y) received 250 ml of Red Bull energy drink or a control drink prior to car simulator test. Control drink consisted of identical drink minus the caffeine, taurine and glucuronolactone.</td>
<td>Compared with the control, the energy drink significantly reduced sleep-related driving incidents and subjective sleepiness for the 1st 90 minutes of the drive.</td>
<td>Reyner &amp; Horne 2002</td>
</tr>
<tr>
<td>Randomized, double-blind, 5 way cross-over, placebo-controlled</td>
<td>Placebo (250 ml contains: water with flavour and sweeteners). Drink 1 (250 ml contains: water with flavour, sweeteners and 75 mg caffeine) Drink 2 (250 ml: water with flavour, sweeteners and 37.5 g glucose) Drink 3 (250 ml contains: water with flavour, sweeteners, 12.5 mg ginseng extract, 2 mg ginkgo biloba extract) Unspecified energy drink (250 ml contains: water with flavour, sweeteners, 75 mg caffeine, 37.5 g glucose, 12.5 mg ginseng extract, 2 mg ginkgo biloba extract)</td>
<td>20 subjects (14 women, 6 men, mean age 21 y) received 1 of 5 drinks: placebo, drink 1, drink 2, drink 3 or an energy drink for a total of 6 study days, each 7 days apart.</td>
<td>Compared with placebo, the energy drink resulted in significantly improved performance on secondary memory and speed of attention factors.</td>
<td>Scholey &amp; Kennedy 2004</td>
</tr>
<tr>
<td>Study Design</td>
<td>Test material (composition)</td>
<td>Methods</td>
<td>Results</td>
<td>Reference</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------</td>
<td>---------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Randomized, double-blind, cross-over, placebo-controlled</td>
<td>Sugar-free Red Bull Energy Drink (2 mg/kg caffeine; ~146 mg caffeine) Placebo (decaffeinated, sugar-free, lemon-lime flavoured soft drink, tonic water, and lime juice)</td>
<td>17 subjects (9 men, 8 women, mean age 21 y) received either sugar-free Red Bull energy drink or decaffeinated, sugar-free placebo on 3 days of testing, during which they performed physical activity.</td>
<td>No significant difference in run time-to-exhaustion, perceived exertion or calcium lactate between groups.</td>
<td>Candow et al. 2009</td>
</tr>
<tr>
<td>Randomized, double-blind, cross-over, placebo-controlled</td>
<td>Red Bull Energy Drink (2 mg/kg caffeine; ~146 mg caffeine) Placebo (isooenergetic, isovolumetric, non caffeinated)</td>
<td>15 subjects (11 men, 4 women, mean age 21 y) received Red Bull Energy Drink (2 mg/kg caffeine) or non-caffeinated placebo separated by 7 days. Muscle endurance assessed by the maximum number of repetitions over 3 sets. Three Wingate cycling tests were used to assess peak and average power output.</td>
<td>Red Bull Energy Drink significantly increased upper body muscle endurance but had no effect on anaerobic peak or average power.</td>
<td>Forbes et al. 2007</td>
</tr>
<tr>
<td>Randomized, double-blind, cross-over, placebo-controlled</td>
<td>Red Bull Energy Drink (500 ml contains: 2 g taurine, 1.2 g glucuronolactone, 160 mg caffeine, 54 g carbohydrate, 40 mg niacin, 10 mg pantothentic acid, 10 mg vitamin B6, 10 ug vitamin B12) Placebo (500 ml contains: flavoured drink)</td>
<td>12 trained cyclists (6 men, 6 women, mean age 27 y) consumed 500 ml of either placebo or Red Bull Energy Drink 40 minutes before simulated cycling time trial.</td>
<td>Performance significantly improved with energy drink compared to placebo but no difference in rating of perceived exertion between treatments.</td>
<td>Ivy et al. 2009</td>
</tr>
</tbody>
</table>

1 Test material composition is listed as it is described in the published report.

Table 3. Studies investigating behavioural/performance effects of energy drinks
Randomized,
double-blind,
placebo-controlled | Unspecified energy drink (12 fl oz contains: carbonated water, citric acid, natural flavours (lemon-lime), sucralose, 60 mg vitamin C, 1.7 mg riboflavin, 20 mg niacin, 2 mg vitamin B6, 6 ug vitamin B12, 300 ug biotin, 10 mg pantothenic acid, 50 mg calcium, 50 ug chromium, 6 mg sodium, 1810 mg combined taurine, guarana extract, green tea leaf extract, caffeine, glucuronolactone, ginger extract (total 200 mg caffeine)) | 38 subjects (male, 18-45 years old) received energy drink + exercise, energy drink, placebo, or placebo + exercise for 10 weeks (1 drink per day) | Significantly greater decreases in fat mass and percentage body fat, as well as power output at ventilatory threshold were observed in energy drink + exercise compared to placebo + exercise. | Lockwood et al. 2009

| Placebo (12 fl oz contains: carbonated water, citric acid, natural flavours (lemon-lime), sucralose) |

Table 4. Studies investigating energy drinks and exercise

3.4 Energy Drinks and Alcohol

Due to concerns with the combination of energy drinks and alcohol, Health Canada has recommended since 2004, the date of licensing of the first Energy Drinks as NHPs, that these products should not be mixed with alcohol (Health Canada: It’s Your Health 2010). Nonetheless, the ingestion of energy drinks with alcohol has become increasingly popular (Health Canada: It’s Your Health 2010). A survey of 496 American college students examined the frequency of energy drink use for six “situations”: insufficient sleep, to increase energy, while studying, driving long periods of time, drinking with alcohol, and to treat hangover. The majority of users consumed one energy drink to treat most situations (namely, hangover, insufficient sleep, increase energy, driving a car for a long period of time) although using three or more to drink with alcohol while partying was a common practice (49%) (Malinauskas et al. 2007). In a survey of 4271 American college students, 24% (697 students) reported consuming energy drinks with alcohol (O’Brien et al. 2008). A summary of studies investigating the use of energy drinks and alcohol can be found in Table 5 below.

Basic physiology suggests that the carbonation of the energy drink permits a quicker absorption of alcohol while the caffeine of the energy drink may mask the drowsiness associated with alcohol intake. Although there is little direct evidence for it, when mixing energy drinks and alcohol, users may not feel the symptoms of alcohol intoxication which may increase the potential for alcohol-related injury (Ferreira et al., 2006). A survey of American college students by O’Brien et al. (2008) found that in comparison to those who consumed alcohol alone, students who consumed alcohol mixed with energy drinks had a significantly higher prevalence of alcohol-related consequences, including: being taken advantage of, or taking advantage of another student sexually, riding in an automobile with a driver under the influence of alcohol, or being hurt or injured. In addition, mixing energy drinks with alcohol was associated with increased heavy episodic drinking and episodes of weekly drunkenness. Thombs et al. (2010) conducted a field study in a U.S. bar district, interviewing 802 randomly selected and self-selected participants and found that those who mixed energy drinks with alcohol were at a 3-fold risk of leaving a bar highly intoxicated as well as a 4-fold risk of intending to drive upon leaving the bar district, compared to those who did not mix alcohol with energy drinks.

In Germany, the Federal Institute for Risk Assessment (BfR) recommends that “adverse effects cannot be ruled out when larger amounts of these beverages are consumed in conjunction with intensive physical activity or with the intake of alcohol beverages”. The BfR looked at case reports from their Swedish regulatory counterpart, the National Food Administration. Information obtained from the Swedish literature search is described in Table 6 below.

---

While this manuscript was in preparation, a study was published which suggested that energy drinks did not mask the effect of alcohol (Alford et al., 2012). As well, a statement was published by the Committee on Toxicity(UK) 2012, which concluded that the limited currently available evidence does not support a harmful interaction between alcohol and caffeine.
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Test material</th>
<th>Methods</th>
<th>Results</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, placebo-</td>
<td>Green Monster</td>
<td>27 female subjects (mean age: 22 years) consumed Green Monster energy</td>
<td>Energy drink plus alcohol significantly lowered post-test performance on a global score of neuropsychological status, specifically visuospatial/ constructional and language performance scores.</td>
<td>Curry and Stasio 2009</td>
</tr>
<tr>
<td>controlled</td>
<td>(16 oz contains: 160 mg caffeine, 52 g sugar, 2000 mg taurine, 400 mg ginseng, unstated amount of guarana)</td>
<td>drink alone (1 drink), with alcohol, or a non-caffeinated control.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcoholic,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>caffeinated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>beverage (16 oz contains: 6% alcohol, 87 mg caffeine, 47 g sugar, unstated amounts of taurine, ginseng and guarana)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-alcoholic, non-caffeinated beverage (16 oz contains: 5 g sugar)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized, double-blind</td>
<td>Red Bull energy drink (250 ml can)</td>
<td>26 male subjects (mean age 23 y) received Red Bull Energy drink (1 can) plus vodka (0.6 g/kg or 1 g/kg) or alcohol alone or energy drink alone.</td>
<td>When compared to the ingestion of alcohol alone, the ingestion of alcohol + energy drink significantly reduced subjects’ perception of headache, weakness, dry mouth, and impairment of motor coordination.</td>
<td>Ferreira et al. 2006</td>
</tr>
<tr>
<td>Survey and field test</td>
<td>Unspecified energy drinks</td>
<td>496 US college students completed questionnaires</td>
<td>The majority of users reported consuming energy drinks for insufficient sleep (67%), to increase energy (65%), and to drink alcohol while partying (54%). Common practice to drink 3 or more energy drinks with alcohol (49%). Weekly jolt and crash episodes were experienced by 29% of the users, 22% reported ever having headaches, and 19% heart palpitations from consuming energy drinks.</td>
<td>Malinauskas et al. 2007</td>
</tr>
<tr>
<td>Web-based random sample survey</td>
<td>Unspecified energy drinks</td>
<td>Survey was conducted in 4271 college students from 10 universities in North Carolina</td>
<td>697 students (24%) reported consuming alcohol with energy drinks. Students who were male, white, intramural athletes, fraternity or sorority members or pledges, and younger were significantly more likely to consume alcohol with energy drinks. Consumption of energy drinks with alcohol was associated with significantly increased heavy episodic drinking, and twice as many episodes of weekly drunkenness. Students consuming alcohol with energy drinks also had significantly higher prevalence of alcohol-related consequences.</td>
<td>O'Brien et al. 2008</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>Unspecified energy drinks</td>
<td>450 college students filled out the questionnaire</td>
<td>56.9% students declared using energy drinks. 48.4% of users frequently associated energy drinks with alcohol.</td>
<td>Oteri et al. 2007</td>
</tr>
<tr>
<td>Randomized, field interview</td>
<td>Unspecified energy drinks</td>
<td>802 patrons from 7 bars over 4 consecutive nights. Every 3rd patron exiting bar was approached.</td>
<td>3-fold increased risk of leaving a bar highly intoxicated and 4-fold increased risk of intending to drive upon leaving the bar district, compared to patrons who did not mix energy drinks with alcohol.</td>
<td>Thombs et al. 2010</td>
</tr>
</tbody>
</table>

1 Test material composition is listed as it is described in the published report.

Table 5. Studies investigating the energy drinks consumed with alcohol
that caffeine/3 affects happened relatively quickly, and usually in young adults. The studies conducted in humans show that caffeine produces subjective and behavioral effects that are similar to those of typical psychomotor stimulant drugs that are known to be dopaminergically mediated (e.g., amphetamines, cocaine). Caffeine, like amphetamine and cocaine, enhances feelings of well-being, motivation for work, energy, and concentration, delays sleep, and enhances vigilance performance on psychomotor tasks (Garrett & Griffiths 1997).

Overall, the evidence does not conclusively indicate a harmful toxicological interaction between energy drinks and alcohol. However, the data are limited and there is substantial uncertainty. It was noted that adverse events associated with energy drink and alcohol co-consumption happened most frequently with young adults. This affected subpopulation is relatively inexperienced as alcohol consumers and relatively susceptible to peer pressure. The advice to recommend not to mix energy drinks and alcohol could therefore be argued to be a prudent safety measure.\(^3\)

### 3.5 Canadian adverse reaction reports

Health Canada’s Marketed Health Products Directorate (MHPD) conducted a search of the Canada Vigilance Adverse Reaction Database\(^4\) from January 01, 1965 to July 20, 2010 and found 61 adverse reactions associated with the consumption of energy drinks.\(^5\) Thirty-two of these reactions are considered “serious”, 15 of which involved the cardiac system (arrhythmia, increased heart rate, palpitations and chest pain). Six of these 15 cardiac events occurred in individuals aged 13–17 years. Based on these reports, analysis of available scientific literature, MHPD detected a safety signal\(^6\) indicating an association between adverse cardiac events and the consumption of energy drinks. Almost all of the reports are in healthy young individuals without concurrent disease or medications. Therefore, alternative causes such as underlying disease or drug interaction were not apparent. Four (4) adverse cardiac reactions were assessed to be of probable causality and 8 were assessed to be of possible causality, using the WHO causality assessment algorithm\(^6\). Three adverse reactions, including the 2 deaths that were associated with energy drinks, could not be assessed because of lack of information. The incidence of cardiac events in the healthy young population is rare and not well characterized in the scientific literature. In addition, the absence of observational and clinical trial data on energy drink use prevents a comparison between reactions associated with these products and the background incidence of cardiac events.

Reported adverse reactions rates are known to be under reported, particularly for NHPs. Both consumers and healthcare practitioners, generally regard NHPs as safe and are usually unaware that adverse reactions can occur with these products and that they can be reported to Health Canada. Even though energy drinks have been regulated as NHPs (therefore health products, subject to adverse reaction reporting) from 2004 to 2011; they may not have been recognized as such, given the way they have been made available (grocery stores next to other beverages, convenience stores, gas stations). Being perceived as beverages (i.e. food) did not support consistent adverse reaction reporting associated with these products.

While these adverse reactions are important to note, they are to be put into perspective, considering the comparatively small number of reported adverse reactions in view of the number of product units sold (around 91 million units in Canada per year, according to 2009 AC Nielsen data). This comparison is an over-simplification. It would be better to compare the number of adverse effects to the number of product, as neither the total number of reactions occurring, nor the number of patients exposed to the health product, is known.

\(^3\) While this manuscript was in preparation, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment published a statement on the interaction of caffeine and alcohol (2012). The Committee concluded that the overall current evidence does not support a harmful interaction between caffeine and alcohol. However, it states that there is substantial uncertainty in this conclusion.

\(^4\) The number of adverse reports in the Canada Vigilance Adverse Reaction Database should not be used as a basis for determining the incidence of a reaction or for estimating risk of a particular

<table>
<thead>
<tr>
<th>Subject</th>
<th>Product</th>
<th>Effects</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female 19 y()</td>
<td>6 drinks made from Red Bull and vodka</td>
<td>Hemorrhagic pulmonary edema</td>
<td>Death; clear cause not established</td>
</tr>
<tr>
<td>Female 31 y()</td>
<td>Drank Red Bull plus vodka</td>
<td>Loss of responsiveness, collapse, ventricular fibrillation</td>
<td>Death; clear cause not established</td>
</tr>
<tr>
<td>Male 20 y()</td>
<td>Drank Red Bull plus vodka</td>
<td>Acute seizures, epilepsy as child but no further attacks since 8 y</td>
<td>Unknown, clear cause not established</td>
</tr>
</tbody>
</table>

Table 6: Swedish case reports investigating energy drinks mixed with alcoholic beverages

---

\(^5\) The first authorized energy drink was Red Bull in 2004.

\(^6\) A signal is reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously (World Health Organization 1991).
consumers of energy drinks, but at this time, Canadian consumption data are not available. Nonetheless, it can be said that the number of adverse reactions reported to Health Canada is relatively small compared to general consumption.

3.6 Summary

Energy drinks, like other beverages containing added sugars, are often associated with a high caloric intake. These drinks are not to be considered “sports drinks” as they contain at least one ingredient that is a stimulant (caffeine). Despite some study results suggesting that energy drink consumption prior to exercise may have some performance benefits, there are concerns, as caffeine may delay the return to a resting heart rate. Limited study results have shown increases in systolic blood pressure and heart rate associated with moderate intakes of energy drinks (2 servings). However, across the various studies, transitory changes in blood pressure did not reach hypersensitive levels with consumption of energy drinks. These effects were deemed to be similar to the effects on blood pressure demonstrated in conjunction with caffeine intake (Riksen et al., 2009).

Surveys also suggest that in social settings (e.g., bars, parties) moderate or high consumption of energy drinks with alcohol is not uncommon, and could lead to risky behaviour since energy drinks may mask the effects of alcohol. There have been adverse reactions associated with the consumption of energy drinks, whether alone or in combination with other physiologically active substances, in Canada. Only 4 of the 15 reported cardiac adverse reactions were assessed as having a probable causality. The significance of these reported adverse reactions is to be discussed in the context of their limited number versus the number of energy drink units consumed and the absence of observational and clinical trial data, which prevents a comparison between reactions associated with these products and the “background” incidence of cardiac events.

There were insufficient toxicological data to characterize the health hazard associated with energy drinks as a single product. As a consequence, the major individual ingredients were assessed for hazard identification and hazard characterization, and this was considered a means to gain insight into the hazard characterization of energy drinks.

4. Assessment of Individual Ingredients of Energy Drinks

4.1 Introduction

In other jurisdictions, the approach used for assessments on energy drinks considered the nutritional and toxicological aspects of the individual ingredients in these products. This approach was taken because the published literature on energy drinks was limited to a few clinical studies and case reports. No relevant preclinical (animal) studies have been conducted. One study did administer an energy drink to mice for up to 13 weeks but the work was not considered to be useful in the safety assessment, since the amount consumed did not constitute a very high dose of the energy drink (cited in EFSA 2009). In contrast, there is a good biological understanding and a broad toxicological database for many of the individual ingredients that constitute energy drinks. Therefore, this approach was also used in this hazard characterization.

Energy drinks can be generally characterised as containing the following ingredients: caffeine, taurine, glucuronolactone, inositol and a variety of B vitamins, including thiamine, niacin, vitamin B6, vitamin B12, pantothenic acid and riboflavin (as mentioned in Table 1). The dietary sources, nutritional aspects and toxicity of these ingredients are reviewed below.

4.2 Caffeine

Caffeine is consumed as a natural constituent of coffee, tea, chocolate and other natural sources, such as guarana and yerba mate. It is also used as a food additive and is present in certain carbonated soft drinks. It is also present in some therapeutic products, such as cold remedies and allergy medicines. In Canada, it is estimated that male and female adults have a respective mean intake of 281 and 230 mg of caffeine per day (Canadian Community Health Survey, 2004). These amounts are about three times the 80 mg of caffeine present in a single 250 ml serving of a typical energy drink.

When a single serving of a caffeinated beverage containing 40-120 mg of caffeine is consumed the main biological effect of caffeine is that it acts as a stimulant and promotes alertness, enhances cognitive performance, relieves fatigue and promotes physical endurance (Doherty and Smith, 2004; Lorist and Tops, 2003; Astorino and Robertson, 2010) A single serving can also cause transient adverse effects, such as insomnia, headaches and nervousness in caffeine-sensitive individuals (Nawrot et al. 2003; Higdon and Frei, 2006).

In an extensive review of the literature, Health Canada assessed more than 300 studies that examined the potential health effects of caffeine (Nawrot et al. 2003). It was concluded that a healthy adult could tolerate a maximum intake of 400 mg of caffeine per day (equivalent to 6 mg/kg bw/day for a 65 kg adult). This amount of caffeine was not associated with adverse effects such as general toxicity, cardiovascular effects, effects on bone status, changes in

---

2 Generally, a serving of tea or cola can contain around 40 mg of caffeine while coffee, depending on the type and brewing method, can contain around 120 mg caffeine and higher.
behaviour, effects on male fertility or increased incidence of cancer development.

Further, the assessment concluded that reproductive-aged women could tolerate a maximum intake of up to 300 mg caffeine per day (equivalent to 4.6 mg/kg bw/day for a 65 kg adult), based on reproductive considerations (spontaneous abortion, retarded fetal growth). Finally children, aged 4 to 12 years, were considered to tolerate a maximum of 45 to 85 mg of caffeine per day (equivalent to 2.5 mg/kg bw/day for a child weighing 18 to 34 kg), based on transient mild behaviour changes.

There were insufficient data to recommend a daily maximum intake of caffeine for adolescents, aged 13 to 18 years. However, the adult recommendation could be considered inappropriate since many adolescents may have a lighter body weight than the average adult. More importantly, adolescents are less developed than adults and their growing bodies may be more susceptible to adverse effects of caffeine. One author has suggested that caffeine may adversely affect the growing adolescent brain (Temple 2009). Alternatively, adolescents may be less habituated to consuming caffeine and therefore may be more susceptible. In any case, there is substantial uncertainty as to whether the adult recommendation should be applied. As a precaution, it would be prudent to recommend that an adolescent have a daily intake of caffeine no greater than the amount calculated from the dose used to determine the recommended maximal intake for children (2.5 mg/kg bw/day) and the individual adolescent body weight (estimated range of adolescent body weights: 40-70 kg). This dose would suggest that adolescents could consume 100 to 175 mg of caffeine daily, depending on the individual body weight of the adolescent.

It should be noted that all of these recommended maximum intakes of caffeine are considered a daily amount that would be the result of cumulative consumption throughout the day. The ingestion of the daily maximum intake in a brief period of time, that is 1-2 hours, may cause adverse reactions, such as insomnia, headache, stomach ache, nervousness, nausea or more serious reactions. For example, studies have shown that a single ingestion of more than 250 mg of caffeine by a healthy adult can also cause an increase in blood pressure (Maughan and Griffin, 2003) while more than 450 mg of caffeine may result in tachycardia (Nawrot et al. 2003).

4.3 Taurine

Taurine is an amino acid that is naturally present in the diet. Specifically, it is found in meat and seafood. Estimates of human daily intake of taurine range from 40 mg to 400 mg (Hayes and Trautwein 1994). These dietary levels of taurine are relatively low compared with the 1000 mg of taurine present in a single serving of a typical energy drink.

Taurine is also synthesized in the liver from the amino acid cysteine, as well as from other sulphur compounds. It has a role in several biological processes, including the formation of bile salt, cell membrane stability, the modulation of calcium flow and neuronal excitability (FSPB 2002). Taurine is considered essential for the normal development of infants and consequently it is a standard ingredient in infant formula, such that newborns ingest about 280 mg daily (equivalent to a dose of 17 mg/kg bw/day).

Taurine is one of the most abundant amino acids in the human body. It is present in relatively high amounts in skeletal and cardiac muscle (Timbrell et al., 1995) and evidence in experimental animals suggests that it is essential to normal muscle maintenance and function (Warskulat et al., 2007). Limited literature has suggested that taurine supplements may have a beneficial effect in persons with congestive heart failure, hypertension, diabetes and skeletal muscle disorders (references cited in Bouknooghe et al., 2006; Shao and Hathcock, 2008).

Human studies suggest that taurine is readily absorbed from consumed food and that plasma level of taurine peak within an hour after ingestion (SCF 2003). This observation is consistent with the findings of a study where rats received taurine as a single oral dose of 300 mg/kg bw. It was observed that the exogenous taurine is quickly absorbed into the body, equilibrates with endogenous pools of taurine and that excess amounts are rapidly eliminated by the kidneys. The study also showed that a 14-day repeat treatment with taurine did not change the fate of the last single oral dose (Sved et al. 2007), which suggests that the body can metabolically handle relatively large amounts of taurine daily.

The acute oral toxicity of taurine is considered relatively low, such that no adverse effects have been observed following a single administration in rats up to 7000 mg/kg bw or in humans up to 150 mg/kg bw (equal to 10,500 mg for a 70 kg adult).

In short-term studies with human subjects, the ingestion of up to 6000 mg per day for 42 days and 1500 mg per day for 90 days showed no evidence of adverse effects (SCF 2003). In a 90-day study in rats, taurine was administered by gavage to groups of animals (20 animals/sex/dose) at doses of 0, 300, 600 or 1000 mg/kg bw/day. No taurine-related changes of standard toxicological parameters were observed. The exception was a dose-related behavioural change (increased activity, self-injury) that was observed in all three treated
generally groups and in both sexes of the test animal (SCF 2003). Subsequently, a second 90-day study was conducted, where taurine was administered by gavage to groups of rats (20 animals/sex/dose) at doses of 0, 600 or 1000 mg/kg bw/day, and another set of rats (20 animals/sex/dose) received taurine in drinking water at doses of 0, 1000 or 1500 mg/kg bw/day. In addition to standard toxicological parameters, a functional observational battery and locomotor activity data were collected at 0, 6 and 12 weeks of the study and conducted in a blind manner (the previous 90-day study’s findings were argued by the study’s author to be biased since they were not blinded). The results indicated that there were no taurine-related deaths, clinical toxicities, body weight changes, food or water consumption differences, or macroscopic changes. The functional observational battery and locomotor activity data did not show any taurine-related effect. There were no adverse behavioural effects observed in this second study. A NOAEL for taurine was established at the level of 1000 mg/kg bw/day, based on the highest dose tested in the first 90-day study, which included a histopathological assessment (EFSA 2009).

A developmental toxicity study in mice showed that when orally administered at a dose of 4000 mg/kg bw/day on days 7 to 14 of gestation, taurine was not a teratogen, that is, it did not cause birth defects (Takahashi et al. 1972).

In the additional studies conducted, taurine has not shown any mutagenic or genotoxic potential in bacterial or mammalian cell in vitro assay systems (S.A. Laidlaw et al. 1989; R. Cossi et al. 1995).

There are no long-term toxicity or carcinogenicity studies conducted to assess the carcinogenic potential of taurine; however, there is no indication that taurine is a carcinogen based on short-term toxicity studies.

In over thirty studies with adult, child and infant subjects, the use of taurine has not demonstrated any safety concerns. Most of these studies involved the ingestion of taurine on a daily basis with doses in the range of 3000 to 6000 mg for periods of up to one month or longer without any apparent adverse health effects (EFSA 2009).

One double-blind study in human volunteers (14 subjects) showed that a combination of caffeine and taurine, at levels present in a typical energy drink, had no effect on short-term memory, as indicated by an abbreviated version of a standard test for short-term memory. However, this combination did induce a decrease in heart rate and an increase in mean arterial blood pressure. This finding is unexpected since caffeine generally stimulates heart rate. Further investigation into the combination of these two substances is warranted (Bichler et al., 2006).

4.4 D-Glucurono-γ-lactone

D-Glucurono-γ-lactone (glucuronolactone) is the γ-lactone of glucuronic acid. It is a normal human metabolite and formed from glucose and glucuronic acid. It seems to be found naturally in only a small number of foods such as wine and plant gums (e.g. guar gum, gum Arabic). An estimate of the mean daily intake is 1.2 mg/day and a high daily intake is suggested to be 2.3 mg/day (SCF 1999). These intake values are very small when compared to the intake of glucuronolactone of 600 mg from the consumption of a single serving of a typical energy drink. It is claimed that glucuronolactone is a quick energy source and may assist in the detoxification of xenobiotics (SCF 1999).

Human and rat studies show that when ingested, glucuronolactone is rapidly absorbed, metabolised and excreted as glucaric acid, xylitol and L-xylulose. These compounds are not considered to be toxicologically significant (ANZFA 2001). In contrast to humans, mice and rats have an additional metabolic pathway that allows them to use glucuronic acid to synthesise vitamin C. Rodents can also use exogenous glucuronolactone to yield glucuronic acid and then generate vitamin C. This additional pathway in the rodent created some uncertainty with respect to the appropriateness of rodents as a model for humans (SCF 1999). However, further examination of the issue has determined that the rodent metabolic pathway is relatively minor in the animal’s handling of glucuronolactone, which suggests that toxicological results from rodents are relevant to the human situation (SCF 2003).

The acute oral toxicity of glucuronolactone is very low, such that in mice the oral LD₅₀ is greater than 20000 mg/kg bw and in rats it is approximately 11000 mg/kg bw. The short-term oral toxicity of glucuronolactone was assessed in a study where groups of rats (20 animals/sex/dose) were administered a single daily gavage dose of 0, 300, 600 or 1000 mg/kg bw, for up to 90 days (SCF 2003). The results showed no treatment-related deaths, no significant difference in body weights, food consumption, hematological or clinical chemistry parameters. Urinalysis showed that males treated with 1000 mg/kg bw group had urine with a lower pH than the control group, and males in the 600 and 1000 mg/kg groups had a lower specific gravity than the control group. Results from histopathological examination showed vacuolisation and inflammatory changes localised to the papilla of the kidney in females such that at doses of 0, 300, 600 and 1000 mg/kg bw/day, the incidences were respectively 11/20, 9/20, 11/20 and 11/20. The incidence of effect was not dose-related but reviewers of the study noted that the severity of this kidney lesion showed an increase with dose. At doses of 0, 300, 600 and 1000 mg/kg bw/day, the incidences of a grade 2 lesion.
(mild severity) were respectively 1/20, 1/20, 5/20 and 8/20. The reviewers concluded that the NOAEL for the study was 300 mg/kg bw/day.

In a second 90-day study in rats, the toxicity of glucuronolactone was assessed with specific focus on the kidneys (SCF 2009). The previous gavage study was repeated with an additional four sets of animals (20 animals/sex/dose) that received glucuronolactone in drinking water; with both routes of administration animals received nominal doses of 0, 300, 600 or 1000 mg/kg bw for 90 days. There were no treatment-related deaths, no effects on clinical observations, food or water consumption, body weights, clinical parameters, organ weights or clinical chemistry parameters related to renal function. Urinalysis demonstrated no treatment-related effects and no differences between the gavage and drinking water groups. Lastly there were no test material-related gross or microscopic findings. This included the kidneys which showed typical amounts of background lesions for this strain of rat. There was no test material-related vacuolisation of the cells lining the collecting tubules of the kidney. This suggests that the kidney lesions observed in the first study were not significant, since the drinking water administered in the second study was more relevant to the human situation. The NOAEL for the study was set at 1000 mg/kg bw/day, the highest dose tested.

Reproductive and developmental toxicity studies for glucuronolactone were not available but were not considered necessary to conduct, as part of the safety evaluation since glucuronolactone in the body hydrolyses to glucuronic acid, which is an endogenous metabolite in humans and present in normal human diets (EFSA 2009).

Glucuronolactone was shown not to be mutagenic in a bacterial reverse mutation system (Kuroda et al. 1986).

One study (Ahrens et al. 1987) assessed the long-term toxicity of glucuronolactone. Groups of 25 male rats were administered orally 0 mg (water), 125 mg of glucuronic acid, 250 mg of glucuronic acid or 125 mg of glucuronolactone per day from the age of about 1 year to death (about 3 years of age). The daily amount of glucuronolactone was equivalent to about 250 mg/kg bw/day. There were no significant differences between the treatment groups with respect to cause of death, body weights at death or autopsy findings. The carcinogenic potential of glucuronolactone was not assessed in this or any other study, however, there is no indication that glucuronolactone is a carcinogen, based on short-term toxicity studies and its role in normal human metabolism.

It has been reported that glucuronolactone has been used at doses of 1 to 3 g/day (1000 to 3000 mg/day) in long-term therapy for carriers of the typhoid organism because of its ability to inhibit viral and bacterial β-glucuronidase. Its use was not observed to cause any adverse effects (Kohler and Schmid 1980).

4.5 Inositol

Myo-inositol (inositol) is a constituent of phosphatidylinositol, a phospholipid, which plays an essential role in growth, metabolism regulation and signal transduction. Inositol is a normal component of human tissue and can be synthesized in some tissues. It is a normal part of food derived from plants in the form of phytate and from animals in the form of free and phosphorylated inositol and as inositol phospholipid. It is estimated that adults ingest about 500 to 1000 mg of inositol daily. This amount is relatively large compared to the 50 mg of inositol present in a single serving of a typical energy drink, as described in Table 1. Potential benefits of inositol may include decreased cholesterol levels and thus a lowered risk of cardiovascular disease (ANZFA 2001).

The toxicity associated with inositol is very low. In mice the oral LD_{50} is reported to be 10000 mg/kg bw. There are no reductive or developmental toxicity studies or genotoxicity studies that assessed inositol. Although inositol was not tested as a carcinogen, several studies assessed its ability to prevent cancer development in mouse models. The results showed that a 3% level in the diet (equivalent to a dose of 6000 mg/kg bw/day) did not increase cancer formation (Estensen and Wattenberg 1993).

In humans, inositol has been used as an experimental therapy for depression, panic disorder, and obsessive compulsive disorder. There is a report of people consuming up to 20,000 mg of inositol daily for 2 weeks (Anrendrup et al. 1989). Another report cites the administration of 18 g of inositol daily for 6 weeks (Koponen et al. 1997). In these reports and several others, no adverse effects were observed (Colondy and Hoffman 1998).

4.6 B Vitamins

Most energy drinks contain added B vitamins including thiamine, riboflavin, niacin, vitamin B6, vitamin B12, and pantothentic acid.

4.6.1 Thiamine (Vitamin B1)

Thiamine is widely found in foods, including meat, legumes, and whole or enriched grain products. The Recommended Dietary Allowance (RDA)\(^8\) for thiamine for adult males is 1.2 mg/day and for adult females, 1.1

\(^8\)The Dietary Reference Intakes (DRIs) are nutrient reference values that replace the 1990 Recommended Nutrient Intakes (RNIs) in Canada and the 1989 Recommended Dietary Allowances in the United States (Health Canada, http://www.hc-sc.gc.ca/fn-an/nutrition/reference/dri_using-util_anref-eng.php). The DRIs include Recommended Dietary Allowance (RDA) and Adequate Intake (AI).
mg/day (IOM 1998). Based on data from the Canadian Community Health Survey (CCHS) (2004), the 95th percentile of dietary intake indicates that adults consume up to 4 mg of thiamine per day. The formulation of a typical energy drink product as described in Table 1 does not contain thiamine; however, other energy drinks may contain up to 5 mg of thiamine per serving.

The US Institute of Medicine (IOM) was not able to set a tolerable upper intake level (UL) for thiamine due to the lack of data on adverse effects (IOM 1998). In addition, the European Commission concluded that while it is not possible to derive a UL for thiamine, current levels of intake from all sources do not represent a health risk for the general population (European Commission 2001). However, the Australia New Zealand Food Authority (ANZFA) set a maximum limit for thiamine of 20 mg/250 ml in formulated caffeinated beverages as a conservative limit that was based on a maximum one-day quantity of 40 mg thiamine (ANZFA 2001).

Orally ingested thiamine has a long history of use as a supplement without reported adverse effects. There are no reports of adverse effects of oral thiamine, even at dosages of several hundred milligrams per day (European Commission 2001). A Canadian evaluation of micronutrient safety classified thiamine as a nutrient with no known adverse effects (Program on Food Safety 1996).

4.6.2 Riboflavin (Vitamin B2)

Riboflavin is found in a wide variety of foods but milk and milk products are thought to contribute the majority of dietary riboflavin. Eggs, meat, and legumes also provide riboflavin in significant quantities (Groff & Gropper 2000). The RDA for riboflavin for adult males is 1.3 mg/day and for adult females, 1.1 mg/day (IOM 1998).

Based on data from CCHS (2004), the 95th percentile of dietary intake indicates that adults consume up to 4.5 mg of riboflavin per day. The typical energy drink product formulation, as described in Table 1, contains 1.65 mg of riboflavin per 250 ml serving while other energy drinks may contain up to 5 mg of riboflavin per serving.

IOM was not able to set a UL for riboflavin due to the lack of data on adverse effects (IOM 1998). In addition, the European Commission concluded that while it is not possible to derive a UL for riboflavin, current levels of intake from all sources do not represent a risk to human health (European Commission 2000). However, ANZFA set a maximum limit for riboflavin of 20 mg/day in formulated caffeinated beverages based on the composition of Red Bull and knowledge of regular consumption of 500 ml per day of this product (ANZFA 2001).

The toxicity of riboflavin is considered to be extremely low due in part to ready excretion of excess amounts (ANZFA 2001). Available sub-chronic data from human studies and pharmacokinetic studies do not show reported effects on oral toxicity of riboflavin. Apart from a few minor gastrointestinal disorders, which are not clearly related to riboflavin intake, it is free from serious side effects (European Commission 2000).

4.6.3 Niacin (Vitamin B3)

Niacin is the term used to describe vitamin B3; nicotinic acid and niacinamide are two different forms of niacin. The best dietary sources of niacin include tuna, beef, other meats, and cereal grains (Groff & Gropper 2000). The RDA for niacin for adult males is 16 mg/day and for adult females, 14 mg/day (IOM 1998). Based on data from CCHS (2004), the 95th percentile of dietary intake indicates that adults consume up to 76.7 mg of niacin per day.

The typical energy drink, as defined in Table 1, contains 18 mg of niacin per 250 ml serving while other energy drinks may contain up to 40 mg of niacin per serving. The niacin in these products is generally present in the form of niacinamide and is most likely added due to its role in energy metabolism.

The Institute of Medicine (IOM) in the United States (1998) set a UL of 35 mg/day for niacin based on the adverse effect of flushing. Flushing is first observed after excess niacin intake and is generally observed at lower doses than are other effects. Flushing that results in patients deciding to change the pattern of niacin intake (i.e., reduce the amount taken at a time or withdraw from treatment) was selected as the most appropriate endpoint on which to base a UL. Although nicotinamide appears not to be associated with flushing effects, a UL for nicotinic acid that is based on flushing is considered protective against potential adverse effects of nicotinamide (IOM 1998).

Other jurisdictions have set ULs for both nicotinic acid and nicotinamide. However, as nicotinamide is typically found in energy drinks, only the ULs relating to this form of niacin are discussed. The European Commission set a UL of 900 mg/day (12.5 mg/kg bw/day) for nicotinamide based on a NOAEL of 25 mg/kg bw/d, derived from studies in subjects with or at risk of diabetes. (European Commission, 2002).

---

9 While this manuscript was in preparation, Health Canada published the document Category Specific Guidance for Temporary Marketing Authorization: Caffeinated Energy Drinks (March 2012). A daily maximum level of 5 mg/day was set for the addition of thiamine to energy drinks.

10 Health Canada’s Category Specific Guidance for Temporary Marketing Authorization: Caffeinated Energy Drinks (March 2012) set a daily maximum level of 27 mg/day for the addition of riboflavin to energy drinks.

11 Flushing refers to a transitory sensation of extreme heat.
The Expert Group on Vitamins and Minerals (Food Standards Agency 2003) set a guidance level of 560 mg/day for nicotinamide as the limited data on the occurrence of nicotinamide toxicity indicates that it is quite low.

ANZFA set a maximum limit for niacin of 40 mg/day (2 cans of 20 mg/250 ml) in formulated caffeinated beverages based on their assessment (ANZFA 2001).12

There is no evidence of adverse effects from the consumption of normal levels of niacin in foods. Adverse effects have been observed with intakes of nicotinamide greater than 3000 mg/day compared with intakes of nicotinic acid of 1500 mg/day (ANZFA 2001). Adverse effects can be observed following high intakes of nicotinic acid, which may be achieved through consumption of pharmacological preparations or dietary supplemental products. Adverse effects associated with the use of nicotinic acid as a drug, especially in doses of 1 g or more per day include:

- Possible injury to the liver, as indicated by elevated serum levels of enzymes of hepatic origin (e.g., transaminases) and by obstruction of normal bile flow from the liver to the small intestine;
- Development of dermatological problems such as itching; and
- Elevation of plasma glucose levels (Groff and Gropper 2000).

4.6.4 Pyridoxine (Vitamin B6)

Excellent sources of vitamin B6 in commonly consumed foods are bananas, navy beans, and walnuts (Groff & Gropper 2000). The RDA for vitamin B6 for adult males is 1.3-1.7 mg/day and for adult females, 1.3-1.5 mg/day (IOM 1998). Based on data from CCHS (2004), the 95th percentile of dietary intake indicates that adults consume up to 4.5 mg of vitamin B6 per day. The typical energy drink, as described in Table 1, contains 2 mg of vitamin B6 per 250 ml serving while other energy drinks may contain up to 10 mg of vitamin B6 per serving.

IOM set a UL for vitamin B6 of 100 mg/day based on a NOAEL of 200 mg/day and applying an uncertainty factor of 2 to account for the limitations in data (IOM 1998). The European Commission set a UL of 25 mg/day for vitamin B6 (European Commission 2000) by taking the average intakes of vitamin B6 (100 mg) from the study by Dalton and Dalton (1987) and applying an uncertainty factor of 4 to account for long-term intake.

ANZFA set a maximum limit for vitamin B6 of 10 mg/day in formulated caffeinated beverages based on history of use, rather than the U.S. UL (ANZFA 2001).

There are no safety concerns in relation to vitamin B6 intake from food sources. However, adverse neurological effects have been detected in humans after very high doses (>500 mg/day, equivalent to approximately 8 mg/kg/day)13. Minor neurological symptoms may be apparent at doses of 100 mg/day or more if consumed for long periods. There are no subgroups that are known to be unusually susceptible to the adverse effects of vitamin B6 (European Commission 2000).

4.6.5 Cobalamin (Vitamin B12)

The only dietary sources of vitamin B12 for humans are from animal products, which have derived their cobalamins from microorganisms. The best sources of cobalamins are meat and meat products, poultry and eggs. The RDA for vitamin B12 for adult males and females is 2.4 mcg/day (micrograms/day) (IOM 1998). Based on data from CCHS (2004), the 95th percentile of dietary intake indicates that adults consume up to 6 mcg of vitamin B12 per day. The typical amount used for energy drinks, as described in Table 1, contains 1 mcg of vitamin B12 per 250 ml serving while other energy drinks may contain up to 20 mcg of vitamin B12 per serving.

IOM was not able to set a UL for vitamin B12 due to the lack of data on adverse effects (IOM 1998). Similarly, the European Commission concluded that it is not possible to derive a UL for vitamin B12 as there are no clearly defined adverse effects produced from this vitamin (European Commission 2000). ANZFA set a maximum limit for vitamin B12 of 10 mcg/day in formulated caffeinated beverages based on history of use (ANZFA 2001).

No adverse effects have been associated with excess vitamin B12 intake from food or supplements in healthy individuals (European Commission 2000).14

4.6.6 Pantothenic acid (Vitamin B5)

Meats (especially liver), egg yolk, legumes, and whole grain cereals are good sources of pantothenic acid. The adequate intake (AI) for pantothenic acid for adult males and females is 5 mg/day (IOM 1998). CCHS (2004) did not have any dietary intake data on pantothenic acid; however, another source indicates that average intakes of adults range between 3-12 mg/d (European Commission 2002). The typical energy drink, as defined in Table 1,15

12 Health Canada’s Category Specific Guidance for Temporary Marketing Authorization: Caffeinated Energy Drinks (March 2012) set a daily maximum level of 450 mg/day for the addition of nicotinamide to energy drinks.

13 At doses less than 500 mg/day, the adverse effects were reversible.

14 Health Canada’s Category Specific Guidance for Temporary Marketing Authorization: Caffeinated Energy Drinks (March 2012) set a daily maximum level of 25 mcg/day for the addition of vitamin B12 to energy drinks.
contains 6 mg of pantothenic acid per 250 ml serving while other energy drinks may contain up to 10 mg of pantothenic acid per serving.

IOM was not able to set a UL for pantothenic acid due to the lack of data on adverse effects (IOM 1998). In addition, the European Commission concluded that while it is not possible to derive a UL for pantothenic acid, current levels of intake from all sources do not represent a health risk for the general population (European Commission 2000). ANZFA set a maximum limit of 10 mg/day for pantothenic acid in formulated caffeineinated beverages based on the composition of the reference product known as Red Bull™ and knowledge of regular consumption of 500 mL per day of this product (ANZFA 2001).

There are no reports of pantothenic acid or panthenol toxicity in humans. Minor gastrointestinal effects such as occasional diarrhea and water retention occurred only at very high intakes (10-20 g/day) (European Commission 2002).15

4.7 Summary

Health hazard data on energy drinks are extremely limited and therefore the hazard assessment was based on individual ingredients. Caffeine was identified as the ingredient in energy drinks having the greatest potential for intakes of health concern. Assuming no additional caffeine from the diet, it was determined that no more than 5 servings per day of a typical energy drink should be consumed by the general adult population. At this level of consumption, the levels of taurine and glucuronolactone in a typical energy drink are not expected to pose a health hazard in the short term. Although there are limited hazard data on energy drinks as formulated in the published literature, actual use of energy drinks has been associated with some adverse reactions. However, due to the absence of long-term safety data on high levels of consumption of taurine and glucuronolactone, the potential interaction of these substances with caffeine, and for most consumers, the known addition of caffeine from other dietary sources, it was concluded that the long-term consumption of 5 servings of energy drinks per day could not be considered to represent no health concern for the general adult population.

Also, the evidence examined suggests that most of the B vitamins and other constituents of a typical energy drink would not pose a health hazard in the short term, but long-term safety data were not available for this level of consumption.

The health hazard assessment concluded that the general adult population could consume 2 servings of a typical energy drink per day with no expected negative health consequences. This conclusion was based on the safety of the non-caffeine ingredients of energy drinks (i.e. taurine, glucuronolactone, inositol and B vitamins) at this level of consumption, and the fact that caffeine from other dietary sources in addition to that in 2 servings of energy drinks would not pose a health risk to the general adult population.

More specifically, the respective mean daily intakes of caffeine from all dietary sources for adult Canadian males and females are 281 and 230 mg. With body weights of 80 and 65 kg, these intakes are equivalent to a daily dose of 3.5 and 3.1 mg/kg bw, respectively (Statistics Canada, Canadian Community Health Survey, 2004). The consumption of two servings of a typical energy drink containing 80 mg of caffeine per serving would result in the addition of 160 mg caffeine to the diet. In males, this would result in a daily dose of 5.5 mg/kg bw and in females, a daily dose of 6.0 mg/kg bw.16 Health Canada’s recommended maximum daily intake of caffeine for adults is 6.5 mg/kg bw or about 400 mg for an adult weighing 65 kg (Nawrot et al., 2003). Given that the addition of two servings of a typical energy drink to the diet would not exceed the recommended maximum daily intake of caffeine, it can be concluded that this level of consumption would not pose an additional health hazard based on the caffeine content of these products.

The consumption of energy drinks by subpopulations, such as children and pregnant and breastfeeding women, is not generally recommended. Based on caffeine content, consumption of such drinks by any group should be limited to their recommended maximum daily intake of caffeine. Excess consumption of energy drinks would be expected to result in health consequences similar to those from excess exposure to caffeine.

5. Surveys and Studies on Energy Drink Consumption Levels and Patterns

5.1 Introduction

A limited number of qualitative and quantitative surveys and studies on energy drink consumption have been carried out in other jurisdictions since the late 1990’s. Data on levels of intake as well as patterns of consumption were collected for various age groups as described in the survey and study summaries below.

15 Health Canada’s Category Specific Guidance for Temporary Marketing Authorization: Caffeinated Energy Drinks (March 2012) set a daily maximum level of 50 mg/day for the addition of pantothenic acid to energy drinks.

16 In males, this would result in a daily dose of 5.5 mg/kg bw (≈ 441 mg of caffeine/ 80 kg bw = 281 mg of caffeine + 160 mg from 2 servings of energy drinks / 80 kg bw) and in females in a daily dose of 6.0 mg/kg bw (≈ 390 mg of caffeine / 65 kg bw = 230 mg of caffeine + 160 mg from 2 servings of energy drinks / 65 kg bw).
5.2 International survey data

Data from the European Commission (EC 1999) indicated that 9% of the population could be described as ‘regular consumers’ of energy drinks, with intake by these consumers likely to be in the order of 500 ml per day (2 x 250 ml cans).²⁷

An Australian survey assessed the incidence of consumption of energy drinks within a two-week period in 1999. However, this study did not record quantities consumed or frequency of consumption. The results from this survey are given in Table 7.

<table>
<thead>
<tr>
<th>Sample</th>
<th>% Consumers</th>
</tr>
</thead>
<tbody>
<tr>
<td>141</td>
<td>27% males aged 8-12 years</td>
</tr>
<tr>
<td></td>
<td>12% females aged 8-12 years</td>
</tr>
<tr>
<td>240</td>
<td>24% males aged 12-18 years</td>
</tr>
<tr>
<td></td>
<td>20% females aged 12-18 years</td>
</tr>
</tbody>
</table>

Table 7. Energy drink consumption in Australia in a Two Week Period during 1999

New Zealand data are available from the Panorama survey of 12 000 respondents aged 10 years and over, conducted by ACNielsen in 1999. Two hundred and sixty-four (264) individuals aged 10 to 14 years were interviewed regarding their consumption of energy drinks, and the resultant data for the 64 (24%) who reported drinking them are presented in Table 8.

<table>
<thead>
<tr>
<th>Consumption rate</th>
<th>No. consumers</th>
<th>Percentage 10-14 year olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least once per day</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Once a week</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>At least once a month</td>
<td>37</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 8. Energy drink consumption in New Zealand by 10 to 14 year olds

In 2001, Red Bull Gmbh conducted a survey of energy drink consumption in Austria. The survey was conducted on 8500 Austrians aged 15 years and over. Forty-two percent of the sample consumed energy drinks at least occasionally and 12% were regular users which were defined as those who consumed at least one energy drink per week. For the surveyed population, mean chronic consumption, chronic consumption at the 95th percentile, and acute consumption at the 90th percentile were approximately 0.47 cans per day, 1.4 cans per day and 2.6 cans per day, respectively (1 can = 250 mL).

A market research survey of 1260 people aged 11-35 years was conducted in Northern Ireland and the Republic of Ireland in 2001. The results of the survey were similar to those obtained in the Austrian survey. In Northern Ireland and Republic of Ireland respectively, 51% percent and 37% of participants reported ‘ever’ consuming energy drinks and 10% and 11% reported consuming energy drinks frequently. Among ‘ever’ consumers, average consumption was 3 (250mL) cans/week and for the 95th percentile consumers, it was 8 cans/week. The most number of cans consumed in a single session among ‘ever’ consumers averaged approximately 3 cans, rising to 8 cans among the highest consumers; the comparable figure for 11-14 year-olds was approximately 2 cans.

In the Ireland survey, energy drink consumption was strongly related to alcohol consumption. Among those who ever consumed energy drinks, 84% of all respondents had consumed the drink with alcohol, while 56% reported consuming the drinks with alcohol regularly.

O’Dea (2003) conducted a study to obtain qualitative data about the type of nutritional supplements and drinks consumed by adolescents in Australia. Semi-structured focus group interviews were conducted among 78 participants aged 11-18 years. Participants reported consuming sport drinks, a number of nutritional supplements and energy drinks. Results of the study indicated that adolescents appear to be incorrectly attributing the ‘creation’ of energy to these supplements when the actual effect is a stimulant effect caused by caffeine, and other stimulants in products such as energy drinks. The author noted that many of the misguided ‘energy creation’ beliefs may be attributed to information provided to consumers in advertising and marketing of these products. According to the author, the adolescents in the study had deliberately sought an ‘energy boost’, and had received it in the form of a stimulant effect from the caffeine-containing supplements and drinks.

Malinauskas et al. (2007) conducted a survey of energy drink consumption patterns among United States college students wherein consumption patterns of 496 randomly surveyed college students were assessed. Fifty one percent of those surveyed reported consuming greater than one energy drink each month in an average month for the semester. The majority of users consumed energy drinks for insufficient sleep (67%), to increase energy (65%), and to drink with alcohol while partying (54%). The majority of users consumed one energy drink in most situations, although consuming three or more with alcohol while partying was a common practice (49%). For the majority of students (73-86%), energy drinks were consumed 1-4 days in a month. Five to 12% of students consumed energy drinks eleven or more days a month.

²⁷ While this manuscript was in preparation, the European Food Safety Authority (EFSA) released a study, Gathering consumption data on specific consumer groups of energy drinks. (Zucconi et al., 2013), detailing the consumption of energy drinks by Europeans.
5.3 Canadian survey data

Based on the most recent Canadian Community Health Survey (CCHS), 2004, a determination of daily exposure levels is not possible due to the limited reporting of energy drink consumption in that survey.

ACNielsen carried out surveys from 2006-2009 to provide national sales and consumer purchase and demographic data for Natural Health Products (NHPs) of interest. While the ACNielsen data offer an indication of the relative size, strength and demand for energy drinks in Canada, the data do not provide sufficient information to determine daily consumption levels of energy drinks by Canadians.

5.4 Summary

The Canadian and international consumption data for energy drinks are considered very limited. In addition, international data that are available from early 2000 may not reflect current energy drink consumption patterns in Canada as these products have become much more pervasive in the Canadian marketplace in recent years.

6. Modelling Exposure Scenario

The health risk assessment of the ingredients in a typical energy drink determined that caffeine has the greatest potential to present a hazard. A single 250 ml serving of a typical energy drink contains 80 mg of caffeine. Although this amount is half the 160 mg of caffeine that a single 250 ml serving of coffee can contain, it is double the 40 mg present in a 355 ml serving of a caffeinated carbonated soft drink (CSD). In any case, the amount of caffeine in a typical energy drink can make a significant contribution to the total dietary caffeine intake.

In order to determine the total dietary intake of caffeine, Health Canada accessed data on the consumption of a wide variety of foods, including foods containing caffeine, by various age groups (Statistics Canada, Canadian Community Health Survey Cycle 2.2., 2004). Using food intake data from this survey, caffeine consumption was determined from all food sources, including coffee, tea and soft drinks. However, intake data specific to energy drinks were not available because there was an insufficient number of respondents who reported energy drink consumption in the 2004 survey. In the absence of intake data specific to energy drinks, the patterns of potential exposure to components of energy drinks can be determined from intake data for a food for which consumption can be assumed to be similar to that of energy drinks. In the following exposure assessment patterns, intake data for caffeinated carbonated soft drinks were used as surrogate data for energy drinks in order to generate possible patterns of an exposure model that includes energy drinks.

<table>
<thead>
<tr>
<th>Age in years (gender)</th>
<th>Median intake for All persons (consumers) of CSDs (mg/kg bw/day)</th>
<th>Median intake for All persons (consumers) of CSDs by volume (mg/kg bw/day)</th>
<th>Median intake for consumers of CSDs (mg/kg bw/day) if consumed</th>
<th>Median intake for consumers of CSDs if EDS substituted for CSDs by volume (mg/kg bw/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3</td>
<td>0.06</td>
<td>0.06</td>
<td>0.98</td>
<td>2.62</td>
</tr>
<tr>
<td>4-5</td>
<td>0.13</td>
<td>0.13</td>
<td>1.18</td>
<td>3.19</td>
</tr>
<tr>
<td>6-8</td>
<td>0.14</td>
<td>0.14</td>
<td>1.35</td>
<td>3.41</td>
</tr>
<tr>
<td>9-11 (male)</td>
<td>0.15</td>
<td>0.15</td>
<td>1.19</td>
<td>2.94</td>
</tr>
<tr>
<td>9-11 (female)</td>
<td>0.14</td>
<td>0.14</td>
<td>0.97</td>
<td>2.46</td>
</tr>
<tr>
<td>12-14 (male)</td>
<td>0.18</td>
<td>0.18</td>
<td>1.05</td>
<td>2.81</td>
</tr>
<tr>
<td>12-14 (female)</td>
<td>0.15</td>
<td>0.15</td>
<td>0.86</td>
<td>2.65</td>
</tr>
<tr>
<td>15-16 (male)</td>
<td>0.37</td>
<td>0.47</td>
<td>1.00</td>
<td>2.57</td>
</tr>
<tr>
<td>15-16 (female)</td>
<td>0.17</td>
<td>0.17</td>
<td>1.08</td>
<td>2.89</td>
</tr>
<tr>
<td>17-19 (male)</td>
<td>0.55</td>
<td>1.26</td>
<td>1.17</td>
<td>2.55</td>
</tr>
<tr>
<td>17-19 (female)</td>
<td>0.62</td>
<td>0.95</td>
<td>0.98</td>
<td>2.75</td>
</tr>
<tr>
<td>20+ (male)</td>
<td>2.23</td>
<td>2.66</td>
<td>2.67</td>
<td>4.19</td>
</tr>
<tr>
<td>20+ (female)</td>
<td>2.21</td>
<td>2.46</td>
<td>2.70</td>
<td>4.07</td>
</tr>
<tr>
<td>Pregnant</td>
<td>0.48</td>
<td>0.53</td>
<td>1.19</td>
<td>2.18</td>
</tr>
</tbody>
</table>

1 Caffeinated carbonated soft drinks were substituted with energy drinks on a volume basis. The caffeine concentration of caffeinated carbonated soft drinks ranged from 73 to 140 ppm and of energy drinks was 320 ppm.

Table 9. Exposure modelling of total dietary caffeine intake for (1) All persons (consumers and non-consumers of caffeinated carbonated soft drinks (CSDs)), (2) All persons, if all CSDs are replaced by typical energy drinks (EDs), (3) Consumers of CSDs, (4) Consumers of CSDs if all CSD consumption is replaced by typical energy drinks.

The absence of consumption modelling for energy drinks is acknowledged. Therefore, the model below would be more a representation of a worst case scenario, as opposed to a description of an expected consumption pattern. Other factors such as taste, cost and the time between servings (binging) may ultimately influence the least conservative and the worst case models for energy drink consumption.
Table 10. Potential Health Risk for (1) All persons (consumers and non-consumers of caffeinated carbonated soft drinks (CSDs), (2) All persons if CSD consumption is replaced by typical energy drinks (EDs)

Table 9 shows exposure to caffeine for all persons and for consumers of caffeinated carbonated soft drinks in various age groups, expressed as mg/kg bw/day. Median caffeine intake from all dietary sources is depicted for consumers of soft drinks containing caffeine at "current market use" levels. Table 9 also shows the median dose of caffeine from all dietary sources for all persons and consumers of caffeinated carbonated soft drinks, if energy drinks were substituted for caffeinated carbonated soft drinks on a volume basis ("substituted by volume"). This is not to be construed as an estimate of exposure in the true population since energy drink consumption is likely to be less on a volumetric scale than caffeinated carbonated soft drinks.

7. Potential Health Risk

The potential health risk posed by the caffeine in energy drinks can be characterized by considering the hazard due to caffeine and the potential exposure to all sources of dietary caffeine, including energy drinks, within an age group or subgroup of the population.

Health Canada used scientific data on the health hazard posed by caffeine to establish recommended maximum daily intake (RMDI) values for children (2.5 mg/kg bw/day), adults (6.0 mg/kg bw/day) and women of reproductive age (4.6 mg/kg bw/day). There are
insufficient data to determine a separate RMDI for adolescents. As a precautionary approach, adolescents can be considered to be as sensitive as children to caffeine, in which case, the RMDI for children can be conservatively applied to adolescents.

The results of exposure modelling indicate that the median total dietary caffeine intake by all consumers (Table 10) and by consumers of caffeinated carbonated soft drinks (Table 11) do not exceed the RMDI in any of the age groups. The situation for median intake remains essentially unchanged for all persons when energy drinks are substituted for caffeinated carbonated soft drinks, that is no age group exceeds its RMDI (Table 10). In contrast, when energy drinks are substituted for caffeinated carbonated soft drinks, the median total dietary caffeine intake by CSD consumers in every population group of children and adolescents meets or exceeds its RMDI, while those of adults and pregnant women do not (Table 11). The results also show that the percentage of consumers in each population group who exceed their RMDI increases dramatically when energy drinks are substituted for caffeinated carbonated soft drinks both for all persons (Table 10) and CSD consumers (Table 11). For example, the greatest increase (from 3% to 57%) in the percentage of CSD consumers who exceed their RMDI is observed in 2- to 3-year-olds (although it is considered that this scenario would be highly unlikely, given that this age group would normally not be given energy drinks to consume) (Table 11).

Using the data from Tables 10 and 11, a comparison for exposure modelling purposes is made in Table 12 of the percentage of all persons and consumers of CSDs who exceed their RMDI for caffeine under two scenarios. The first scenario assumes current market use, while the second assumes that all CSDs were replaced with energy drinks. Since only a portion of any given population group consumes CSDs, the percent of CSD consumers that exceeds the RMDI for that population group can be much greater than the percentage of all persons that exceed the RMDI. For example, among 2- to 3-year-olds, only 6% consume CSDs. Replacing CSDs with energy drinks in this age group brings the percentage of consumer who exceed the RMDI to 57% compared to only 5% of all persons who do so.

The previous section presented a worst case exposure scenario in which the consumption of energy drinks was patterned after that of caffeinated carbonated soft drinks and resulted in more than 50% of children and adolescents, about 30% of adults and 15% of pregnant females exceeding their respective recommended maximum daily intake (RMDI) for caffeine. It is important to assess how realistic this worst case exposure scenario is.

![Table](image)

<table>
<thead>
<tr>
<th>Age in years (gender)</th>
<th>All persons (consumers and non-consumers of CSDs)</th>
<th>Consumers of CSDs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent consuming CSDs¹</td>
<td>% All persons, including CSD consumers, exceeding RMDI</td>
</tr>
<tr>
<td>2-3</td>
<td>6%</td>
<td>2.3</td>
</tr>
<tr>
<td>4-5</td>
<td>7%</td>
<td>3.5</td>
</tr>
<tr>
<td>6-8</td>
<td>12%</td>
<td>3.1</td>
</tr>
<tr>
<td>9-11 (male)</td>
<td>19%</td>
<td>3.8</td>
</tr>
<tr>
<td>9-11 (female)</td>
<td>16%</td>
<td>2.9</td>
</tr>
<tr>
<td>12-14 (male)</td>
<td>29%</td>
<td>3.4</td>
</tr>
<tr>
<td>12-14 (female)</td>
<td>22%</td>
<td>2.4</td>
</tr>
<tr>
<td>15-16 (male)</td>
<td>36%</td>
<td>6.7</td>
</tr>
<tr>
<td>15-16 (female)</td>
<td>25%</td>
<td>10.3</td>
</tr>
<tr>
<td>17-19 (male)</td>
<td>40%</td>
<td>14.6</td>
</tr>
<tr>
<td>17-19 (female)</td>
<td>27%</td>
<td>17.8</td>
</tr>
<tr>
<td>20+ (male)</td>
<td>24%</td>
<td>14.3</td>
</tr>
<tr>
<td>20+ (female)</td>
<td>16%</td>
<td>15.0</td>
</tr>
<tr>
<td>Pregnant</td>
<td>18%</td>
<td>4.7</td>
</tr>
</tbody>
</table>

¹ Data from The Canadian Community Health Survey 11 Cycle 2.2 on Nutrition, Statistics Canada, 2004.
² RMDI is the recommended maximum daily intake. The value for children, adults and pregnant females are 2.5, 6.0 and 4.6 mg/kg bw/day, respectively. Adolescents are conservatively assumed to have a RMDI equal to children.

**Table 12.** A comparison of percent of total dietary caffeine intakes that exceed the caffeine RMDI between (1) consumers of caffeinated carbonated soft drinks (CSDs), with or without energy drink substitution; and (2) “all persons” (consumers and non-consumers of CSDs), with or without energy drink substitution.

It may be reasonably argued that the diet of children (2-11 years old) is monitored and that parents, knowing the potential of adverse effects of excessive caffeine, are unlikely to permit these beverages in their children’s diet. Further, young children (2-8 years old) do not readily have the ability to purchase these products, which are therefore much less likely to be part of their diet. The percentage of children exceeding the RMDI for caffeine from the consumption of energy drinks is therefore very
unlikely to be in the range of 48 to 69% as indicated in Table 11 and 12, which is based on the scenario that energy drinks would replace caffeinated carbonated soft drinks for this age group.

It can also be argued that adults (20 years and older) are capable of monitoring their own caffeine intake and would recognize the acute adverse events associated with excess caffeine intake and then moderate their consumption accordingly. Excess energy drink consumption would result in similar effects as excess coffee consumption (a typical energy drink contains 80 mg of caffeine per 250 ml compared to cup of coffee with 76-180 mg of caffeine per 237 ml). Similarly pregnant women are capable of monitoring their own caffeine intake. For these reasons, it is unlikely that the worst case exposure scenario would apply to these groups within the general population.

Adolescents (12-19 years old) present a more complicated situation. In the absence of adequate safety data to establish a RMDI of caffeine for adolescents, Health Canada followed a precautionary approach and applied the maximum daily dose recommended for children (2.5 mg/kg bw/day) to adolescents. The application of the children’s RMDI to adolescents is likely very conservative. There is no compelling safety reason to suggest that 19-year-old adolescents can only consume 2.5 mg/kg bw/day of caffeine whereas adults (20 years and older) can consume 6 mg/kg bw/day. It is more likely that adolescents could increase their maximum daily intake of caffeine from 2.5 to 6 mg/kg bw/day as they mature without appreciable health risks. Nevertheless, in the absence of data to allow the establishment of a specific RMDI for adolescents, it was considered prudent to set the maximum recommended daily intake of caffeine by adolescents closer to that recommended for children than that recommended for adults.

In the worst case exposure scenario, described in the previous section, the percentage of adolescents who exceeded their RMDI ranged from 47% to 61% of caffeinated carbonated soft drinks consumers, depending on age and gender (Table 12). As suggested in the paragraph above, it is likely most adolescents can tolerate greater amounts of caffeine than their RMDI. As shown in Table 11, the median intakes of caffeine by subgroups of adolescents are less than 3.0 mg/kg bw/day, and therefore only slightly greater than the RMDI of 2.5 mg/kg bw/day.

The intake in excess of the RMDI is similar to what an adolescent (12-19 years old) who drank a cup of strong coffee (180 mg of caffeine/237 ml) would be exposed to. For example, the caffeine intake from a single cup of coffee would result in a dose of 3.14 and 2.8 mg/kg bw/day for an adolescent female (about 57 kg bw) and male (about 64 kg bw) respectively. Since these caffeine intakes are very close to the conservative recommended maximum daily intake of 2.5 mg/kg bw/day, they would be unlikely to pose a health hazard.

One or two servings of a typical energy drink (80 mg of caffeine/serving) would therefore be unlikely to pose an acute health hazard based on caffeine content. However, it is known that some very young (12-14 year) adolescent males (about 56 kg bw) and females (about 52 kg bw) will consume a large volume of carbonated soft drink in a single episode, about 760 ml and 519 ml, respectively (Canadian Community Health Survey 2.2, 2004). This is further corroborated by the prevalence of larger volumes of energy drink cans, in comparison to other soft drink cans (710 ml cans versus 355 ml cans). If this pattern of consumption is applied to energy drinks, then there could be very young adolescents who drink two containers of a 250 ml energy drink, or one container of a 473 ml energy drink, and young adolescent males who could drink a full 710 ml energy drink in a single episode. Given the amount of caffeine in typical and some non-typical energy drinks, these adolescents could have excessive caffeine intake, especially when consuming large format energy drinks.

Given that marketing for energy drinks tend to target some subsets of adolescents, that they are capable of purchasing these products (unlike children), and are less familiar with adverse effects of excessive caffeine (unlike adults), it is reasonable to conclude that the caffeine present in energy drinks could pose a health risk for adolescents.

7.1 Summary

Based on the hazard characterisation of each of the ingredients in a typical energy drink, as defined in Table 1, it was determined that the exposure assessment should focus on caffeine. However, limited information is available to date on actual consumption of energy drink products in Canada. Research is being considered to fill consumption data gaps and to provide further insights into whether the label instructions related to consumption advice on energy drinks are effective (i.e. are followed).

In the absence of critical consumption data, exposure modelling was conducted by substituting, on a volume basis, energy drinks for caffeinated carbonated soft drinks, for which there is intake data. This approach conservatively assumes that energy drinks are consumed in a manner similar to that for caffeinated carbonated soft drinks, and that energy drink label instructions are not followed. It also assumes that a volume basis of substitution is a more likely than a serving basis of substitution.

The results of the exposure assessment that considered a worst case scenario determined that of the consumers
who replace caffeinated carbonated soft drinks with energy drinks, more than 50% of children and adolescents, about 30% of adults and 15% of pregnant females would exceed their respective recommended maximum daily intakes of caffeine and therefore may be susceptible to the adverse effects associated with excess caffeine consumption. Consumers of caffeinated carbonated soft drinks represent roughly 8% of young children (1-8 years old), 22% of older children (9-14 years old), 32% of adolescents, 20% of the adult population and 13% of pregnant females.

The amount of caffeine in energy drinks would pose a health concern if consumed by children (2-11 years old). However, parents are likely to be aware that excessive caffeine can be harmful and would keep energy drinks out of their children’s diets. Energy drinks are therefore not a health concern for this age group.

Adults (20 years and older) and pregnant women are capable of monitoring their own caffeine intake. They would recognize acute adverse events associated with excess intake and moderate their consumption accordingly.

The situation of adolescents (12-18 years old) is more complex. Because of inadequate safety data currently available, Health Canada conservatively applied the RMDI for children (2.5 mg/kg bw/day) to this age group using a worst case scenario (patterning energy drink use on caffeinated carbonated soft drink consumption) to determine potential health risk. The percentage of adolescents who exceeded their RMDI ranged from 47% to 61% of caffeinated carbonated soft drinks consumers. But, at less than 3.0 mg/kg bw/day, median intakes were only slightly greater than the RMDI and likely to be tolerated. The caffeine content of one or two servings of a typical energy drink (80 mg caffeine/serving) would be unlikely to pose an acute health hazard.

However, some young adolescents (12-14 year) consume large volumes of caffeinated carbonated soft drinks (up to 760 ml) in a single episode. Applying this pattern of consumption to energy drinks could result in excessive caffeine intake by a proportion of young adolescents.

In conclusion, the modelling exposure scenario as applied to children and adults is unlikely to represent a realistic health risk. However, for adolescents the likelihood of a health risk is greater, which may reflect the conservative assumptions made about this subpopulation.

8. Overall Summary and Conclusions

The purpose of this document is to provide a health risk assessment of energy drink products when they are consumed as foods in Canada.

In this document a typical energy drink formulation was defined by its ingredients and serving size, where a single can serving of 250 ml contains 80 mg of caffeine, 1000 mg of taurine, 600 mg of glucuronolactone and several B vitamins.

The literature on health effects of energy drinks is limited to less than a dozen studies, each with a small number of subjects (N< 50 subjects/study). These studies demonstrate that consuming 1-2 servings of a typical energy drink formulation will temporarily increase alertness and attentiveness, as well as temporarily increase blood pressure and heart rate, in a manner similar to other caffeinated beverages.

Studies that examine energy drink use prior to exercise showed that it may enhance physical endurance. In contrast, the consumption of an energy drink after exercise may result in a delay of the return to a resting heart rate.

Studies also suggest that the combined consumption of energy drinks and alcohol may pose a health risk. The potential consequence is that a person consuming an energy drink with alcohol may become intoxicated more quickly and may be less aware of their physical impairment, which may lead to risky behaviour, such as excessive alcohol consumption. At present, clear evidence supporting this suggestion is lacking but it merits further investigation.

It was concluded that the published information available on energy drinks was insufficient to characterize the hazard that this product as a whole may pose. For this reason, a review of each of the major ingredients contained in a typical energy drink was conducted, i.e., the potential health effects of caffeine, taurine, glucuronolactone, inositol and the B vitamins were assessed. In doing so, and in contrast with previously published information, the adverse reaction data related to each of the ingredients in the formulation that were presented in this document attempted to reflect to the extent possible “the real world use” of the products as formulated, in various user populations.

With respect to caffeine, an earlier review conducted by Health Canada’s Food Directorate concluded that a healthy adult could tolerate a maximum intake of 400 mg caffeine per day, which could be equivalent to 5 servings of a typical energy drink per day. This amount of caffeine was not associated with adverse effects such as general toxicity, cardiovascular effects, effects on bone status, changes in behaviour, effects on male fertility or increased incidence of cancer development. Further, the study concluded that reproductive-aged women could tolerate a maximum intake of 300 mg caffeine per day, based on reproductive considerations. It was also concluded that children, aged 4
to 12 years, could tolerate a maximum of 45 to 85 mg of caffeine per day, based on transient mild behaviour changes. Concerning adolescents, aged 13 to 18 years, there were insufficient data to determine a daily maximum intake of caffeine. However, the adult recommended maximum daily intake was considered inappropriate since many adolescents have a lower body weight than the average adult, but more importantly the growing adolescent was considered to be more sensitive to caffeine. Due to this uncertainty, it was more recently concluded that, as a precaution, adolescents should consume a dose no greater than that for children (2.5 mg/kg bw/day). At this dose, adolescents could consume 100 to 175 mg of caffeine daily, depending on the individual body weight (estimated to range from 40–70 kg). Lighter-weight adolescents (40 kg, bw) would meet the suggested maximum intake of caffeine with slightly more than a single serving of a typical energy drink, whereas heavier teens (70 kg) could consume 2 servings per day in the absence of other sources of dietary caffeine.

Taurine, glucuronolactone and inositol were considered to be normal constituents of the diet and easily handled by ordinary metabolic processes. While generally considered to be of very low or low toxicity, there was some uncertainty about the safety of the levels of these substances in a typical energy drink, since the levels of some greatly exceeded the amount consumed through a normal diet. For example, a high dietary intake of taurine is estimated to be 400 mg/adult/day, whereas the intake from 5 servings of a typical energy drink would provide 5000 mg/adult/day. Glucuronolactone has an estimated daily dietary intake of 2.3 mg/adult/day, compared to the 3000 mg/adult/day intake from 5 servings of a typical energy drink. Based on a review of 90-day feeding studies in laboratory animals, knowledge of the metabolism of these two substances and information about their experimental therapeutic use, it was concluded that no hazard was demonstrated at the level of 5 servings per day in the short-term; however, long-term use in the diet posed an uncertainty. Further, there was uncertainty about the possible interaction of taurine with caffeine on the nervous system.

Concerning the B vitamins, it was concluded that the consumption of 5 servings of a typical energy drink per day would not exceed the tolerable upper limit of most of these vitamins and they would be unlikely to pose a health risk in the short term. There is uncertainty in the safety of life-long consumption at this level since the rest of the diet would also contribute to the total intake of these substances, which could lead to excessive intake and potential adverse health effects. Niacin, which can be present as nicotinamide or nicotinic acid, was a unique case. When present as nicotinic acid, the amount in 1 serving of a typical energy drink (20 mg) was not greater than the tolerable upper limit for niacin (35 mg/adult/day) and is unlikely to pose a health concern. However, the consumption of 2 servings per day could potentially result in flushing. In contrast, when niacin is present as nicotinamide, there are no health concerns at the consumption level of 5 servings per day, since some jurisdictions have tolerable upper limits of nicotinamide up to 900 mg/adult/day.

Based on caffeine content alone, it could be suggested that a healthy adult could consume up to 5 servings of a typical energy drink per day in the absence of any other dietary source of caffeine. A typical energy drink contains 80 mg of caffeine and 5 servings would be equal to 400 mg, the maximum daily intake of caffeine for an adult. Five servings per day would be equal to 5000 mg of taurine, 3000 mg of glucuronolactone and 300 mg of inositol. Considered individually, these ingredients consumed at these levels would not be expected to cause adverse effects in the short-term, based on animal studies. However, long-term studies on taurine and glucuronolactone have not been conducted. In the absence of such studies, a better understanding of the human metabolism and physiological impact of these high doses would be required to increase confidence in the conclusion that those levels would not likely cause adverse effects.

In conclusion, consuming 5 servings per day for an adult, where a serving is represented by 250 ml of the typical energy drink product formulation, cannot be recommended based on possible exposure to other dietary sources of caffeine, uncertainties about the long-term effects of some ingredients, the potential interaction between ingredients and the impact of chronic consumption of high levels of certain B vitamins (see table in Appendix I).

Despite the uncertainties about possible interactions between some of the ingredients, 2 servings of a typical energy drink per day would not be expected to pose a health risk for the general adult population. This conclusion was based on the safety of the non-caffeine ingredients of energy drinks at this level of consumption and the fact that caffeine from other dietary sources in addition to that in 2 servings of energy drinks would not exceed Health Canada’s recommended maximum daily intake of caffeine for the general adult population. The consumption of energy drinks by other sub-groups would need to be limited based on the respective recommended maximum daily intake of caffeine. However, it can be noted that current caffeinated energy drink product labels do not recommend consumption by children, pregnant or breastfeeding women, or caffeine-sensitive persons.

This assessment would also apply to other energy drinks, described in this report, which contain major ingredients at levels greater than those in the typical formulation of.
energy drink products. These products may be consumed by adults at a level equivalent to 2 servings of a typical energy drink. However, there is uncertainty about the safety of consuming greater amounts of these other formulations. It was also noted that several products contain other bioactive ingredients such as nutrients (e.g. folic acid) or other herbal or natural extracts (e.g. ginkgo biloba). These other formulations would need to be reviewed on a case-by-case basis.

Exposure data to energy drinks in Canada are limited, in that consumption information is not reliable based on Canadian survey data. In the absence of estimates of real consumption data, the health risk posed by energy drinks due to the caffeine content was estimated by modelling exposure using caffeinated soft drink consumption data as a surrogate for energy drink consumption.

In a worst case modelling exposure scenario, energy drinks were substituted for caffeinated carbonated soft drinks on a volume basis and the energy drink caffeine concentration set to 320 ppm for modelling purposes. The results showed that of the consumers who drink caffeinated carbonated soft drinks, more than 50% of the children and adolescents would be above the recommended maximum daily caffeine intake if all carbonated soft drinks were replaced by a typical energy drink. Further, slightly less than 30% of male and female adults and about 15% of pregnant females would exceed the Health Canada’s recommended maximum daily intake for caffeine. Consumers of caffeinated carbonated soft drinks are however only a subset of the population and represent roughly 8% of young children (1-8 years old), 22% of older children (9-14 years old), 32% of adolescents, 20% of the adult population and 13% of pregnant females.

Although the intake modeling showed that children (2-11 years old) would exceed Health Canada’s recommended levels for caffeine, the corresponding health concern is limited, given, that children are less likely to obtain these products on their own and that parents are expected to keep energy drinks out of their children’s diets. It was also concluded that adults (20 years and older) and pregnant women are capable of monitoring their own caffeine intake. They would also be more likely to recognize acute adverse events associated with excess intake and moderate their consumption accordingly.

Applying these hypothetical consumption patterns of energy drinks to adolescents has identified a potential to exceed the recommended caffeine intake by a significant proportion of young adolescents. These scenarios could not be excluded, given that energy drinks tend to be marketed to adolescents who (unlike children) are capable of accessing these products, including the larger volumes, but may be less likely than adults to adhere to consumption recommendations. Attention may therefore be warranted as to the levels of caffeine present in energy drink products made available for sale in a large volume container (710 ml), which are becoming prevalent and likely to be consumed by this subset of the population.

Specific risk management measure to address potentially high caffeine levels in larger volume energy drink products would help mitigate some risks associated with exceeding Health Canada’s maximum recommended caffeine intake in one consumption setting.

Health Canada’s proposed risk management approach for energy drinks announced in October 2011 (http://hc-sc.gc.ca/ahc-asc/media/pr-cp/_2011/2011-132-eng.php) and updated in 2012 (http://hc-sc.gc.ca/in-an/legislation/guide-ld/guidance-caf-drink-boiss-tma-amt-eng.php) helps address a number of these concerns, through setting caffeine concentration limits, total caffeine amount limits, and maximum levels of vitamins, minerals and other formulation constituents. Caffeine and other nutrition labelling requirements were also imposed. These measures contribute to mitigating some of the risks related to the consumption / overconsumption of energy drink products in those areas where intervention is possible by a federal food regulator within the Canadian food regulatory system.

Given the behavioural aspects related to some of the potential risks - co-consumption with alcohol, over exposure to caffeine due to excessive and uninformed consumption – it is acknowledged that other areas of intervention, such as responsible marketing and advertising, as well as education and awareness, would be required in a concerted fashion.

More research and surveillance would be required to ascertain the effectiveness of the various facets of the proposed risk management approach.

Various data gaps have been noted in this assessment, in particular:

- Data that support the hazard characterisation in particular as they pertain to possible interaction of the effects of the various active ingredients in energy drink product formulation (e.g. the combined effect of taurine and caffeine at high consumption levels)

- Data that support an improved characterisation of energy drink consumption patterns in Canada by various population subsets (e.g. older children and adolescents).

Efforts are currently underway to initiate research activities enabling some aspects of the data collection. This assessment will therefore be updated upon availability of new Canadian data and taking into account any new findings on the safety of energy drinks domestically and internationally.
### 9. Appendix 1

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Required daily intake</th>
<th>Daily dietary intake</th>
<th>Amount per serving</th>
<th>Amount per 2 servings</th>
<th>Amount per 5 servings</th>
<th>Upper tolerable limit (UL)/Maximum recommended intake (MRI)/Maximum Limit (ML)</th>
<th>Other safety data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Not applicable</td>
<td>160 mg</td>
<td>80 mg</td>
<td>160 mg</td>
<td>400 mg</td>
<td>400 mg – MRI</td>
<td></td>
</tr>
<tr>
<td>Taurine</td>
<td>Not applicable</td>
<td>40 – 400 mg</td>
<td>1000 mg</td>
<td>2000 mg</td>
<td>5000 mg</td>
<td>Not established</td>
<td>6000 mg/day = NOAEL in 42 day human study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1000 mg/kg bw/day = NOAEL in 90-day rat study</td>
</tr>
<tr>
<td>Glucuronolactone</td>
<td>Not applicable</td>
<td>1.2-2.4 mg</td>
<td>600 mg</td>
<td>1200 mg</td>
<td>3000 mg</td>
<td>Not established</td>
<td>3000 mg/day = NOAEL as experimental therapy in human</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1000 mg/kg bw/day = NOAEL in 90-day rat study</td>
</tr>
<tr>
<td>Inositol</td>
<td>Not applicable</td>
<td>500-1000 mg</td>
<td>50 mg</td>
<td>100 mg</td>
<td>250 mg</td>
<td>Not established</td>
<td>18000 mg/day = NOAEL in 42 day therapy in human</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6000 mg/kg bw/day = NOAEL in 24 week mouse study</td>
</tr>
<tr>
<td>Thiamine</td>
<td>1.1-1.2 mg</td>
<td>4 mg</td>
<td>5 mg</td>
<td>10 mg</td>
<td>25 mg</td>
<td>40 mg – ML</td>
<td>Little danger of thiamine toxicity associated with oral intake of large amounts (500 mg daily for 1 month)</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>1.1-1.3 mg</td>
<td>4.5 mg</td>
<td>1.65 mg</td>
<td>3.30 mg</td>
<td>8.25 mg</td>
<td>20 mg – UL</td>
<td>50 mg/kg bw/day = NOAEL in 13 week feeding study in rats. No published data with toxic effects in humans.</td>
</tr>
<tr>
<td>Niacin (nicotinamide)</td>
<td>16 mg</td>
<td>77 mg</td>
<td>18 mg</td>
<td>36 mg</td>
<td>90 mg</td>
<td>900 mg – UL</td>
<td>3-9 g/day nicotinamide for several days resulted in nausea in single subject and hepatitis in another subject.</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>1.3-1.7 mg</td>
<td>0.9-4.5 mg</td>
<td>2 mg</td>
<td>4 mg</td>
<td>10 mg</td>
<td>Not established</td>
<td>100 -500 mg causes neurological symptoms</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>2.4 mcg</td>
<td>2-6 mcg</td>
<td>1 mcg</td>
<td>2 mcg</td>
<td>5 mcg</td>
<td>20 mcg – ML</td>
<td>Oral and parenteral supplementation with dosages between 1-5 mg every 2 weeks or month have been given for up to at least 5 years, in patients with compromised vitamin B12 absorption, without any identified adverse effects.</td>
</tr>
<tr>
<td>Pantothenic Acid</td>
<td>5 mg</td>
<td>3-12 mg</td>
<td>6 mg</td>
<td>12 mg</td>
<td>30 mg</td>
<td>20 mg – ML</td>
<td>10000 mg causes gastrointestinal effects in humans</td>
</tr>
</tbody>
</table>

Notes: MLs for thiamine, vitamin B12 and pantothenic acid were specifically assigned to energy drinks by NHPD. These figures are not ULs or MLs for these B vitamins for the total diet. UL for niacin was determined by the European Community.

**Table A1.** Summary of Safety Assessments of the Ingredients in a Typical Energy Drink
10. References


(http://www.nap.edu/catalog.php?record_id=6015)


[69] SCF (Scientific Committee on Food Authority), 2003. Opinion of the Scientific Committee on Food on Additional information on “energy” drinks (expressed on 5 March 2003). European Commission, Brussels.


