

STRAIGHT TOX

Caffeine: The People's Drug

By Dwain Fuller, D-FTCB, TC-NRCC

It is inhumane, in my opinion, to force people who have a genuine medical need for coffee to wait in line behind people who apparently view it as some kind of recreational activity. I bet this kind of thing does not happen to heroin addicts. I bet that when serious heroin addicts go to purchase their heroin, they do not tolerate waiting in line while some dilettante in front of them orders a hazelnut smack-a-cino with cinnamon sprinkles. ~Dave Barry

Love it or hate it, it is here to stay. We are for all practical purposes addicted to our caffeine. With many of us it is coffee, perhaps the more refined among us drink tea, the younger set crave their energy drinks, the runners their caffeine-infused jelly beans, perhaps those less in denial, or just more pragmatic, go straight for the NoDoz®.

Caffeine is ubiquitous in our society. So much so, that several years ago I was involved in a research project where I was tasked with determining serum levels of caffeine. I remember two technical issues presented themselves: First, no deuterated standard was yet available and since caffeine is rather unique in its extraction chemistry compared to other drugs, it was difficult to find a suitable internal standard. I overcame this first obstacle by synthesizing a butylated caffeine analog from theobromine. However, as difficult as overcoming that obstacle was, the second was perhaps even more daunting; finding a caffeine-free human serum in which to prepare standards and controls was essentially impossible.

So what brings me to write about caffeine now? After covering synthetic cannabinoids, bath salts, and polonium 210, in the last several issues, caffeine is just not all that sexy. However, a news item caught my eye: **“Hagerstown Teen’s Death Prompts Lawsuit Against Monster Energy.”** The suit involves the family of a 14-year-old girl with an underlying heart condition, who drank two 24-ounce Monster® drinks in 24 hours and



subsequently died. The drinks each purportedly contain 240 milligrams of caffeine. The article somewhat breathlessly exclaims that this is approximately seven times the amount of caffeine found in a 12-ounce Coca Cola®. However, according to McCusker, et al. each 24-oz Monster Energy would contain less than one 16-ounce (Grande) Starbucks® regular coffee, which they found to contain 259 mg of caffeine. Thus this level of caffeine intake is not out of the ordinary for many of us on a daily basis. I will leave the opinions in this case to the retained experts and the decision to the jury, but it does raise the question, “Just how safe or unsafe is caffeine?”

Caffeine is structurally similar to adenosine, an inhibitory neurotransmitter, and, not surprisingly, is an adenosine receptor antagonist. It has been argued that it is the accumulation of adenosine throughout the day that causes increasing sleepiness. Caffeine has also been shown to be an acetylcholinesterase inhibitor. The combined effect of these two actions is that caffeine causes an increase of acetylcholine, epinephrine, dopamine, serotonin, norepinephrine, and glutamate, resulting in overall stimulation and wakefulness in humans.



Caffeine has a bioavailability of 99%, a C_{max} of approximately 1-1.5 hours, a volume of distribution of 0.4 – 0.6 L/kg, and a half-life of approximately 5 hours. However, the half-life is influenced by gender, 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 hours, but gradually approaches that of an adult by 6 months of age. The half-life in females using oral contraceptives is approximately twice that observed for ovulatory females. During pregnancy, the metabolic half-life increases steadily from 4 hours during the first trimester to 18 hours during the third trimester. Cigarette smoking is associated with about a twofold increase in the rate at which caffeine is eliminated. Caffeine is metabolized in the liver by CYP1A2 enzymes to paraxanthine, theophylline and theobromine, with only a small percent being excreted unchanged in the urine. Caffeine has a pK_a of 0.8, thus it is significantly protonated only at very low pH's.

Many studies have been performed to determine if moderate doses of caffeine produce adverse effects in the human body. Most of the studies are consistent in determining that caffeine in moderate doses of less than or equal to 400-450 mg/day (the doses studied) have minimal to no effect on cardiovascular health, bone and calcium balance, mutagenicity, genotoxicity, and carcinogenicity. Studies suggest that caffeine intake of

greater than 300 mg/day may adversely affect female fertility, fetal development, and increase the risk of miscarriage. Thus it may be prudent for women who are pregnant or are planning on becoming pregnant to limit their caffeine consumption to less than 300 mg/day.

How about the beneficial effects of caffeine? Beside the raving reviews from those of us who are long time devotees of the “drug”, there is growing scientific support for a number of benefits of caffeine. Caffeine’s alerting effects are well-documented, and that alone is enough for most of us. However, while more study is needed, several potential positive effects are now being reported: lower risk of cardiovascular disease and diabetes, minimization of age-related cognitive decline, reduced risk of cancer development, and the reduced risk of Parkinson’s disease. Of note to most of us interested in drugs and driving, a recent study by Mets, et al. reports a positive effect of small doses (80 mg) of caffeine on driving performance during monotonous driving conditions.

Regardless of the relative safety of caffeine, the Drug Abuse Warning Network (DAWN) reported approximately a tenfold increase in emergency room visits due to the use of caffeine-containing energy drinks between 2005 and 2009. Additionally, there are documented cases of caffeine overdose resulting in death. The acute lethal dose of caffeine has been estimated to be 10 grams, however deaths have occurred from oral use of as little as 5.3 grams, and survival has been reported after the ingestion of as much as 24 grams. A recent news article reports that a British man died after ingesting two spoonfuls of pure caffeine powder and washed it down with an energy drink. The coroner reported that this would be equivalent to ingesting 70 cans of Red Bull®. Baselt reports 14 cases of death due to oral ingestion of caffeine ranging from 5.3 – 50 grams with postmortem whole blood concentrations ranging from 79 – 344 mg/L (mean = 183 mg/L). Kerrigan and Lindsey report a case with a postmortem femoral blood concentration of 567 mg/L. There appears to be significant overlap in toxic and fatal concentrations, with perhaps the deciding factor being medical intervention. Dietrich and Mortensen report the survival of a child who ingested 2 – 3 grams of caffeine resulting in a peak plasma concentration of 385 mg/L.

Caffeine Content of Selected Products

Product	Serving Size	Caffeine (mg)
Coffee, generic brewed	8 oz.	133 (range 102-200)
Coffee, generic decaffeinated	8 oz.	5 (range 3-12)
Starbucks Brewed Coffee (Grande)	16 oz.	320
Einstein Bros., regular coffee	16 oz.	300
Dunkin’ Donuts, regular coffee	16 oz.	206
Starbucks Vanilla Latte (Grande)	16 oz.	150
Starbucks Espresso, doppio	2 oz.	150
Starbucks Espresso, decaffeinated	1 oz.	4
Tea, brewed	8 oz.	53 (range 40-120)

Starbucks Tazo Chai Tea Latte (Grande)	16 oz.	100
Nestea	12 oz.	26
Snapple, Just Plain Unsweetened	16 oz.	18
Arizona Iced Tea, green	16 oz.	15
Jolt Cola	12 oz.	72
Coca Cola Classic	12 oz.	35
Mountain Dew, regular or diet	12 oz.	54
Diet Coke	12 oz.	47
Dr. Pepper	12 oz.	42
Diet Dr. Pepper	12 oz.	44
Pepsi	12 oz.	38
Diet Pepsi	12 oz.	36
5-Hour Energy	1.93 oz.	207
Monster Energy	16 oz.	160
Full Throttle	16 oz.	144
Red Bull	8.3 oz.	80
Amp	16 oz.	143
Hershey's Special Dark Chocolate Bar	1.45 oz.	31
Hershey's Chocolate Bar	1.55 oz.	9
NoDoz (Maximum Strength)	1 tablet	200
Vivarin	1 tablet	200
Excedrin (Extra Strength)	2 tablets	130
Anacin (Maximum Strength)	2 tablets	64

(From Center for Science in the Public Interest)

While, as DAWN points out, "energy drink consumption by itself can result in negative health events serious enough to require emergency care", a purely pharmacological (one not exacerbated by underlying pathology or medical condition) fatal caffeine overdose is quite rare due to the extremely large amounts of caffeine required. Typically a fatal event requires the ingestion of relatively pure caffeine in the form of powder or tablets. While I can't claim to have performed an exhaustive literature search, I am unaware of any well-established and documented fatal overdose attributable to caffeine alone, where the source of the caffeine was coffee, tea, a beverage, or food substance sold as a consumer product.

As I am happy to report, it appears that the safety profile of caffeine is quite good, with it being nearly impossible for a healthy individual to incur a fatal overdose from ingesting coffee, tea, sodas, chocolate, or even energy drinks, due to the large quantities that would be required. However, adverse effects are still possible with high intake and when combined with other drugs or alcohol.

I leave you with this disclaimer about the conditions under which this article was produced:

"As soon as coffee is in your stomach...there is a general commotion. Ideas begin to move...memories charge in at full gallop...metaphors arise...the artillery of logic rushes up...on imagination's orders, sharpshooters sight and fire; forms and shapes and characters rear up; the paper is covered with ink." ~ Honore de Balzac (1799-1859)

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