Regulatory Toxicology and Pharmacology 74 (2016) 81–92

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Neurobehavioral hazard identification and characterization for caffeine

Duncan Turnbull*, Joseph V. Rodricks, Gregory F. Mariano

Ramboll Environ US Corporation, 4350 North Fairfax Drive, Arlington, VA 22203, USA

ARTICLE INFO

Article history:
Received 19 October 2015
Received in revised form
1 December 2015
Accepted 9 December 2015
Available online 15 December 2015

Keywords:
Caffeine
Sleep disturbance
Anxiety
Risk-taking

ABSTRACT

This report evaluates the scientific literature on caffeine with respect to potential central nervous system (CNS) effects, specifically effects on sleep, anxiety, and aggression/risk-taking. Caffeine has been the subject of more scientific safety studies than any other food ingredient. It is important, therefore, to evaluate new studies in the context of this large existing body of knowledge. The safety of caffeine can best be described in a narrative form, and is not usefully expressed in terms of a "bright line" numerical value like an "acceptable daily intake" (ADI). Caffeine intake has been associated with a range of reversible physiological effects, in a few studies at levels of less than 100 mg in sensitive individuals. It is also clear that many people can tolerate much greater levels – perhaps up to 600–800 mg/day or more – without experiencing such effects. The reasons for this type of variability in response are described in this report. Based on all the available evidence, there is no reason to believe that experiencing such effects from caffeine intake has any significant or lasting effect on health. The point at which caffeine intake may cause harm to the CNS is not readily identifiable, in part because data on the effects of daily intakes greater than 600 mg is limited. Effects of caffeine on risk-taking and aggressive behavior in young people have received considerable publicity, yet are the most difficult to study because of ethical concerns and limitations in the ability to design appropriate studies. At present, the weight of available evidence does not support these concerns, yet this should not preclude ongoing careful monitoring of the scientific literature.

1. Introduction

Caffeine (1,3,7-trimethylxanthine) is a central nervous system (CNS) stimulant alkaloid that is found in various plants such as coffee and cocoa beans, tea leaves, guarana berries, and the kola nut. It has been described as the most frequently ingested pharmacologically active food substance in the world (IOM, 2014). As noted in the proceedings of Institute of Medicine (2014) workshop on caffeine, "years of scientific research have shown that moderate consumption by healthy adults of products containing naturally occurring caffeine is not associated with adverse health effects." And a similar conclusion was reached by the European Food Safety Authority (EFSA, 2015).

This report evaluates the scientific literature on caffeine relative to possible CNS effects, especially effects on: sleep/sleep disturbance; anxiety; and aggression/risk-taking behavior, particularly at levels of intake higher than the "moderate" levels identified by IOM and EFSA. A fourth area of investigation relates to possible caffeine tolerance, and withdrawal.

While there is substantial scientific evidence of beneficial effects of caffeine, including evidence that chronic caffeine consumption may have neuroprotective effects and is associated with better cognitive performance later in life, e.g., inverse correlations with the risk of developing Parkinson's and possibly Alzheimer's disease (Costa et al., 2010; Prediger, 2010; Santos et al., 2010; Yang et al., 2010), these effects are not addressed in this report.

2. Approach and methodology

We identified relevant, high-quality studies in humans from authoritative secondary sources e.g., European Food Safety Authority (EFSA) 2015; Nawrot et al., 2003; Institute of Medicine (IOM) 2001; Oak Ridge National Laboratory (ORNL) 2011, as well as through an updated literature search for more recent relevant studies using the PubMed bibliographic database.

* Corresponding author.
E-mail address: dturnbull@ramboll.com (D. Turnbull).

http://dx.doi.org/10.1016/j.yrtph.2015.12.002

The updated literature search included studies published in 2014 through March, 2015 and included the following terms:

(((caffeine[Title/Abstract] OR coffee[Title/Abstract])) OR (caffeine[MeSH Terms]) AND ((adult* OR adolescent* OR child* OR female OR male OR woman OR women OR man OR men) NOT (baby OR babies OR infant*)[Title/Abstract])) OR ((adult* OR adolescent* OR child* OR female OR male) NOT (baby OR babies OR infant*) [MeSH Terms]) AND (("adverse effect*" OR "health effect*" OR *toxic* OR behaviour OR behavior OR attention OR psych* OR sleep OR anxiety OR aggression OR "risk taking" [MeSH Terms])) OR (adverse effect*" OR "health effect*" OR *toxic* OR behaviour OR behavior OR attention OR psych* OR sleep OR anxiety OR aggression OR "risk taker*" OR "risk taking" [Title/Abstract])

((((adult*[Title/Abstract] OR adolescent*[Title/Abstract] OR child*[Title/Abstract] OR female[Title/Abstract] OR male[Title/Abstract] OR woman[Title/Abstract] OR women[Title/Abstract] OR man[Title/Abstract] OR men) NOT (baby[Title/Abstract] OR babies [Title/Abstract] OR infant*))[Title/Abstract])) AND (adverse effect*"[Title/Abstract] OR "health effect*"[Title/Abstract] OR *toxic*[Title/Abstract] OR behaviour[Title/Abstract] OR behavior [Title/Abstract] OR attention[Title/Abstract] OR psych*[Title/Abstract] OR sleep[Title/Abstract] OR anxiety[Title/Abstract] OR aggression[Title/Abstract] OR "risk taker*"[Title/Abstract] OR "risk taking"[Title/Abstract]).

Studies for evaluation were identified on the basis of their citation by authoritative bodies, appropriate design, adequate study sample size, and appropriate control of potential confounders. Because of the inability of observational studies to identify causation, particular emphasis was placed on experimental or interventional studies in which exposures could be well controlled, and responses to those exposures carefully measured or monitored. High-quality observational studies were also considered to assist in evaluation of potential effects of prolonged exposure, since experimental studies were all of relatively short duration.

Following the identification of potentially relevant studies, we reviewed them in more detail to determine which studies examined the potential relationship between caffeine dose and the relevant CNS effects. Following the identification of these studies, we extracted data to assess how the occurrence of these CNS effects varies in incidence/severity with caffeine dose and duration of exposure among the subpopulations of interest. Almost 200 studies were included in the database of pertinent studies (see Supplemental Materials).

2.1. Glossary

Adolescent: adolescence is generally thought to be the period from puberty to adulthood. Although there is a range for the onset of puberty, we have used the range of 11–13 to 19 as a "working range."

Anxiety: an emotion characterized by feelings of tension and worried thoughts, generally assessed (in the studies evaluated here) by standardized questionnaire (e.g., profile of mood states – POMS), or using a visual analog scale.

Dependence: A state in which an organism functions normally only in the presence of a drug, commonly manifest in the context of withdrawal when physiological reactions occur that can range from mild and short-term (e.g., caffeine withdrawal headache) to life-threatening (alcoholic delirium tremens).

Habitual: Daily (or near-daily) consumption.

Naïve: Never or rare consumption.

Sleep disturbance: Significant change in normal sleep pattern/sleep parameters, particularly increased sleep latency (delay in falling asleep after retiring), decreased sleep duration, increased nocturnal awakening, or alterations in sleep stages.

2.2. Background

In a recent survey of caffeine consumption in the US population, results showed that 84% of the US population consumes at least one caffeinated beverage per day, and the mean daily caffeine intake from all beverages was 165 ± 1 mg for all ages combined (Mitchell et al., 2014). Similar levels of intake have been reported for adults by Fulgoni et al. (2015), based on data from the National Health and Nutrition Examination Survey (NHANES) for 2001 through 2010. At such levels of intake, caffeine can produce a number of physiological effects related to the central nervous system (CNS). Caffeine "bioactivity" has been known for well over a century and is widely (if not completely) understood by consumers. In these respects, caffeine is unique among common constituents of foods.

The physiological activities of caffeine are known to vary among individuals. An important contributor to variability relates to the well-known fact that individuals develop tolerance to certain physiological effects of caffeine. Thus, with repeated and regular intake, the level of intake needed to induce caffeine's physiological effects increases. Individuals who are not habitual users do not develop tolerance, and thus, when they do ingest caffeine, they typically experience the compound's physiological effects at lower levels of intake than do habitual users.

In addition, several genetic polymorphisms have been identified that affect the metabolism of caffeine and its interaction with receptors that mediate its CNS effects.

For all of these reasons, it is not possible to identify a single level of intake for the general population that would otherwise induce caffeine's physiological CNS effects. Moreover, the ordinary physiological CNS effects of caffeine are not known to cause any harm to health. The physiological CNS effects that result are transient and reversible and have no known long-term health consequences – they are not adverse (in fact, some clearly have benefits, such as increased alertness and mental acuity).

Also, some people can consume greater levels than others. For example, in the recent study of US caffeine consumption (Mitchell et al., 2014), the 90th percentile consumption level among adults aged 50–64 was 467.4 mg/day. To establish so-called "safe" levels of intake based on non-adverse physiological effects of the most sensitive individuals – even when those effects are not in the true sense adverse – would disproportionately deprive the very large numbers of people who can consume higher levels of caffeine without a corresponding increase in public health benefit. Such an approach would be analogous to setting limits on milk intake based on tolerable levels of lactose intake by lactose-intolerant individuals.

Truly unsafe levels of intake, as noted previously, will likely not occur until very high levels, e.g., >100 mg/kg bw/day (more than 6000 mg/person/day; Boyd et al., 1965) – associated with *bona fide* adverse effects resulting in acute caffeine toxicity – are achieved. Individuals consuming caffeine at varying levels of intake may experience non-adverse physiological CNS effects that are simultaneously transient and reversible, and most may adjust intakes if they perceive those effects as undesirable, i.e., they will self-titrate (Soroko et al., 1996; Rétey et al., 2007). Even if they do not adjust intake, those physiological CNS effects will not result in harm to their health. As a result, a single "bright line" between safe and unsafe intakes (as in a traditional "acceptable daily intake" – ADI) is unnecessary to avoid adverse health effects.

2.3. Definition of an adverse health effect

When evaluating the effects of caffeine consumption, it is important to differentiate between a physiological CNS effect and an adverse effect. Caffeine can cause subtle, reversible physiological

effects at relatively low doses, such as increased alertness, that are clearly not adverse. Indeed, many individuals appreciate this beneficial effect of caffeine, which can be demonstrated experimentally at dose levels at or below 100 mg. Of course, exaggeration of this effect due to excessive intake can interfere with normal sleep, or produce other undesirable effects, but which are not necessarily adverse from a health outcome perspective.

Adverse effects have been defined as follows:

> "the causation, promotion, facilitation and/or exacerbation of a structural and/or functional abnormality, with the implication that the abnormality produced has the potential of lowering the quality of life, contributing to a disabling illness, or leading to a premature death" (Sherwin, 1983)

and:

> "Adverse effects are considered to be functional impairments or pathological lesions that may affect the performance of the whole organism or that reduce an organism's ability to cope with an additional challenge. One of the major problems encountered with this concept is the reporting of 'observed effect levels' as contrasted to 'observed adverse effect levels.' The terms 'adverse' and 'not adverse' are at times satisfactorily defined, but because more subtle responses continue to be identified due to increasingly sophisticated testing protocols, scientific judgment is needed regarding the exact definition of adversity" (USEPA, 1994).

Effects that are transient, reversible, and do not have long-term detrimental health consequences should not be considered adverse.

It is important to note that this report does not address "Adverse Event Reports" (AERs) associated with consumption of caffeine-containing products. The FDA's Adverse Event Reporting System (FAERS) is a database containing information on adverse event and medication error reports submitted to FDA. In medical terminology, an adverse event arises in the context of clinical trials of pharmaceuticals, and is used to refer to any occurrence during a clinical trial that would be considered adverse whether or not it has anything to do with the treatment being studied. For example, if someone in such a trial was shot during a bank robbery, or hit by an out-of-control truck, that would be classified as an adverse event. AERs may also result from emergency room visits where the medical staff collects all sorts of information that may have some bearing on the incident, though it is generally not possible to determine cause-and-effect relationships. More specifically, it is not possible to determine whether an adverse event report has any causal relationship to a particular exposure (such as consumption of a caffeinated beverage).

2.4. Possible variability in responses to caffeine

There are a variety of factors that may influence an individual's response to caffeine. Drawing broad conclusions about the effects of various intake levels of caffeine for the general population is thus challenging. An individual's response may be influenced by pharmacokinetic factors that affect how rapidly caffeine is absorbed, distributed, metabolized and eliminated (ADME) after being ingested, or by pharmacodynamics factors that influence the interaction between caffeine and its site(s) of action and the effects of that interaction on the body. Some of this variability results from genetic polymorphisms – naturally occurring mutations in genes involved in the metabolism of caffeine (particularly differences in activity of cytochrome P450 1A2 which plays a major role in caffeine metabolism) or in adenosine receptors. Adenosine receptors are a class of purinergic G protein-coupled cell membrane receptors with adenosine as endogenous ligand that are found throughout the body, including the central nervous system (Fredholm et al., 2001). Caffeine is a competitive antagonist of adenosine at the A1 and A2A receptors (ADORA1 and ADORA2A), and this antagonistic effect is believed to be responsible for many of the physiological effects of caffeine (Nehlig 2007; Baraldi et al., 2008). As discussed below, carriers of certain genetic polymorphisms of CYP1A2 and ADORA2A show differential effects of caffeine exposure, though no differential effects have been reported to date for ADORA1 polymorphisms (Rogers et al., 2010; Thorn et al., 2012).

2.5. ADME differences

Differences in ADME (including delayed gastric emptying which can delay absorption), and metabolism (particularly differences in activity of cytochrome P450 1A2 (CYP1A2)), lead to differences in plasma caffeine levels and time course from the same dose (Arnaud, 1993). For example, Birkett and Miners (1991) reported an 8-fold range in steady-state plasma caffeine concentration in six adult volunteers given 150 mg caffeine every 8 h for 6 days.

The vast majority of ingested caffeine is metabolized, largely in the liver, prior to excretion. The metabolic pathways are relatively complex (Arnaud, 1993, 2011; see Fig. 1). At least 16 metabolites at levels of 0.1% or more of administered caffeine dose may be found in the urine of humans. In humans, the principal initial step is 3-demethylation of caffeine (1,3,7-trimethylxanthine) to paraxanthine (1,7-dimethylxanthine); 72–80% of ingested caffeine follows this route, and paraxanthine plasma levels exceed those of caffeine within 8–10 h of ingestion (Bonati et al., 1982; Tang-Liu et al., 1983). 3-Demethylation in humans appears to be catalyzed specifically by cytochrome P450 1A2 (CYP1A2) (Butler et al., 1989).

There is substantial inter-individual variability of CYP1A2 activity that influences the disposition of a substrate such as caffeine and these variations may be due to factors such as gender, race, genetic polymorphisms, exposure to enzyme inducers, age, exercise, and pregnancy (Dorne et al., 2001; Vistisen et al., 1990). In particular, at least 6 different polymorphic forms of CYP1A2 (CYP1A2*1A, CYP1A2*1D, CYP1A2*1F, CYP1A2*1L, CYP1A2*1V and CYP1A2*1W) have been reported (Arnaud, 2011). Four other CYP isoforms (CYP1A1, CYP2E1, CYP3A, and CYP2D6-Met) also have minor roles in the metabolism of caffeine (Arnaud, 2011).

Caffeine half-lives of 2.5–4.5 h were measured in humans at dose levels of 4 mg/kg body weight (bw) (Arnaud, 1993). The ADME profile appears to be age-dependent in rats but not so in humans (Feely et al., 1987; Latini et al., 1980; Blanchard and Sawers, 1983), except in the very young; half-lives of 50–103, 14.4, and 2.6 h have been observed in premature/newborn, 3–5 month and 5–6 month infants, respectively (Gorodischer and Karplus, 1982; Parsons and Neims, 1981; Aldridge et al., 1979; Paire et al., 1988; Pearlman et al., 1989). Thus, caffeine clearance reaches or exceeds adult levels by 5–6 months of age (Aranda et al., 1979; von Borstel, 1983).

Longer half-lives have been observed in breast-fed than in formula-fed infants (Le Guennec and Billon, 1987), and in women in the last trimester of pregnancy compared with controls (Knutti et al., 1981, 1982). This effect contributes to the recommendation to limit caffeine intake during pregnancy.

Caffeine half-lives have also been found to increase up to 50–160 h in humans with severe liver diseases (Statland et al., 1976; Statland and Demas, 1980; Desmond et al., 1980; Scott et al., 1988).

2.6. Physiological differences

The other major source of variability in response to caffeine is differences in the receptors in the brain involved in expression of caffeine's physiological effects related to the central nervous system (Yang et al., 2010).

In producing its physiological effects, the main receptor targets for caffeine action on the CNS are adenosine A_1 and A_{2A} receptors (ADORA1 and ADORA2A), where it acts competitively to adenosine. Adenosine acts as an inhibitory neurotransmitter via A_1 receptors, which are located on both inhibitory and excitatory neurons throughout the CNS. A_1 receptors mediate the release of other neurotransmitters, such as glutamate, acetylcholine, and dopamine. Stimulatory effects of caffeine are thought to be due to the reversal of the tonic inhibition of dopamine. Adenosine has inhibitory properties on A_{2A} receptors, which are located mainly in the striatum, together with dopamine D_2 receptors. Adenosine's action inhibits D_2 transmission. These inhibitions are antagonized by caffeine, which is thought to be responsible for its stimulatory effects on the psychomotor system (as reviewed in Yang et al., 2010). Several single nucleotide polymorphisms (SNPs) in the *ADORA2A* gene (though not in the *ADORA1* gene) have been associated with variations in sensitivity to caffeine's physiological CNS effects (Alsene et al., 2003; Childs et al., 2008; Rogers et al. 2010; Yang et al., 2010; Thorn et al., 2012).

Another gene polymorphism that seems to affect caffeine sensitivity is in the gene for adenosine deaminase, an enzyme responsible for the clearance of extracellular adenosine (Mazzotti et al., 2011). These authors found that individuals carrying the A allele (*ADA* G22A; rs73598374) who consumed caffeine in the day prior to polysomnography demonstrated higher sleep efficiency and REM sleep percentage compared to non-carriers of that allele, after adjustment for potential confounders. No effect was observed in the absence of caffeine.

2.7. Age considerations

Concerns have been raised in some fora that children may be more sensitive than adults to the effects of caffeine and that, therefore, children's exposure to caffeine should be restricted. However, other than young infants, whose metabolic abilities may not be completely developed until they are about six months old, there is no evidence that children are inherently any more sensitive than adults when their body weight is taken into consideration.

3. Results

3.1. Overview of literature

Numerous studies in humans were identified as potentially relevant. These included 122 experimental studies (mostly randomized controlled trials) and 41 observational epidemiology studies. Of these, 96 experimental, and 24 observational studies were included in the final analysis because they included information on caffeine dose and examined the relevant CNS effects. This included 7 experimental and 12 observational studies in children. In some of the observational studies, dose information related to caffeine intake was presented in values that were too imprecise to draw firm conclusions about specific dose effects. For example, some studies only report group means by endpoint, or present a very general intake level (e.g., ≥1 drink per day).

All of the studies identified and retrieved are summarized in the associated Excel spreadsheet database. These spreadsheet entries go into greater detail on all aspects of the studies and should be consulted for specific information.

The wealth of studies on these aspects of caffeine's CNS effects is rare for a food ingredient, and permits a thorough evaluation of caffeine's possible CNS effects. It must be recognized, however that even this extensive database has limitations. While the extensive human experimental studies are of great benefit, most involve only a single or a few repeated administrations, thus limiting to some extent our understanding of the effects of long-term caffeine consumption, though many of these limitations are balanced by the substantial number of observational epidemiology studies that address long-term consumption.

One additional limitation is that relatively few studies examined high doses (i.e., >600 mg/day) never mind very high doses (i.e., >1200 mg/day), making it difficult to identify clear adverse effect levels. The latter provides the scientific basis to establish a minimum threshold of 600 mg/day as an appropriate safety default absent data supporting higher levels.

In the following sections, each of the primary CNS endpoints of interest, sleep, anxiety, and aggression/risk-taking are addressed. These three primary sections are followed by a brief discussion of the phenomena of tolerance and withdrawal.

3.2. Sleep/sleep disturbance

The advent of the 24-h society has contributed to prevalence of sleep disturbance among the population (Rajaratnam and Arendt 2001). While extreme forms of sleep disturbance may rise to the level of a clinical disease, and could represent an "adverse health effect," the effects of caffeine on sleep are typically mild – a slight delay in falling asleep and slightly decreased sleep duration. They are also entirely reversible when caffeine intake is reduced, and are such a well-known effect of caffeine that individuals typically modify their caffeine consumption if they find that it interferes with sleep (Soroko et al., 1996; Rétey et al., 2007). Also, as discussed above, individuals vary in their sensitivity to these effects of caffeine.

A total of 54 studies (42 experimental, 12 observational) examined the potential relationship between caffeine intake and various sleep endpoints. These endpoints were studied primarily among adult participants, with 8 observational studies of children.

Few studies examined the effects of low levels of caffeine (<100 mg) on sleep (1 experimental study and 1 observational study). "Virtually no effect on sleep patterns" was observed among 18 young adult males (who normally drank 1–4 cups of coffee per day) when they consumed instant coffee containing 1.1 mg/kg body weight (bw) caffeine 30 min before bedtime for 13 days (Karacan et al., 1976). Interestingly, boys, but not girls, aged 10–12 years who drank less than one energy drink or cola per day (caffeine dose not otherwise identified) reported significantly more sleeping problems compared to children with no caffeine intake in the observational study (Kristjansson et al., 2014), as described more fully further below.

Doses as low as 100 mg within 2 h of bedtime can have subtle effects on sleep parameters (Landolt et al., 1995a), with clearer, dose-related effects reported at higher doses (ingestion of 300–400 mg caffeine increased sleep latency and decreased amounts of slow-wave sleep and total sleep time). Some studies suggest a lack of effect on sleep when given 6- or 16-h before sleep (Snel, 1993; Bonnet and Arand, 1992; Pontifex et al., 2010), though Landolt et al. (1995b) report a residual effect on some sleep parameters measured during the night (11 pm–7 am) following consumption of 200 mg caffeine at 7:10 am, compared to nights when a placebo was consumed in the morning in 9 adult male subjects. In six studies where caffeine intake was greater than 600 mg caffeine per day, the authors reported reductions in total sleep time and sleep quality, and increased sleep latency and

number of awakenings (Bonnet and Arand, 1992, 1996; LaJambe et al., 2005; Sanchez-Ortuno et al., 2005; Shilo et al., 2002; Youngstedt et al., 2000). In one study where 12 young adult male participants received 1200 mg/day caffeine (divided in three doses) for seven days, a variety of sleep parameters were negatively affected including total sleep time, sleep latency, wake time, sleep efficiency, number of wakes, and arousal index (Bonnet and Arand, 1992). Significant effects observed on day one of the trial disappeared for many of these parameters after the first day of caffeine intake (total sleep time, sleep latency, wake time, sleep efficiency, number of wakes), suggesting evidence of acclimation and a reversal of effects even while ingesting a high dose of caffeine for several more days.

Among the 8 observational studies of children, the dose information reported in five of the studies was too imprecise to draw any firm conclusions about specific dose-effects (Calamaro et al., 2009; Lee et al., 1999; Ludden and Wolfson, 2010; Mindell et al., 2009; Pollak and Bright, 2003). Kristjansson et al. (2014), as noted above, reported that in a study involving 11,267 children, boys, but not girls, aged 10–12 years who drank less than one energy drink or cola per day (caffeine intake not otherwise identified) reported significantly more sleeping problems compared to children with no caffeine intake. Both boys and girls who reported drinking more than one cola or energy drink per day reported significantly more sleeping problems than children with no caffeine intake. The results suggested a stronger relationship between energy drinks and sleeping problems than for cola drinks among boys, though the cross-sectional design of the study precludes any inference of causation. Also, sleeping problems were reported significantly more commonly by girls than by boys, though consumption of energy drinks was twice as common among boys than among girls, further limiting the conclusions that can be drawn from this study. Orbeta et al. (2006) reported that in a study involving 15,686 children in grades 6–10 – i.e., eleven to sixteen years of age – those who drank 1 coffee or soda per day (caffeine intake not otherwise identified) were significantly more likely to report difficulty sleeping compared to children with very low intake (<1/week). Children with low intake (1/week) were not significantly more likely to report difficulty sleeping.

Santos et al. (2012) reported that in a study involving 885 infants, maternal consumption of ≥300 mg/day caffeine during the 1st, 2nd, or 3rd trimester, during the whole pregnancy, or at 3 months postpartum was not significantly associated with >3 nighttime wakings per night among infants at 3 months of age.

Eleven experimental studies included testing of salivary caffeine levels in participants to ensure compliance as well as to examine the relationship between an objective measure of caffeine levels that might otherwise differ among individuals due to differences in caffeine metabolism in the liver, and potential sleep-related effects (Carrier et al., 2007, 2009; Drapeau et al., 2006; Hale et al., 1995; James, 1998; Lader et al., 1996; Landolt et al., 1995a, 1995b; Paterson et al., 2007; Rétey et al., 2007; Sicard et al., 1996). Previous studies have shown a close association between saliva and plasma levels of caffeine (Landolt et al., 1995a). As salivary caffeine is correlated with plasma caffeine in a ratio of 0.74 ± 0.08, circulating caffeine can be estimated by salivary caffeine assays (Sicard et al., 1996). Following intakes ranging from 100 to 600 mg, caffeine intake was associated with increased sleep latency, reduced sleep efficiency, decreased sleep duration, and altered sleep EEG parameters (reduced slow wave activity; alterations in spectral power in different brain wave bands) among participants. Although these objective sleep parameters were altered following caffeine intake, participants may not have actually experienced any subjective effects on their sleep quality as reported in Landolt et al. (1995a).

Two studies examined the relationship between adenosine deaminase (Mazzotti et al., 2011) and adenosine receptor (Rétey et al., 2007) polymorphisms and caffeine intake on sleep parameters. In a study of 958 adults, Mazzotti et al. (2011) reported that carriers of an adenosine deaminase polymorphism (A allele carriers) had lower sleep latency, higher sleep efficiency, a higher REM sleep percentage, and fewer minutes awake following caffeine consumption of at least 1 cup of a caffeine-containing beverage (caffeine intake not otherwise identified) the day prior compared to non-A allele carriers. These differences were not observed among those who did not consume caffeine.

Rétey et al. (2007) reported that caffeine consumption (400 mg) was significantly associated with subjectively reduced sleep quality (sleep latency longer than 20 min, and frequent awakenings) in 12 caffeine-sensitive, but not in 10 caffeine-insensitive respondents (based on questionnaire). A higher prevalence of the ADORA2A c.1083C/C polymorphism was observed in the caffeine sensitive group, while fewer sleep disturbances as well as less of an effect on sleep EEG activity was observed among carriers of the ADORA2A c.1083T allele.

3.3. Anxiety

Anxiety is defined as an emotion characterized by feelings of tension and worried thoughts. In the studies evaluated here, it is generally assessed by standardized questionnaires (e.g., profile of mood states – POMS), or using a visual analog scale It is, therefore, subjective, and does not constitute an adverse effect, except in the case of medically diagnosed anxiety disorder.

A total of 57 studies (47 experimental, 10 observational) examined the potential relationship between caffeine intake and various endpoints related to anxiety (e.g., anxiety test scales, tension, self-reported jitteriness). These endpoints were studied primarily among adult participants, with 4 observational and 3 experimental studies of children. Drawing conclusions from observational studies on these endpoints is problematic given that only associations can be evaluated, not cause-and-effect. Moreover, it is difficult to distinguish between outcomes associated with caffeine intake *per se* versus those relative to both an individual's personality and preference for caffeinated products or higher caffeine intake. Some individuals may in fact be consuming caffeine to self-medicate for anxiety symptoms resulting from personal disinhibition (Trapp et al., 2014). For example, the authors of two studies reported higher mean anxiety scores among those who were “dependent” on caffeine compared to those who were non-dependent, even though the dependent groups consumed less caffeine (Bernstein et al., 2002; Oberstar et al., 2002). In these studies, identification of “dependence” or personal disinhibition was based on DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Ed.) substance dependence criteria – meeting at least three of four criteria (reported tolerance, endorsement of withdrawal symptoms when stopping or cutting down consumption, persistent desire or unsuccessful efforts to control use, and reported drinking caffeine despite physical or psychological problems associated with caffeine use).

Another important point to consider is the potential effect of abstaining from caffeine during an experimental study that could itself lead to an increase in anxiety symptoms due to withdrawal symptoms experienced by regular or high caffeine users (Goldstein et al., 1969; Rapoport et al., 1984; Rogers et al., 2003, 2010).

Among 8 experimental (Botella and Parra, 2003; Childs and de Wit, 2006; Childs et al., 2008; Huppe and Janke, 2001; Lieberman et al., 1987; Miller et al., 1998; Peacock et al., 2014; Richardson et al., 1995) and 4 observational (Eaton and McLeod, 1984; Gold et al., 2007; Oberstar et al., 2002; Trapp et al., 2014) studies that

examined the potential relationship between low levels of caffeine intake (<100 mg) and anxiety, the authors of one study reported an effect associated with caffeine intake that was potentially related to anxiety (Richardson et al., 1995). Richardson et al. (1995) reported a significant excess in jitteriness – an undesirable but not adverse effect – among adults (49 "moderate" caffeine consumers and 18 non-consumers) that received 70 mg of caffeine compared to those that received none. However, the authors noted that the increase in jitteriness paralleled a decrease in hand-steadiness and could have been related to an increase in muscle tremors rather than an increase in anxiety. In a survey of 1062 young adults, Trapp et al. (2014) reported a significant association between energy drink intake ≥250 mL/day (≥80 mg caffeine/day) and anxiety symptoms in young adult males (mean age 20 ± 3), but not in females, while anxiety symptoms were not significantly increased among participants of either sex who drank < 250 mL/day. The results of the remaining studies indicated no effect – undesirable or otherwise – of low levels of caffeine on measures of anxiety. Two of the studies however did report lower anxiety scores following caffeine intakes ranging from 50 to 100 mg (Hüppe and Janke, 2001; Peacock et al., 2014).

Most of the studies involved an examination of the effects of caffeine at doses ranging from 150 to about 500 mg. Increases in self-reported symptoms of anxiety were reported in some individuals at dose levels as low as 150 mg (Alsene et al., 2003; Botella and Parra, 2003; Childs et al., 2008; Goldstein et al., 1969). Among the studies that examined the effects of caffeine at doses ranging from 150 to 500 mg/day results were generally mixed. Among studies where participants received caffeine doses as high as 400–500 mg or more, some reported no significant changes in anxiety symptoms (Azcona et al., 1995; Bonnet and Arand, 2003; Hughes and Boland, 1992), while several others did report a significant association (Attwood et al., 2007; Bruce et al., 1992; Brunye et al., 2010; Childs et al., 2008; Kaplan et al., 1997; Nardi et al., 2007a,b; Nardi et al., 2008; Rapoport et al., 1981, 1984). Among three studies that examined the effects of caffeine at doses ranging from 700 to 1200 mg in individuals whose normal caffeine consumption was low (<100 mg/day) to moderate (<400 mg/day), all reported a significant increase in anxiety symptoms following caffeine consumption (Bonnet and Arand, 2003; Motl and Dishman, 2004; Youngstedt et al., 1998).

Ten experimental studies included testing of salivary caffeine levels in participants (Bernstein et al., 1994; Brice and Smith, 2002; Bruce et al., 1992; Childs and de Wit, 2006; James and Gregg, 2004; Lader et al., 1996; Rapoport et al., 1981, 1984; Rogers et al., 2010; Smith et al., 2006). Among these studies, caffeine doses ranging from 200 to 500 mg (roughly equivalent to 3–7 mg/kg bw) were statistically significantly associated with an increase in measures of anxiety. Two studies reported no effect on anxiety following ingestion of 2.5–5.25 mg/kg bw/day caffeine when administered in a single dose, or recurrently for a period of 4 weeks (Bernstein et al., 1994; James and Gregg, 2004). In addition, one study (Lieberman et al., 1987) measured plasma caffeine 3-h after caffeine ingestion, and noted a clear relationship between caffeine dose (32–256 mg) and plasma concentration (about 0.8–4.5 μg/mL), but no effect on anxiety or other mood state.

Certain factors appeared to modify the purported effects caffeine had on various measures of anxiety. These included caffeine habit, genetics, and pre-existing anxiety disorders. Anxiety effects following caffeine intake were generally increased among naïve caffeine users (low or no regular consumption) compared to regular or high consumers of caffeine (Goldstein et al., 1969; Rapoport et al., 1984; Rogers et al., 2010; Smith et al., 2006). Individuals with pre-existing anxiety disorders (e.g., general anxiety disorder, panic disorder) were at greater risk of experiencing anxiety symptoms following a single caffeine dose of 250 mg (Bruce et al., 1992), but no increase in panic attacks at that dose level (Matthew and Wilson, 1990) while an increase in panic attacks was reported in panic disorder patients, but not in normal individuals or individuals with other mental disorders given a single caffeine dose of 480 mg (Nardi et al., 2007a,b; 2008).

Susceptibility to anxiogenic effects of caffeine is influenced by adenosine receptor gene polymorphisms. Childs et al. (2008) found carriers of two ADORA2A polymorphisms displayed increased symptoms of anxiety after 150 mg caffeine, while non-carriers showed effects only at 450 mg. Rogers et al. (2010) reported a similar relation between ADORA2A polymorphism and anxiogenic effect of caffeine, but also reported that tolerance to the anxiogenic effect of caffeine was illustrated by the fact that carriers of the "sensitive" polymorphism whose normal caffeine intake was medium (128 ± 46 mg) or high (346 ± 129 mg) did not show an increase in anxiety following caffeine dosing (100 mg + 125 mg 90-min later), while subjects whose normal caffeine intake was low or zero did show increased anxiety when dosed in the same way. Thus, tolerance to caffeine consumption occurs when habitual users of caffeine – including genetically susceptible individuals – become desensitized to its physiological effects such that additional intake does not contribute to any further increase in these effects.

Among the four observational studies of children, the dose information reported in three of the studies was too imprecise to draw any firm conclusions about specific dose-effects (Bernstein et al., 2002; Ludden and Wolfson, 2010; Oberstar et al., 2002). Among the three experimental studies of children (age 8 to 13) who consumed caffeine doses ranging from 2.5 to 10 mg/kg bw (mean body weight 37–39 kg), a significant increase in anxiety symptoms were reported only at doses of 10 mg/kg bw (Rapoport et al., 1981, 1984).

3.4. Aggression/risk-taking behavior

Aggression/risk-taking behavior was addressed in the studies evaluated by several methods, including observation of subjects by a researcher and identification of behaviors thought to represent aggression, collection of self-reported feelings of anger or aggressive behavior, or participation in computer games designed to record responses believed by the study authors to be indicative of aggressive or risk-taking behaviors.

A total of 15 studies (10 experimental, 5 observational) included an evaluation of the potential relationship between caffeine intake and various endpoints related to aggression and/or risk-taking behavior (e.g., mood state, performance on gambling tasks, behavior). These endpoints were studied primarily in adult populations. There was only one study of children with a mean age of 14 years of age. As with anxiety-related endpoints, drawing conclusions from observational studies of these endpoints is problematic as only associations can be explored, not cause-and-effect. Differentiating between outcomes associated with caffeine intake *per se* versus outcomes relative to both an individual's personality and propensity for risk-taking and preference for caffeinated products is challenging. The primary strengths of the experimental studies include the assessment of baseline behavior or risk-taking propensity prior to the assessment of these measures during specified sessions involving caffeine intake. This allows any potential differences in risk-taking behavior or mood to be more confidently attributed to specific caffeine doses.

Among the five observational epidemiology studies, a variety of caffeinated products were examined including energy drinks (Miller, 2008; Spierer et al., 2014), coffee (Baethge et al., 2009), and caffeinated beverages in general including soda, tea, or coffee (Jones and Lejuez, 2005; Martin et al., 2008). These studies present

several limitations. The design of these cross-sectional observational studies does not allow one to determine a temporal relationship (i.e., whether consumption of energy drinks preceded an individual's propensity for risk-taking behavior or vice versa). The dose-information provided in the study of coffee drinkers and the studies involving energy drinks were not precise enough to determine specific dose-related associations. Observational studies involving the use of energy drinks often do not account for variables such as motivations for use, expectancies prior to use, personality, or genetics, which may be related to both the decision to use them in the first place and to engage in risk-taking behavior. The results of the remaining two studies were mixed. Jones and Lejuez (2005) reported no significant difference in scores on a risk-taking task between 30 high (mean: 423 mg/day, range: 241–1471 mg/day) and 30 low (mean: 14 mg/day, range: 0.41–24 mg/day) consumers of caffeine. Martin et al. (2008) reported significantly higher aggressive behavior scores among high consumers of caffeine (≥4 drinks/day) compared to medium (2–3 drinks/day) or low (0–1 drinks/day) consumers in a study of 132 adolescents.

Three experimental studies examined the effects of low levels of caffeine intake (<100 mg) on aggressive (Baer, 1987; Cherek et al., 1983) or risk-taking behavior (Peacock et al., 2013). Cherek et al. (1983) tested the effects of 0, 1, 2, or 4 mg/kg bw caffeine in 8 adult subjects using a test measuring aggression towards other opponents in a game. Caffeine had a suppressive effect on aggressive responding, which was statistically significant at the highest dose (4 mg/kg bw). Peacock et al. (2013) reported significantly more pumps in a balloon pumping exercise among 28 adult participants who consumed roughly one energy drink (~3.57 ml/kg bw Red Bull), suggesting a propensity for risk taking among this group. Baer (1987) investigated the effects of a single, sugar-free cola on classroom behavior (including aggressive behavior) on 6 kindergarten children, and noted no consistent effect.

Among five experimental studies that examined the effects of moderate levels of caffeine ranging from about 150 to 400 mg, most did not find a significant effect on subjective feelings of anger (Arciero et al., 1998; Arciero and Ormsbee, 2009) or aggressive behavior (Cherek et al., 1983, 1984). Similar to the results reported by Cherek et al. (1983), discussed previously, Cherek et al. (1984) reported that consumption of 500 ml of regular instant coffee compared to decaffeinated coffee produced decreases in aggressive responses in 8 adults. Arciero et al. (1998) and Arciero and Ormsbee (2009) reported no significant increase in feelings of anger among men and women that consumed 5 mg/kg bw caffeine. Anger tended to decrease following caffeine consumption in 10 older and 10 younger women in the 2009 study, and tended to decrease in 10 older, but not 10 younger men, in the 1998 study. Attwood et al. (2007) reported a significantly increased rating of “tense negative mood” (including: tense, jittery, angry, dejected) among those who consumed 400 mg caffeine compared to placebo. More negative effects were observed among 24 moderate consumers (<200 mg caffeine/day) compared to 21 heavy consumers (>200 mg caffeine/day), which the authors suggested may have been due to the development of a tolerance for the aversive effects of caffeine by the high consumers.

Three experimental studies examined the effects of caffeine intake of 600 mg or more on risk taking behavior following sleep deprivation. Killgore et al. (2007, 2008, 2011) examined the effect of caffeine consumption on risk-taking behavior through the use of gambling tasks or application of a self-report questionnaire indicating propensity for risk-taking. Caffeine intake had no effect or led to a reduction in risk-taking behavior. After 44 h of sleep deprivation, Killgore et al. (2008) reported declines in some measures of risk-taking that were unaffected by caffeine (600 mg) in 54 healthy adults (29 M, 25 F). Killgore et al. (2007) reported similar results following 75 h of sleep deprivation and intake of 800 mg of caffeine in 26 healthy adults (21 M, 5 F). After 75 h of sleep deprivation, Killgore et al. (2011) reported increased risk-taking in 25 adults (21 M, 4 F) that was counteracted by 800 mg caffeine (200 mg every 2 h during the last night prior to testing).

While more than a dozen studies have attempted to examine whether there is a relationship between caffeine consumption and risk-taking or aggressive behavior, no clear pattern emerges (Mahoney et al., 2012). Experimental studies that examined the effects of high doses of caffeine reported either no effect, or a reduction in risk-taking behavior.

3.5. Tolerance/withdrawal

Tolerance or acclimation to some of the acute effect of caffeine develops with repeated and regular intake. For example, while caffeine may result in a slight increase in the blood pressure of naive individuals, regular caffeine consumers rapidly develop tolerance and no longer respond to caffeine intake with an increase in blood pressure (Robertson et al., 1981).

Tolerance also develops to increases in tension, anxiety, and jitteriness associated with caffeine administration (Morelli and Simola, 2011). Thus, tolerance to caffeine consumption may be characterized as a desensitization to effects from caffeine among habitual users – including genetically susceptible individuals – such that additional moderate intake does not contribute to any further increase in physiological effects. Very high doses are required to elicit adverse effects.

Abrupt discontinuation of caffeine consumption results in a mild withdrawal syndrome, characterized by headache, fatigue, drowsiness, irritability, depressed mood, and anxiety, starting after 12–24 h of abstinence, and peaking 20–48 h later. Symptoms of caffeine withdrawal vary considerably between different individuals. The withdrawal syndrome is usually not harmful, and is self-limiting (Morelli and Simola, 2011).

4. Summary and conclusions

This investigation has confirmed what has long been known, that caffeine, even at acute doses of 100 mg or less in an adult can produce physiological CNS effects. The most sensitive effect seems to be caffeine's beneficial effect on alertness. Caffeine can also have subtle effects on sleep parameters at similar or slightly higher doses when consumed close to the normal sleep time. These two effects likely both represent manifestations of caffeine's interaction with the adenosine receptor, counteracting adenosine's inhibitory actions, and affecting its role in sleep-wake regulation. This effect of caffeine is both well known to consumers and self-limiting, i.e., self-titration, leading many consumers to refrain from consuming caffeinated beverages late in the day. The effect is also transient and completely reversible when consumption stops, and does not result in any adverse health effects.

Studies examining effects on anxiety showed mixed results at doses in the range of 150–500 mg (in adults), but clearer effects at doses of 700–1200 mg (10 mg/kg bw or more). In the few studies that examined effects in children, similar results were seen, with a clear increase in anxiety symptoms at doses above 10 mg/kg bw, similar to that for adults. There is some evidence of possible increased effects on subjective anxiety in carriers of certain adenosine receptor polymorphisms (Childs et al., 2008), with carriers of some polymorphisms showing signs of increased anxiety with caffeine doses of 150 mg, while non-carriers showed effects only at 450 mg, and carriers of some other polymorphisms showed reduced anxiety following caffeine ingestion. Differences noted on

Table 1
Summary of key findings on CNS effects of caffeine.

Intake	Sleep	Anxiety	Aggression/risk-taking
<100 mg	One experimental study reported "virtually no effect on sleep patterns," among 18 young adult men when administered 30-min before retiring (Karacan et al., 1976). In one cross-sectional study of 11,267 children, "sleeping problems" were reported in 10–12 year old boys, but not girls who consumed <1 caffeinated drink/day (time of consumption not recorded) (Kristjansson et al., 2014).	Among 8 experimental and 4 observational studies (Botella and Parra, 2003; Childs and de Wit, 2006; Childs et al., 2008; Huppe and Janke, 2001; Lieberman et al., 1987; Miller et al., 1998; Peacock et al., 2014; Richardson et al., 1995; Eaton and McLeod, 1984; Gold et al., 2007; Oberstar et al., 2002; Trapp et al., 2014), the authors of just a single study (Richardson et al., 1995) reported a significant excess in "jitteriness" – an undesirable but not adverse effect – among adults that received 70 mg of caffeine compared to those that received none. The results of the remaining studies indicated no adverse effect of low levels of caffeine on measures of anxiety, while two of the studies reported lower anxiety scores following caffeine intakes (Hüppe and Janke, 2001; Peacock et al., 2014).	Cherek et al. (1983) tested the effects of 0, 1, 2, or 4 mg/kg bw caffeine in 8 subjects using a test measuring aggression towards other opponents in a game. Caffeine had a suppressive effect on aggressive responding, which was statistically significant at the highest dose (4 mg/kg bw). Peacock et al. (2013) reported significantly more pumps in a balloon pumping exercise – a surrogate indicator for risk-taking behavior – among 28 participants that consumed roughly one energy drink (3.57 ml/kg Red Bull), suggesting a propensity for risk-taking among this group. Baer (1987) investigated the effects of a single, sugar-free cola on classroom behavior (including aggressive behavior) in 6 kindergarten children, and noted no consistent effect.
100–600 mg	Subtle effects on sleep parameters were observed at doses as low as 100 mg when given immediately prior to retiring (Landolt et al., 1995a), with clear dose-related effects at higher doses. Some studies suggest a lack of effect on sleep when caffeine is given 6–16 h before sleep (Snel, 1993; Bonnet and Arand, 1992; Pontifex et al., 2010). Similar results were observed among 11 studies where salivary caffeine levels were also measured, including increased sleep latency, reduced sleep efficiency, decreased sleep duration, and altered electroencephalography (EEG) parameters (e.g., reduced slow wave activity; alterations in spectral power in different brain wave bands) (Carrier et al., 2007; Carrier et al. 2009; Drapeau et al., 2006; Hale et al., 1995; James, 1998; Lader et al., 1996; Landolt et al., 1995a; Landolt et al. 1995b; Paterson et al., 2007; Rétey et al., 2007; Sicard et al., 1996). One study in children (grades 6–10) who drank 1 coffee or soda per day (time of consumption not recorded) were significantly more likely to report difficulty sleeping compared to children with very low intake (<1/week), with no effects in the low intake group (Orbeta et al., 2006). Carriers of the adenosine deaminase polymorphism (A allele carriers) had lower sleep latency, higher sleep efficiency, a higher rapid eye movement (REM) sleep percentage, and fewer minutes awake following caffeine consumption of at least 1 cup of a caffeine-containing beverage the day prior (time not recorded) compared to non-A allele carriers (Mazzotti et al., 2011). Intake of caffeine was significantly associated with subjectively reduced sleep quality in caffeine-sensitive but not in caffeine-insensitive participants (based on questionnaire). A higher prevalence of the ADORA2A c.1083C/C polymorphism was observed in the caffeine-sensitive group (Rétey et al., 2007), Maternal consumption of ≥300 mg/day caffeine during the 1st, 2nd, or 3rd trimester, during the whole pregnancy, or at 3 months postpartum was not significantly associated with >3 night-	Increases in self-reported symptoms of anxiety were reported in some individuals at dose levels as low as 150 mg (Alsene et al., 2003; Botella and Parra, 2003; Childs et al., 2008; Goldstein et al., 1969). Results were generally mixed among studies that examined the effects of caffeine at doses ranging from 150 to 500 mg. Some authors reported no significant changes in anxiety symptoms following doses as high as 400–500 mg (Azcona et al., 1995; Bonnet and Arand, 2003; Hughes and Boland, 1992), while several others did (Attwood et al., 2007; Bruce et al., 1992; Brunye et al., 2010; Childs et al., 2008; Kaplan et al., 1997; Nardi et al., 2007a,b; Nardi et al., 2008; Rapoport et al., 1981, 1984). Mixed results were similarly reported among nine experimental studies that included testing of salivary caffeine levels (Bernstein et al., 1994; Brice and Smith, 2002; Bruce et al., 1992; Childs and de Wit, 2006; James and Gregg, 2004; Lader et al., 1996; Rapoport et al., 1981; Rapoport et al. 1984; Rogers et al., 2010). Individuals with pre-existing anxiety disorders (e.g., general anxiety disorder, panic disorder) were at greater risk of experiencing anxiety symptoms following caffeine intake of 250 mg (Bruce et al., 1992) or panic attacks at 480 mg (Nardi et al., 2007a,b; 2008). Carriers of two ADORA2A polymorphisms displayed increased symptoms of anxiety after 150 mg caffeine, while non-carriers showed effects only at 450 mg (Childs et al., 2008). Another study of ADORA2A polymorphisms reported similar results; however a tolerance to the anxiogenic effects of caffeine were observed among medium and high regular consumers of caffeine (Rogers et al., 2010). Among the three experimental studies of children (age 8 to 13) who consumed caffeine doses ranging from 2.5 to 10 mg/kg bw (mean body weight 37–39 kg), a significant increase in anxiety symptoms were reported only at doses of 10 mg/kg (Bernstein et al., 1994; Rappaport et al., 1981, 1984).	Among five experimental studies that examined the effects of moderate levels of caffeine ranging from about 150 to 400 mg, most did not find a significant effect on subjective feelings of anger or aggressive behavior (Arciero et al., 1998; Arciero and Ormsbee, 2009; Attwood et al., 2007; Cherek et al., 1983, 1984). Decreases in aggressive responses were observed in two studies following higher caffeine intakes (Cherek et al., 1983, 1984). Anger tended to decrease following caffeine consumption in older and younger women, and tended to decrease in older men, but not younger, in two other studies, respectively (Arciero et al., 1998; Arciero and Ormsbee, 2009). One study reported a significantly increased rating of "tense negative mood" (including: tense, jittery, angry, dejected) among those who consumed 400 mg caffeine per day compared to placebo (Attwood et al., 2007). These effects were more commonly observed among 24 "moderate" consumers (<200 mg/day) compared to 21 "heavy" consumers (>200 mg/day). The authors hypothesized that a tolerance for the undesirable aversive effects of caffeine was developed by the heavy consumers.

Table 1 (*continued*)

Intake	Sleep	Anxiety	Aggression/risk-taking
	time wakings per night among infants at 3 months of age (Santos et al., 2012).		
>600 mg	Among six studies in which caffeine was consumed close to retiring, the authors reported reductions in total sleep time and sleep quality, and increased sleep latency and number of awakenings (Bonnet and Arand, 1992, 1996; LaJambe et al., 2005; Sanchez-Ortuno et al., 2005; Shilo et al., 2002; Youngstedt et al., 2000). In one study where participants received 1200 mg/day caffeine (divided in three doses, including one close to retiring) for seven days, a variety of sleep parameters were negatively affected including total sleep time, sleep latency, wake time, sleep efficiency, number of wakes, and arousal (Bonnet and Arand, 1992). Significant differences in effects observed on day one of the trial disappeared for many of these parameters after the first day of caffeine intake (total sleep time, sleep latency, wake time, sleep efficiency, number of wakes), suggesting evidence of acclimation and a reversal of effects.	Among three studies that examined the effects of caffeine at doses ranging from 700 to 1200 mg in individuals whose normal caffeine consumption was low (<100 mg/day) to moderate (<400 mg/day), all reported a significant increase in anxiety symptoms following caffeine consumption (Bonnet and Arand, 2003; Motl and Dishman, 2004; Youngstedt et al., 1998).	Among three experimental studies that examined the effects of caffeine intake of 600–800 mg on risk taking behavior following sleep deprivation, caffeine intake had either no effect or, in fact, led to a reduction in risk-taking behavior (Kilgore et al., 2007, 2008, 2011).
Notes	The strengths of the literature available for this review include the experimental study design for the majority of the studies, specific dose information, as well as objective measures of sleep quality. Although certain objective sleep parameters were altered following caffeine intake in some (but not all) of these studies, individuals may not actually experience any subjective effects on sleep quality as was reported in at least one study. The results reported in these studies do not suggest any serious or long-term harm to health. Any potential undesirable (but not adverse) effects on sleep quality experienced in daily life would likely lead one to adjust their caffeine intake so as to avoid those effects in the future, i.e., self-titrate.	Caffeine habit, genetics, and pre-existing anxiety disorders appeared to modify the effect that caffeine had on various measures of anxiety. Effects were generally increased among naïve caffeine users (low or no regular consumption). The strengths of the literature available for this review include the experimental study design for the majority of the studies with specific dose information. Drawing conclusions from observational studies on anxiety endpoints is problematic given that only associations can be evaluated, not cause-and-effect. Moreover, it is difficult to distinguish between outcomes associated with caffeine intake *per se* versus those relative to both an individual's personality or motivations and preference for caffeinated products and/or higher caffeine intake.	The strengths of the literature available for this review include the experimental study design for the majority of the studies with specific dose information. These studies also include the assessment of baseline behavior or risk-taking propensity prior to the assessment of these measures during specified sessions involving caffeine intake. This allows any potential differences in risk-taking behavior or mood to be more confidently attributed to specific caffeine doses. Drawing conclusions from observational studies of these endpoints is problematic given that observational studies can only evaluate associations, not cause-and-effect. Moreover, it is difficult to distinguish between outcomes associated with caffeine intake *per se* versus those relative to both an individual's personality and propensity for risk-taking, and preference for caffeinated products.

self-reported mood scores for anxiety are also unlikely to represent adverse health effects. One phenomenon that may rise to the level of a true adverse effect is the apparent ability of a fairly high acute dose of caffeine (480 mg) to elicit panic attacks in some individuals with a medically diagnosed panic disorder (Nardi et al., 2007a, b, 2008; 2009), though Mathew and Wilson (1990) reported no increase in anxiety or panic attacks in subjects diagnosed with panic disorder or general anxiety disorder when given a single 250 mg dose of caffeine, suggesting a fairly high threshold for effects even in this group – more than 2½ cups of brewed coffee, or more than 40 ounces of regular cola-type soft drink.

Studies designed to address the existence of a relationship between caffeine consumption and aggression or risk-taking do not support such a relationship. Cross-sectional observational studies can only evaluate associations and suffer from an inability to examine temporal relationships and differentiate cause-and-effect. Moreover, experimental studies do not show a consistent pattern of results Table 1.

Acknowledgment

This work was funded by the American Beverage Association, the trade association that represents America's non-alcoholic beverage industry.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2015.12.002.

Transparency document

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2015.12.002.

References

Aldridge, A., Aranda, J.V., Neims, A.H., 1979. Caffeine metabolism in the newborn. Clin. Pharmacol. Ther. 25, 447–453.

Alsene, K., Deckert, J., Sand, P., de Witt, H., 2003. Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology 28, 1694–1702.

Aranda, J.V., Collinge, J.M., Zinman, R., Watters, G., 1979. Maturation of caffeine elimination in infancy. Arch. Dis. Child. 54, 946–949.

Arciero, P., Gardner, A.W., Benowitz, N., Poehlman, E.T., 1998. Relationship of blood pressure, heart rate and behavioral mood state to norepinephrine kinetics in younger and older men following caffeine ingestion. Eur. Clin. Nutr. 52 (11), 805–812.

Arciero, P.J., Ormsbee, M.J., 2009. Relationship of blood pressure, behavioral mood state, and physical activiity following caffeine ingestion in younger and older women. Appl. Physiol. Nutr. Metab. 34 (4), 754–762.

Arnaud, M.J., 1993. Metabolism of caffeine and other components of coffee. In: Garattini, S. (Ed.), Caffeine, Coffee, and Health. Raven, New York, pp. 43–95.

Arnaud, M.J., 2011. Pharmacokinetics and metabolism of natural methylxanthines in animal and man. Handb. Exp. Pharmacol. 200, 33–91.

Attwood, A.S., Higgs, S., Terry, P., 2007. Differential responsiveness to caffeine and perceived effects of caffeine in moderate and high regular caffeine consumers. Psychopharmacol. Berl. 190 (4), 469–477.

Azcona, O., Barbanoj, M.J., Torrent, J., Jane, F., 1995. Evaluation of the central effects of alcohol and caffeine interaction. Br. J. Clin. Pharmacol. 40, 393–400.

Baer, R.A., 1987. Effects of caffeine on classroom behavior, sustained attention, and a memory task in preschool children. J. Appl. Behav. Anal. 20, 225–234.

Baethge, C., Tondo, L., Lepri, B., Baldessarini, R.J., 2009. Coffee and cigarette use: association with suicidal acts in 352 Sardinian bipolar disorder patients. Bipolar Disord. 11 (5), 494–503.

Baraldi, P.G., Tabrizi, M.A., Gessi, S., Borea, P.A., 2008. Adenosine receptor antagonists: translating medicinal chemistry and pharmacology into clinical utility. Chem. Rev. 108 (1), 238–263.

Bernstein, G.A., Carroll, M.E., Crosby, R.D., Perwien, A.R., Go, F.S., Benowitz, N.L., 1994. Caffeine effects on learning, performance, and anxiety in normal school-age children. J. Am. Acad. Child. Adolesc. Psychiatry 33, 407–415.

Bernstein, G.A., Carroll, M.E., Thuras, P.D., Cosgrove, K.P., Roth, M.E., 2002. Caffeine dependence in teenagers. Drug Alcohol Depend. 66, 1–6.

Birkett, D.J., Miners, J.D., 1991. Caffeine renal clearance and urine caffeine concentrations during steady state dosing. Implications for monitoring caffeine intake during sports events. Br. J. Clin. Pharmacol. 31, 405–408.

Blanchard, J., Sawers, S.J., 1983. Comparative pharmacokinetics of caffeine in young and elderly men. J. Pharmacokinet. Biopharm. 11, 109–126.

Bonati, M., Latini, R., Galletti, F., Young, J.F., Tognoni, G., Garattini, S., 1982. Caffeine disposition after oral doses. Clin. Pharmacol. Ther. 32, 98–106.

Bonnet, M.H., Arand, D.L., 1992. Caffeine use as a model of acute and chronic insomnia. Sleep 15 (6), 526–536.

Bonnet, M.H., Arand, D.L., 1996. Metabolic rate and the restorative function of sleep. Physiol. Behav. 59 (4–5), 777–782.

Bonnet, M.H., Arand, D.L., 2003. Insomnia, metabolic rate and sleep restoration. J. Intern. Med. 254 (1), 23–31.

Botella, P., Parra, A., 2003. Coffee increases state anxiety in males but not in females. Hum. Psychopharmacol. 18 (2), 141–143.

Boyd, E.M., Dolman, M., Knight, L.M., Sheppard, E.P., 1965. The chronic oral toxicity of caffeine. Can. J. Physiol. Pharmacol. 43 (6), 995–1007.

Brice, C.F., Smith, A.P., 2002. Effects of caffeine on mood and performance: a study of realistic consumption. Psychopharmacol. Berl. 164, 188–192.

Bruce, M., Scott, N., Shine, P., Lader, M., 1992. Anxiogenic effects of caffeine in patients with anxiety disorders. Arch. Gen. Psychiat. 49, 867–869.

Brunye, T.T., Mahoney, C.R., Giles, G.E., Lieberman, H.R., Taylor, H.A., 2010. Acute caffeine consumption enhances the executive control of visual attention in habitual consumers. Brain Cogn. 74, 186–192.

Butler, M.A., Iwasaki, M., Guengerich, F.P., Kadlubar, F.F., 1989. Human cytochrome P-450PA (P-450IA2), the phenacetin O-deethylase, is primarily responsible for the hepatic 3-demethylation of caffeine and N-oxidation of carcinogenic arylamines. Proc. Natl. Acad. Sci. U. S. A. 86, 7696–7700.

Calamaro, C.J., Mason, T.B., Ratcliffe, S.J., 2009. Adolescents living the 24/7 lifestyle: effects of caffeine and technology on sleep duration and daytime functioning. Pediatrics 123 (6), e1005–e1010.

Carrier, J., Fernandez-Bolanos, M., Robillard, R., Dumont, M., Paquet, J., Selmaoui, B., Filipini, D., 2007. Effects of caffeine are more marked on daytime recovery sleep than on nocturnal sleep. Neuropsychopharmacology 32 (4), 964–972.

Carrier, J., Paquet, J., Fernandez-Bolanos, M., Girouard, L., Roy, J., Selmaoui, B., Filipini, D., 2009. Effects of caffeine on daytime recovery sleep: a double challenge to the sleep-wake cycle in aging. Sleep. Med. 10 (9), 1016–1024.

Cherek, D.R., Steinberg, J.L., Brauchi, J.T., 1983. Effects of caffeine on human aggressive behavior. Psychiatry Res. 8, 137–145.

Cherek, D.R., Steinberg, J.L., Brauchi, J.T., 1984. Regular or decaffeinated coffee and subsequent human aggressive behavior. Psychiatry Res. 11, 251–258.

Childs, E., de Wit, H., 2006. Subjective, behavioral, and physiological effects of acute caffeine in light, nondependent caffeine users. Psychopharmacol. Berl. 185, 514–523.

Childs, E., Hohoff, C., Deckert, J., Xu, K., Badner, J., de Wit, H., 2008. Association between ADORA2A 2959 and DRD2 polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology 33, 2791–2800.

Costa, J., Lunet, N., Santos, C., Santos, J., Vaz-Carneiro, A., 2010. Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies. J. Alzheimers Dis. 20 (Suppl. 1), S221–S238.

Desmond, P.V., Patwardhan, R.V., Johnson, R.F., Schenker, S., 1980. Impaired elimination of caffeine in cirrhosis. Dig. Dis. Sci. 25, 193–197.

Dorne, J.L., Walton, K., Renwick, A.G., 2001. Uncertainty factors for chemical risk assessment. human variability in the pharmacokinetics of CYP1A2 probe substrates. Food Chem. Toxicol. 39 (7), 681–696.

Drapeau, C., Hamel-Hébert, I., Robillard, R., Selmaoui, B., Filipini, D., Carrier, J., 2006. Challenging sleep in aging: the effects of 200 mg of caffeine during the evening in young and middle-aged moderate caffeine consumers. J. Sleep. Res. 15 (2), 133–141.

Eaton, W.W., McLeod, J., 1984. Consumption of coffee or tea and symptoms of anxiety. Am. J. Public Health 74, 66–68.

European Food Safety Authority (EFSA), 2015. Scientific opinion on the safety of caffeine. EFSA panel on dietetic products, nutrition and allergies (NDA). EFSA J. 13 (5), 4102.

Feely, J., Kelleher, P., Odumosu, A., 1987. The effects of ageing on aminopyrine and caffeine breath tests in the rat. Fundam. Clin. Pharmacol. 1, 409–412.

Fredholm, B.B., Ijzerman, A.P., Jacobson, K.A., Klotz, K.N., Linden, J., 2001. International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. Pharmacol. Rev. 53 (4), 527–552. http://pharmrev.aspetjournals.org/content/53/4/527.full.pdf+html.

Fulgoni III, V.L., Keast, D.R., Lieberman, H.R., 2015. Trends in intake and sources of caffeine in the diets of US adults: 2001–2010. Am. J. Clin. Nutr. 101 (5), 1081–1087. http://ajcn.nutrition.org/content/101/5/1081.full.pdf+html.

Gold, E.B., Bair, Y., Block, G., Greendale, G.A., Harlow, S.D., Johnson, S., Kravitz, H.M., Rasor, M.O., Siddiqui, A., Sternfeld, B., Utts, J., Zhang, G., 2007. Diet and lifestyle factors associated with premenstrual symptoms in a racially diverse community sample: study of women's health across the nation (SWAN). J. Womens Health (Larchmt) 16 (5), 641–656 (Erratum in J Womens Health (Larchmt). 2007 Jul–Aug; 16(6), 934.).

Goldstein, A., Kaizer, S., Whitby, O., 1969. Psychotropic effects of caffeine in man. IV. Quantitative and qualitative differences associated with habituation to coffee. Clin. Pharmacol. Ther. 10 (4), 489–497.

Gorodischer, R., Karplus, M., 1982. Pharmacokinetic aspects of caffeine in premature infants with apnoea. Eur. J. Clin. Pharmacol. 22, 47–52.

Hale, K.L., Hughes, J.R., Oliveto, A.H., Higgins, S.T., 1995. Caffeine self-administration and subjective effects in adolescents. Exp. Clin. Pharmacol. 3, 364–370.

Hughes, G.V., Boland, F.J., 1992. The effects of caffeine and nicotine consumption on mood and somatic variables in a penitentiary inmate population. Addict. Behav. 17 (5), 447–457.

Hüppe, A., Janke, W., 2001. Experimental study of the effect of acetylsalicylic acid combined with caffeine regarding possible abuse potential] [Article in German. Z. Exp. Psychol. 48 (3), 177–187.

Institute of Medicine (IOM), 2001. Caffeine for the Sustainment of Mental Task Performance: Formulations for Military Operations. Committee on Military Nutrition Research, Food and Nutrition Board. National Academies Press. www.nap.edu.

Institute of Medicine (IOM), 2014. Caffeine in Food and Dietary Supplements: Examining Safety: Workshop Summary. National Academies Press. www.nap.edu.

James, J.E., 1998. Acute and chronic effects of caffeine on performance, mood, headache, and sleep. Neuropsychobiology 38, 32–41.

James, J.E., Gregg, M.E., 2004. Effects of dietary caffeine on mood when rested and sleep restricted. Hum. Psychopharmacol. 19 (5), 333–341. Erratum in: Hum. Psychopharmacol. 2005 Jul; 20(5), 376.

Jones, H.A., Lejuez, C.W., 2005. Personality correlates of caffeine dependence: the role of sensation seeking, impulsivity, and risk taking. Exp. Clin. Psychopharm. 13 (3), 259–266.

Kaplan, G.B., Greenblatt, D.J., Ehrenberg, B.L., Goddard, J.E., Cotreau, M.M., Harmatz, J.S., Shader, R.I., 1997. Dose-dependent pharmacokinetics and psychomotor effects of caffeine in humans. J. Clin. Pharmacol. 37 (8), 693–703.

Karacan, I., Thornby, J.I., Anch, M., Booth, G.H., Williams, R.L., Salis, P.J., 1976. Dose-related sleep disturbances induced by coffee and caffeine. Clin. Pharmacol. Ther. 20 (6), 682–689.

Killgore, W.D.S., Lipizz, E.L., Kamimori, G.H., Balkin, T.I, 2007. Caffeine effects on risky decision making after 75 hours of sleep deprivation. Aviat. Space Environ. Med. 78, 957–962.

Killgore, W.D.S., Grugle, N.L., Killgore, D.B., Leavitt, B.P., Watlington, G.I., McNair, S., Balkin, T.J., 2008. Restoration of risk-propensity during sleep deprivation: caffeine, dextroamphetamine, and modafinil. Aviat. Space Environ. Med. 79, 867–874.

Killgore, W.D., Kamimori, G.H., Balkin, T.J., 2011. Caffeine protects against increased risk-taking propensity during severe sleep deprivation. J. Sleep. Res. 20 (3), 395–403.

Knutti, R., Rothweiler, H., Schlatter, C., 1981. Effect of pregnancy on the pharmacokinetics of caffeine. Eur. J. Clin. Pharmacol. 21, 121–126.

Knutti, R., Rothweiler, H., Schlatter, C., 1982. The effect of pregnancy on the pharmacokinetics of caffeine. Arch. Toxicol. 5, 187–192.

Kristjansson, A.L., Sigfusdottir, I.D., Mann, M.J., James, J.E., 2014. Caffeinated sugar-sweetened beverages and common physical complaints in Icelandic children aged 10–12 years. Prev. Med. 58, 40–44.

Lader, M., Cardwell, C., Shine, P., Scott, N., 1996. Caffeine withdrawal symptoms and

rate of metabolism. J. Psychopharmacol. 10 (2), 110–118.
LaJambe, C.M., Kamimori, G.H., Belenky, G., Balkin, T.J., 2005. Caffeine effects on recovery sleep following 27 hr total sleep deprivation. Aviat. Space Environ. Med. 76 (2), 108–113.
Landolt, H.P., Dijk, D.J., Gaus, S.E., Borbely, A.A., 1995a. Caffeine reduces low frequency delta activity in the human sleep EEG. Neuropsychopharmacology 12, 229–238.
Landolt, H.P., Werth, E., Borbély, A.A., Dijk, D.J., 1995b. Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. Brain Res. 675 (1–2), 67–74.
Latini, R., Bonati, M., Marzi, E., Tacconi, M.T., Sadurska, B., Bizzi, A., 1980. Caffeine disposition and effects in young and one-year old rats. J. Pharm. Pharmacol. 32, 596–599.
Lee, K.A., McEnany, G., Weekes, D., 1999. Gender differences in sleep patterns for early adolescents. J. Adolesc. Health 24 (1), 16–20.
Le Guennec, J.C., Billon, B., 1987. Delay in caffeine elimination in breast-fed infants. Pediatrics 79, 264–268.
Lieberman, H.R., Wurtman, R.J., Emde, G.G., Roberts, C., Coviella, I.L., 1987. The effects of low doses of caffeine on human performance and mood. Psychopharmacol. Berl. 92 (3), 308–312.
Ludden, A.B., Wolfson, A.R., 2010. Understanding adolescent caffeine use: connecting use patterns with expectancies, reasons, and sleep. Health Educ. Behav. 37 (3), 330–342. Epub 2009 Oct 26.
Mahoney, C.R., Brunye, T.T., Giles, G.E., 2012. Caffeine effects on aggression and risky decision making. In: Harris, R.K., Lieberman, R.B. (Eds.), Diet, Brain, Behavior. Practical Implications. CRC Press, pp. 293–312.
Martin, C.A., Cook, C., Woodring, J.H., Burkhardt, G., Guenthner, G., Omar, H.A., Kelly, T.H., 2008. Caffeine use: association with nicotine use, aggression, and other psychopathology in psychiatric and pediatric outpatient adolescents. Sci. World J. 8, 512–516.
Mathew, R.J., Wilson, W.H., 1990. Behavioral and cerebrovascular effects of caffeine in patients with anxiety disorders. Acta Psychiatr. Scand. 82, 17–22.
Mazzotti, D.R., Guindalini, C., Pellegrino, R., Barrueco, K.F., Santos-Silva, R., Bittencourt, L.R., Tufik, S., 2011. Effects of the adenosine deaminase polymorphism and caffeine intake on sleep parameters in a large population sample. Sleep 34 (3), 399–402.
Miller, L.S., Lombardo, T.W., Fowler, S.C., 1998. Caffeine, but not time of day, increases whole-arm physiological tremor in non-smoking moderate users. Clin. Exp. Pharmacol. Physiol. 25 (2), 131–133.
Miller, K.E., 2008. Energy drinks, race, and problem behaviors among college students. J. Adolesc. Health. 43 (5), 490–497.
Mindell, J.A., Meltzer, L.J., Carskadon, M.A., Chervin, R.D., 2009. Developmental aspects of sleep hygiene: findings from the 2004 National Sleep Foundation Sleep in America Poll. Sleep. Med. 10 (7), 771–779.
Mitchell, D.C., Knight, C.A., Hockenberry, J., Teplansky, R., Hartman, T.J., 2014. Beverage caffeine intakes in the US. Food Chem. Toxicol 63, 136–142.
Morelli, M., Simola, N., 2011. Methylxanthines and drug dependence: a focus on interactions with substances of abuse. Handb. Exp. Pharmacol. 200, 483–507.
Motl, R.W., Dishman, R.K., 2004. Effects of acute exercise on the soleus H-reflex and self-reported anxiety after caffeine ingestion. Physiol. Behav. 80 (4), 577–585.
Nardi, A.E., Lopes, F.L., Valença, A.M., Freire, R.C., Veras, A.B., de-Melo-Neto, V.L., Nascimento, I., King, A.L., Mezzasalma, M.A., Soares-Filho, G.L., Zin, W.A., 2007a. Caffeine challenge test in panic disorder and depression with panic attacks. Compr. Psychiatry 48 (3), 257–263.
Nardi, A.E., Valença, A.M., Lopes, F.L., de-Melo-Neto, V.L., Freire, R.C., Veras, A.B., Nascimento, I., King, A.L., Soares-Filho, G.L., Mezzasalma, M.A., Zin, W.A., 2007b. Caffeine and 35% carbon dioxide challenge tests in panic disorder. Hum. Psychopharmacol. 22 (4), 231–240.
Nardi, A.E., Valença, A.M., Nascimento, I., Freire, R.C., Veras, A.B., de-Melo-Neto, V.L., Lopes, F.L., King, A.L., Soares-Filho, G.L., Mezzasalma, M.A., Rassi, A., Zin, W.A., 2008. A caffeine challenge test in panic disorder patients, their healthy first-degree relatives, and healthy controls. Depress Anxiety. 25 (10), 847–853.
Nardi, A.E., Lopes, F.L., Freire, R.C., Veras, A.B., Nascimento, I., Valenca, A.M., de-Melo-Neto, V.L., Soares-Filho, G.L., King, A.L., Araujo, D.M., Mezzasalma, M.A., Rassi, A., Zin, W.A., 2009. Panic disorder and social anxiety disorder subtypes in a caffeine challenge test. Psychiatry Res. 169, 149–153.
Nawrot, P., Jordan, S., Eastwood, J., Rotstein, J., Hugenholtz, A., Feeley, M., 2003. Effects of caffeine on human health. Food Add. Contam. 20, 1–30.
Nehlig, A., 2007. Pharmacological Properties and Neurophsyiological Effects of Caffeine. In: Smith, B.D., Gupta, U., Gupta, B.S. (Eds.), Caffeine and Activation Theory: Effects on Health and Behavior. CRC Press, Boca Raton, pp. 43–77.
Oak Ridge National Laboratory (ORNL), 2011. Adverse Health Effects of Caffeine: Review and Analysis of Recent Human and Animal Research. Final Report, October 27, 2011. Prepared for Office of Nutrition, Labeling and Dietary Supplements, Office of Food Additive Safety (Task 2008-39). Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration.
Oberstar, J.V., Bernstein, G.A., Thuras, P.D., 2002. Caffeine use and dependence in adolescents: one-year follow-up. J. Child. Adolesc. Psychopharmacol. 12, 127–135.
Orbeta, R.L., Overpeck, M.D., Ramcharran, D., Kogan, M.D., Ledsky, R., 2006. High caffeine intake in adolescents: associations with difficulty sleeping and feeling tired in the morning. J. Adolesc. Health 38, 451–453.
Paire, M., Lieferinghen, P., Desvinges, V., Dubray, C., Raynaud, E.J., Lavarenne, J., 1988. Cinetique de la cafeine au cours des premiers mois de la vie et implications pratiques. Sem. Hop Paris 64, 1813–1817.
Parsons, W.D., Neims, A.H., 1981. Prolonged half-life of caffeine in healthy tem newborn infants. J. Pediatr. 98, 640–641.
Paterson, L.M., Wilson, S.J., Nutt, D.J., Hutson, P.H., Ivarsson, M., 2007. A translational, caffeine-induced model of onset insomnia in rats and healthy volunteers. Psychopharmacol. Berl. 191 (4), 943–950.
Peacock, A., Bruno, R., Martin, F.H., Carr, A., 2013. The impact of alcohol and energy drink consumption on intoxication and risk-taking behavior. Alcohol Clin. Exp. Res. 37, 1234–1242.
Peacock, A., Bruno, R., Martin, F.H., Carr, A., 2014. Self-reported physiological and psychological side-effects of an acute alcohol and energy drink dose. Appetite 76C, 60–65.
Pearlman, S.A., Duran, C., Wood, M.A., Maisels, M.J., Berlin Jr., C.M., 1989. Caffeine pharmacokinetics in preterm infants older than 2 weeks. Dev. Pharmacol. Ther. 12, 65–69.
Pollak, C.P., Bright, D., 2003. Caffeine consumption and weekly sleep patterns in US seventh-, eighth-, and ninth-graders. Pediatrics 111, 42–46.
Pontifex, K.J., Wallman, K.E., Dawson, B.T., Goodman, C., 2010. Effects of caffeine on repeated sprint ability, reactive agility time, sleep and next day performance. J. Sports Med. Phys. Fit. 50 (4), 455–464.
Prediger, R.D., 2010. Effects of caffeine in Parkinson's disease: from neuroprotection to the management of motor and non-motor symptoms. J. Alzheimers Dis. 20 (1,), S205–S220.
Rajaratnam, S.M.W., Arendt, J., 2001. Health in a 24-h society. Lancet 358, 999–1005.
Rapoport, J.L., Jensvold, M., Elkins, R., Buchsbaum, M.S., Weingartner, H., Ludlow, C., Zahn, T.P., Berg, C.J., Neims, A.H., 1981. Behavioral and cognitive effects of caffeine in boys and adult males. J. Nerv. Ment. Dis. 169, 726–732.
Rapoport, J.L., Berg, C.J., Ismond, D.R., Zahn, T.P., Neims, A., 1984. Behavioral effects of caffeine in children. Relationship between dietary choice and effects of caffeine challenge. Arch. Gen. Psychiatry 41, 1073–1079.
Rétey, J.V., Adam, M., Khatami, R., Luhmann, U.F., Jung, H.H., Berger, W., Landolt, H.P., 2007. A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. Clin. Pharmacol. Ther. 81 (5), 692–698.
Richardson, N.J., Rogers, P.J., Elliman, N.A., O'Dell, R.J., 1995. Mood and performance effects of caffeine in relation to acute and chronic caffeine deprivation. Pharmacol. Biochem. Behav. 52 (2), 313–320.
Robertson, D., Wade, D., Workman, R., Woosley, R.L., Oates, J.A., 1981. Tolerance to the humoral and hemodynamic effects of caffeine in man. J. Clin. Invest. 67, 1111–1117.
Rogers, P.J., Martin, J., Smith, C., Heatherley, S.V., Smit, H.J., 2003. Absence of reinforcing, mood and psychomotor performance effects of caffeine in habitual non-consumers of caffeine. Psychopharmacol. Berl. 167 (1), 54–62.
Rogers, P.J., Hohoff, C., Heatherley, S.V., Mullings, E.L., Maxfield, P.J., Evershed, R.P., Deckert, J., Nutt, D.J., 2010. Association of the anxiogenic and alerting effects of caffeine with ADORA2A and ADORA1 polymorphisms and habitual level of caffeine consumption. Neuropsychopharmacology 35, 1973–1983.
Sanchez-Ortuno, M., Moore, N., Taillard, J., Valtat, C., Leger, D., Bioulac, B., Philip, P., 2005. Sleep duration and caffeine consumption in a French middle-aged working population. Sleep. Med. 6 (3), 247–251.
Santos, C., Costa, J., Santos, J., Vaz-Carneiro, A., Lunet, N., 2010. Caffeine intake and dementia: systematic review and meta-analysis. J. Alzheimers Dis. 20 (1), S187–S204.
Santos, I.S., Matijasevich, A., Domingues, M.R., 2012. Maternal caffeine consumption and infant nighttime waking: prospective cohort study. Pediatrics 129, 860–868.
Scott, N.R., Stambuk, D., Chakraborty, J., Marks, V., Morgan, M.Y., 1988. Caffeine clearance and biotransformation in patients with chronic liver disease. Clin. Sci. (Lond) 74, 377–384.
Sherwin, R.P., 1983. What is an adverse health effect? Environ. Health Perspect. 52, 177–182.
Shilo, L., Sabbah, H., Hadari, R., Kovatz, S., Weinberg, U., Dolev, S., Dagan, Y., Shenkman, L., 2002. The effects of coffee consumption on sleep and melatonin secretion. Sleep. Med. 3 (3), 271–273.
Sicard, B.A., Perault, M.C., Enslen, M., Chauffard, F., Vandel, B., Tachon, P., 1996. The effects of 600 mg of slow release caffeine on mood and alertness. Aviat. Space Environ. Med. 67 (9), 859–862.
Smith, A.P., Christopher, G., Sutherland, D., 2006. Effects of caffeine in overnight-withdrawn consumers and non-consumers. Nutr. Neurosci. 9 (1–2), 63–71.
Snel, J., 1993. Coffee and caffeine: sleep and wakefulness. In: Garattini, S. (Ed.), Caffeine, Coffee, and Health. Raven Press, New York, pp. 255–290.
Soroko, S., Chang, J., Barrett-Connor, E., 1996. Reasons for changing caffeinated coffee consumption: the Rancho Bernardo study. J. Am. Coll. Nutr. 15 (1), 97–101.
Spierer, D.K., Blanding, N., Santella, A., 2014. Energy drink consumption and associated health behaviors among university students in an urban setting. J. Community Health 39 (1), 132–138.
Statland, B.E., Demas, T., Danis, M., 1976. Letter: caffeine accumulation associated with alcoholic liver disease. N. Engl. J. Med. 295, 110–111.
Statland, B.E., Demas, T.J., 1980. Serum caffeine half-lives. Healthy subjects vs. patients having alcoholic hepatic disease. Am. J. Clin. Pathol. 73, 390–393.
Tang-Liu, D.D., Williams, R.L., Riegelman, S., 1983. Disposition of caffeine and its metabolites in man. J. Pharmacol. Exp. Ther. 224, 180–185.
Thorn, C.F., Aklillu, E., McDonagh, E.M., Klein, T.E., Altman, R.B., 2012. PharmGKB summary: caffeine pathway. Pharmacogenet Genomics 22 (5), 389–395. http://

www.ncbi.nlm.nih.gov/pmc/articles/PMC3381939/.
Trapp, G.S.A., Allen, K., O'Sullivan, T.A., Robinson, M., Jacoby, P., Oddy, W.H., 2014. Energy drink consumption is associated with anxiety in Australian young adult males. Depress Anxiety 31 (5), 420–428.
US Environmental Protection Agency (USEPA), 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. USEPA Office of Research and Development, Washington, DC. October 1994. EPA/600/8–90/066F.
Visitisen, K., Loft, S., Poulsen, H.E., 1990. Cytochrome P450IA2 activity in man measured by caffeine metabolism: effect of smoking, broccoli and exercise. In: Witmer, et al. (Eds.), Biological Reactive Intermediates, IV, ed. Plenum, New York, pp. 407–411.
Von Borstel, R.W., 1983. Biological effects of caffeine: metabolism. Food Technol. 37, 40–43.
Yang, A., Palmer, A.A., de Wit, H., 2010. Genetics of caffeine consumption and responses to caffeine. Psychopharmacol. Berl. 211, 245–257.
Youngstedt, S.D., O'Connor, P.J., Crabbe, J.B., Dishman, R.K., 1998. Acute exercise reduces caffeine-induced anxiogenesis. Med. Sci. Sports Exerc 30 (5), 740–745.
Youngstedt, S.D., O'Connor, P.J., Crabbe, J.B., Dishman, R.K., 2000. The influence of acute exercise on sleep following high caffeine intake. Physiol. Behav. 68 (4), 563–570.