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Neurobehavioral hazard identification and characterization for caffeine

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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.

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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

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