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*Via electronic submission to  
<https://oehha.ca.gov/comments>*

Monet Vela  
Office of Environmental Health Hazard Assessment  
P.O. Box 4010  
Sacramento, California 95812-4010

Re: Proposed Adoption of New Section Under Article 7: No Significant Risk Levels  
Section 25704: Exposures to Listed Chemicals in Coffee Posing No Significant Risk

## **CERT'S SUBMISSION NO. 8**

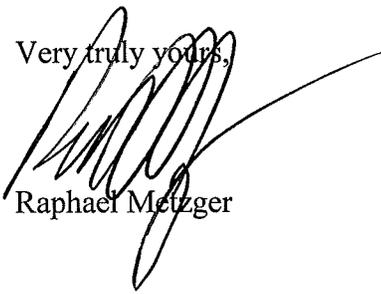
Dear Ms. Vela:

Enclosed herewith are the following documents that are being submitted on behalf of our client, the Council for Education and Research on Toxics (CERT) regarding the Opinions of Dr. Jack James Regarding Adverse Effects of Consumption of Coffee.

1. Exhibit A - Opinions of Dr. Jack James.
2. Exhibit B - Curriculum Vitae of Dr. Jack E. James, Ph.D.

Kindly include these materials of Dr. Jack James in the record for this rulemaking proceeding.

Very truly yours,

  
Raphael Metzger

RM:ip  
encls: as specified

# **EXHIBIT “A”**

## Opinions of Jack James, Ph.D.

### I. Human Exposure to Coffee and Caffeine

#### A. Exposed Populations and Consumption Patterns

1. Fetal Exposure (James & Paull, 1985; James 1991, 1997a, 2001)
  - a. A substantial portion of newborns have pharmacologically active levels of caffeine in blood, which occurs transplacentally through maternal consumption.
  - b. The major source of fetal caffeine exposure is maternal consumption of coffee.
  - c. The fetus is dependent on the mother to metabolize caffeine.
  - d. Newborns cannot metabolize caffeine because fetal liver lacks the metabolic enzyme Cytochrome P450, resulting in a lengthy half-life of about 4 days for kidneys to excrete unmetabolized caffeine.
  - e. Consequently, some newborns suffer caffeine withdrawal at birth.
2. Children and Adolescents (James et al., 2011a, b, 2015; Kristjansson et al., 2011, 2013, 2014, 2015)
  - a. Although caffeine is present in breast milk, lactation is not a major source of caffeine exposure for infants (James 1997).
  - b. At a young age children become exposed to caffeine primarily in the form of caffeinated sugar-sweetened beverages.
  - c. The pattern of childhood caffeine consumption tends to be less regular than the pattern in adults. In contrast to adults, it is common for children and adolescents to consume most of their daily caffeine intake in the evening, often while engaged in screen behaviour. This is consistent with evidence that caffeine is a common source of sleep disruption for adolescents.
  - d. Studies show that about 75% of adolescents consume caffeine daily, primarily from soft drinks, followed by coffee, tea, and energy drinks.
3. Adults and the Elderly (James 1991, 1997a)
  - a. By adulthood caffeine consumption patterns are established.
  - b. The typical caffeine consumption pattern in adults is to start in the morning, followed by intermittent consumption during the day, and tapering off in the evening followed by overnight abstinence.
  - c. More than 80% of the adult population consumes caffeine daily,

and in some communities the proportion is close to 100% (de Leon et al., 2003).

- d. In the United States, the primary source of adult caffeine intake is consumption of coffee, followed by consumption of tea, soft drinks, and energy drinks.
- e. Patterns of adult caffeine consumption remain relatively stable as people age, with some modest reduction in older age.
- f. A distinctive feature of caffeine consumption appears to be that people regulate their intake within a fairly narrow range of consumption levels. This may be because the benign acute effects of caffeine are evident only within that range and exceeding that range of consumption is experienced as unpleasant or aversive.

4. Summary.

- a. Population caffeine exposure is almost universal.
- b. Population caffeine exposure is essentially lifelong.
- c. Caffeine is the only psychoactive compound that is part of the daily diet of most people.

## II. Cardiovascular Disease

### A. Blood pressure (James, 1991, 1994, 1997a, b, c, 2011)

1. Background

- a. Cardiovascular disease is the main cause of death and disability globally.
- b. Blood pressure level is the most important population indicator of cardiovascular disease outcomes.
- c. The relationship between blood pressure and cardiovascular disease is substantially linear.

2. Acute Pressor Effects of Caffeine

- a. Caffeine is known to affect cardiovascular function, which is of concern considering the essentially lifelong and near-universal population exposure to caffeine.
- b. It has been established definitively that caffeine produces acute increases in blood pressure in the range of 5-15 mm Hg systolic and diastolic.

- c. Experimental studies generally show that the acute pressor effects of a single dietary dose of caffeine persist for 2-3 hours.
- d. The average caffeine elimination half-life is about 5 hours. The average coffee consumer drinks about 3-4 cups of coffee per day.
- e. Consequently, habitual coffee/caffeine consumers experience a modest increase in blood pressure throughout most waking hours.

### 3. Tolerance

- a. It is claimed by some that habitual caffeine consumption leads to development of tolerance to its pressor effects.
- b. Suitably controlled experimental studies demonstrate that tolerance is partial (possibly accounting for only about a 25% reduction in response magnitude), leaving a substantial residual pressor effect even among habitual caffeine consumers.
- c. Intervention studies that assess the acute effects of caffeine consumption routinely recruit habitual consumers. Before being allocated to placebo control and caffeine groups participants are typically asked to forego their usual morning caffeinated beverage. In other words, they present to the experiment after overnight abstinence, and under those conditions demonstrate the pressor effect of caffeine. This precisely mirrors what caffeine consumers do anyway, as they routinely abstain from consuming caffeine overnight. Therefore, by showing a pressor effect under experimental conditions, researchers have effectively shown what happens in daily life.
- d. Studies have shown that the pressor effects of caffeine are strongly correlated with plasma caffeine levels. Because plasma caffeine levels are depleted following overnight abstinence, habitual consumers remain responsive to caffeine's pressor effects in the long-term.
- e. The pressor effects of caffeine are evident in men and women, young and old, normotensive and hypertensive individuals with or without blood pressure medication, and are additive to pressor effects from other sources (e.g., smoking).

### 4. Mechanism of Action.

- a. The blood pressure elevating effects of coffee/caffeine are consistent with the known main mechanism of action of caffeine,

- namely, antagonism of endogenous adenosine.
- b. Caffeine has a similar molecular structure to adenosine and is able to occupy adenosine receptors throughout the body. Caffeine has affinity for A1 and A2A adenosine receptors, which are known to be involved in blood pressure regulation.
  - c. Adenosine generally exerts inhibitory actions in the body and, by antagonizing adenosine, caffeine exerts excitatory effects. Whereas adenosine has vasodilatory effects, the pressor action of caffeine is due primarily to vasoconstriction.
5. Adverse Cardiovascular Effects.
- a. Extrapolating from the findings of experimental studies, conservative estimates indicate that the average population blood pressure is likely to be increased by 2-4 mm Hg systolic and diastolic due to caffeine consumption (James, 1997b).
  - b. Based on what is known about the relationship between population blood pressure level and cardiovascular disease outcomes, it has been conservatively estimated that caffeine consumption may be responsible for 10-12% of coronary heart disease and 18-20% of stroke (James 1997b).
  - c. Effects of this magnitude represent a substantial adverse impact on public health. Evidence for adverse cardiovascular effects from coffee/caffeine consumption is extensive and compelling.

**B. Pregnancy Outcomes** (James, 1985, 1991, 1997, 2015)

1. Maternal Exposure to Caffeine During Pregnancy.
  - a. A majority of women consume caffeine before and during pregnancy. This is substantiated by the fact that most newborns have physiologically active levels of caffeine.
  - b. Many women spontaneously reduce caffeine intake during pregnancy because they report a loss of taste for caffeine during pregnancy.
  - c. This is related to the fact that the caffeine elimination half-life is extended during pregnancy as a result of hormonal changes. In other words, pregnant women do not need to consume as much caffeine to maintain usual blood levels of the drug.

2. Fetal Exposure to Caffeine.
  - a. The level of caffeine in fetal blood approximates that of the mother.
  - b. The fetus is not able to metabolize caffeine and is therefore dependent on the mother to do so.
  
3. Pregnancy Outcomes
  - a. Epidemiologic studies have examined associations between maternal coffee consumption during pregnancy and various reproductive outcomes, including infertility and infertility treatment, delayed conception, spontaneous abortion, stillbirth, reduced fetal blood flow, and reduced fetal weight and growth.
  - b. Adverse associations between maternal consumption of coffee during pregnancy and reproductive outcomes have been consistently reported for infertility and infertility treatment, delayed conception, spontaneous abortion, stillbirth, reduced fetal blood flow, and reduced fetal weight and growth.
  - c. Studies have reported adverse reproductive outcomes at caffeine exposures substantially below the 200-300 mg/day levels that have been deemed by some health authorities to be “safe”.
  - d. Reduced fetal blood flow has been demonstrated to result from caffeine exposure (Hoecker et al. 2005, Lane et al. 1999, Momoi et al. 2008). Reduced fetal blood flow may be the principal mechanism of action for some adverse pregnancy outcomes (e.g., birth weight).
  - e. It was hypothesized that adverse pregnancy outcomes might be attributable to first trimester nausea (Stein and Susser 1991). Some women experience nausea during the first trimester of pregnancy, which can be a predictor of a healthy pregnancy. Nausea may discourage some women from drinking coffee during pregnancy. Conversely, women who do not experience nausea may be more likely to continue their habitual caffeine intake. Consequently, the positive association between high caffeine intake and adverse pregnancy outcomes could be confounded by nausea. However, this hypothesis has not been supported by empirical studies (Fenster et al., 1991; Gianelli, 2003).

4. Reduced Fetal Weight and Growth.
  - a. Many studies have reported an association between coffee consumption during pregnancy and low birth weight.
  - b. Several meta-analyses over the past two decades have evaluated the risk of low birth weight from maternal consumption of coffee during pregnancy (Fernandes et al. 1998, Santos et al. 1998, Chen et al. 2014, Greenwood et al. 2014, Rhee et al. 2015).
    - (1) Fernandez reported a greater than 50% increased risk of low birth weight in children whose mothers consumed 1 strong cup of coffee per day during pregnancy (Fernandes 1998).
    - (2) Santos reported that aggregated results show an average decrease in birth weight of nearly 43 grams among newborns of the heaviest caffeine-consuming mothers (Santos et al. 2008).
    - (3) Chen reported that higher caffeine intake during pregnancy was associated with a higher risk of delivering low birth weight infants. In the dose-response analysis, each 100-mg/day increment in maternal caffeine intake (around one cup of coffee) was associated with 13% (RR 1.13, 95% CI 1.06 -1.21) higher risk of low birth weight. The authors concluded that these findings support recommendations to restrict caffeine intake during pregnancy (Chen et al. 2014).
    - (4) Greenwood found similarly and concluded that there is no identifiable threshold below which the association is not apparent. Their results confirm the precautionary guidance adopted by countries recommending limiting coffee/ caffeine consumption during pregnancy (Greenwood 2014).
    - (5) Most recently, Rhee confirmed an increased risk of low birth weight among newborns in association with maternal consumption of caffeine during pregnancy. Comparing the highest versus lowest level of caffeine intake during pregnancy resulted in a 38% increased risk of low birth weight (Rhee et al. 2015).
    - (6) These meta-analyses consistently show adverse effects on birth weight at coffee/caffeine consumption levels below the reputedly safe maximum levels cited by some authorities.

5. **Pregnancy Loss Including Spontaneous Abortion and Stillbirth**
  - a. The findings of studies concerning the association between maternal caffeine consumption during pregnancy and spontaneous abortion mirror those for low birth weight.
  - b. Four meta-analyses have evaluated the risk of spontaneous abortion from maternal consumption of coffee during pregnancy (Fernandes et al. 1998, Greenwood et al. 2014, Chen et al. 2015, Li et al. 2015).
    - (1) Fernandes found a 36% increased risk of spontaneous abortion for women who consumed caffeine during pregnancy (Fernandes et al. 1998).
    - (2) Greenwood reported a 14% increase in risk of spontaneous abortion and a 19% increase in risk of stillbirth among women who consumed caffeine during pregnancy. (Greenwood et al. 2014).
    - (3) Chen found a 7% increased risk of pregnancy loss among women who consumed 100 mg of caffeine per day (Chen et al. 2015).
    - (4) Li reported a dose-response relationship between maternal consumption of coffee/caffeine and pregnancy loss (Li, et al. 2015).
    - (5) As with low birth weight, these meta-analyses consistently show an association between maternal caffeine consumption and pregnancy loss, including spontaneous abortion and stillbirth. These studies strongly indicate that total abstinence from coffee/caffeine during pregnancy is warranted.
6. **Infertility and Infertility Treatment.**
  - a. Studies concerning the effects of coffee/caffeine consumption among couples receiving reproductive therapy have consistently reported adverse effects for both men and women for a variety of reproductive outcomes, including fertilization rates, number of eggs, number of viable embryos, and live births (Rooney and Doma, 2014; Tan et al., 2016).
  - b. It is routine clinical practice for couples seeking fertility treatment to be advised to abstain from caffeine beverages (Tan et al. 2016).
  - c. Adverse effects on fertility have been reported for both male and

- female fertility.
- d. Fertility effects in men.
    - (1) Coffee/caffeine consumption has been associated with sperm head and neck abnormalities (Jurekwicz et al., 2014a).
    - (2) Coffee/caffeine consumption has also been associated with chromosomal abnormalities in sperm (Robbins et al., 1997; Jurekwicz et al. 2014b).
    - (3) Coffee intake was found to have an independent negative effect on sperm quality in more than 1600 male patients undergoing assistive reproductive technologies (Wagatzky et al., 2012).
  - e. Fertility effects in women.
    - (1) Studies have repeatedly reported associations between coffee/caffeine consumption and delayed conception (Wilcox et al, 1988; Williams, 1990).
    - (2) An association between higher caffeine consumption and subfecundity was consistently observed for randomly selected samples of women in each of 5 European countries (Bolumar et al., 1997).
    - (3) As an adenosine receptor antagonist, caffeine may contribute to delayed conception due to altered ovulation and menstrual characteristics (Wesselink et al., 2016).

## **C. Behavioural Disruption**

- 1. Caffeine Withdrawal
  - a. Habitual consumption of caffeine beverages, notably coffee, leads to the development of physical dependence, evidenced by characteristic behavioural, physiological, and subjective withdrawal effects provoked by abstinence (Juliano & Griffiths, 2004).
  - b. The mechanism responsible for caffeine dependence is believed to involve adenosine upregulation resulting in hypersensitivity during abstinence (James, 2014). This hypothesis is consistent with the variety of symptoms experienced by habitual coffee/caffeine consumers during periods of abstinence.
  - c. Sleepiness, lethargy, and headache are common symptoms of

caffeine withdrawal (Evans & Griffiths, 1991; Galletly et al., 1989; Hughes, et al., 199; James, 1998; Lane, 2011; Lane & Phillips-Bute, 1998; Phillips-Bute & Lane, 1998). Cessation of as little as 100 mg (about 1 cup of coffee) per day, and possibly considerably less, can produce symptoms (Lieberman et al., 1987; Smit & Rogers, 2000).

- d. Symptoms are felt within about 12-16 hours, and peak at around 24-48 hours, and generally abate within 3-5 days, but may persist for a week or more (James, 2012; Juliano & Griffiths, 2004).
- e. In addition to physical symptoms coffee/caffeine withdrawal is associated with decrements in mood and psychomotor/cognitive performance (James, 1998; James et al., 2005; Rogers et al., 2003, 2013; Yeomans et al., 2002).
- f. Decreases in psychomotor/cognitive performance not necessarily discernible to the individual are detectable after as little as 6-8 hours since caffeine was last ingested (Heatherley et al., 2005).
- g. Studies show that negative withdrawal effects (e.g., dysphoric mood, inattention, lethargy) are commonplace within the general population of coffee consumers (Griffiths et al., 1990; Hughes et al., 1991, 1992, 1993, 1998; Juliano & Griffiths, 2004).
- h. The occurrence of a syndrome of abstinence-induced withdrawal effects shows that habitual coffee/caffeine consumption encourages the development of physical dependence, which is a prototypic feature of addictive drugs, and for that reason coffee/caffeine may be said to be addictive.

## 2. Cognitive Function

- a. Despite widespread belief that coffee/caffeine enhances mood and cognitive performance, studies have shown that the perceived beneficial effects are almost entirely due to reversal of negative withdrawal effects, leaving the consumer with little or no net benefit from consuming coffee/caffeine (Heatherley et al, 2006; James, 1994, 1998; James et al., 2005; Judelson et al., 2005; Rogers et al., 2005).
- b. Most reports of reputed coffee-induced enhancement of psychomotor/cognitive performance failed to control for reversal of abstinence-induced negative withdrawal effects (James, 1994, 2004a, b). Conversely, study designs that control for withdrawal

and withdrawal reversal have consistently shown that coffee/caffeine has little or no net beneficial effect on cognitive performance in adults (James, 1998; James et al., 2005; Judelson et al., 2005; Rogers et al., 2005) or children (Heatherley et al, 2006).

3. Summary

- a. Contrary to popular belief that coffee/caffeine enhances psychomotor/cognitive performance, mood and performance are frequently disrupted, possibly daily, due to the negative effects of caffeine withdrawal.
- b. Any acute benefits to mood and cognition from coffee/caffeine are at best marginal compared to the recurring disruptive effects of withdrawal.
- c. Understanding of caffeine as an adenosine antagonist provides a strong biologically plausible explanation of coffee/caffeine and the interrelated phenomena of physical dependence, withdrawal, and reversal of withdrawal effects.

**D. Sleep**

1. Endogenous adenosine is known to have an important role in the induction of normal sleep. Consistent with its property as a potent adenosine antagonist, caffeine disrupts normal sleep processes, thereby encouraging wakefulness and insomnia (James & Keane, 2007).
  - a. Studies of animals and humans show that caffeine is disruptive to normal sleep functions, increasing latency-to-sleep (“insomnia”) and sleep fragmentation (difficulty remaining asleep).
  - b. The customary practice of coffee/caffeine consumers to restrict intake to the earlier part of the day and to abstain completely overnight is consistent with caffeine’s sleep-disruptive effects.
2. Knowledge of caffeine physical dependence, withdrawal, and reversal of withdrawal effects has provided new understanding of the dynamic role of caffeine beverages, notably, coffee, in the sleep-wake cycle (James & Keane, 2007).
  - a. The belief that caffeine is capable of restoring psychomotor/cognitive functions degraded by sleep loss and

fatigue derives from studies that failed to control for withdrawal and reversal of negative withdrawal effects.

- b. Caffeine withdrawal-induced sleepiness is reversible by ingesting coffee/caffeine, thereby creating the illusion of a net increase in wakefulness.
- c. When the negative effects of caffeine withdrawal are controlled, caffeine has been found to produce no restorative effects on mood and performance during periods of sleep loss and fatigue, and may even be disruptive when consumed during such states (James et al., 2005; Keane & James, 2008).

## **E. Children and Adolescents**

1. The increasing popularity of energy drinks has coincided with elevated rates of acute complications of caffeine overuse, including seizures, cardiac dysrhythmia, and heart failure among youth (Seifert et al., 2011). Risk of youth fatality appears to be increased when caffeine is combined with alcohol (e.g., mixing alcohol with energy drink) or when experiencing physical stress, such as may occur in high-intensity sports (James, 2014; Pettit & DeBarr, 2011; Schneider et al., 2011; Temple 2009).
2. As an adenosine antagonist, caffeine counteracts the somnogenic effects of alcohol and alcohol may lessen the anxiogenic effects of caffeine (Seifert et al., 2011). By offsetting the sedating effects of alcohol caffeine may reduce the sensation of intoxication, and reduced subjective intoxication can impair judgments about risky behaviour (e.g., drink-driving). Evidence suggests that compared to alcohol alone, the combination of alcohol and caffeine contributes to increased incidence of assaultive and other violent behaviour (Brache & Stockwell, 2011; Ferré & O'Brien, 2011; Howland & Rohsenow, 2012; Miller, 2008; O'Brien et al., 2008).
3. In a series of large epidemiological studies of adolescent consumption of caffeine from all sources including coffee, James and colleagues reported:
  - a. Associations between caffeine consumption and smoking, consumption of alcohol, in-class daytime sleepiness, and feelings of anger (Kristjansson et al., 2011).
  - b. An association between caffeine consumption and poorer academic performance, which was mediated by caffeine-induced daytime

- sleepiness (James et al., 2011).
- c. Higher rates of conduct disorders and violence among adolescents who consume more rather than less caffeine (Kristjansson et al., 2013).
  - d. A dose-response relationship between caffeine consumption from all sources and frequency of common physical complaints, including headaches, stomachaches, sleep problems, and low appetite (Kristjansson et al., 2014).
  - e. A strong association between adolescent caffeine consumption and the consumption of alcohol-caffeine mixtures, which in turn was associated with higher levels of drunkenness (Kristjansson et al., 2015).
  - f. An association between caffeine consumption and adolescent violence, which was mediated by caffeine-induced anger (James et al., 2015).
4. The role of caffeine as an adenosine antagonist has implications for how early caffeine consumption by children and adolescents influences later substance use. Evidence suggests that early exposure to caffeine increases the reinforcing effects of nicotine and other drugs (Cauli & Morelli, 2005). This is consistent with well-established epidemiological findings that caffeine consumption in human adult populations is robustly associated with cigarette smoking and consumption of alcohol. Exposure to caffeine may have lasting neuroadaptive effects that influence later substance-use behaviour. In that regard, early caffeine consumption by children and adolescents may serve as a “gateway” to increased use of nicotine, alcohol, and substances in general (James et al., 2011, 2015; Kristjansson et al., 2011; Reissig et al., 2009; Temple et al., 2009; Thombs et al., 2010).

## **F. Adverse Drug Interactions**

1. Taking account of the ubiquitous consumption of coffee/caffeine, it is inevitable that caffeine is widely consumed against a background of other drugs, including medications, nicotine, alcohol, and illicit drugs.
  - a. Studies indicate that dietary caffeine is capable of reducing the therapeutic efficacy of some medications, including benzodiazepines and some antibiotics (James, 1991, 1997).
  - b. Coffee consumption is known to be positively correlated with

cigarette smoking (Treur et al., 2016), and the evidence indicates reciprocal causation wherein coffee consumption encourages smoking (Brown et al., 1989; Emurian et al., 1982; Lane, 1996; Marshall et al., 1980; Tanda et al., 2000) and vice versa (Bjorngaard et al., 2017). Acknowledging that smoking is a cause of extensive harm to population health, coffee may be said to be causally responsible for smoking-related harm in equal proportion to coffee's influence in encouraging smoking.

### **G. Urinary Incontinence**

1. There is consistent epidemiological evidence supported by consistent evidence from intervention studies implicating coffee/caffeine as a cause of urinary incontinence.
  - a. Epidemiological studies have reported increased incidence of urinary incontinence associated with modest caffeine intake (the equivalent of approximately 2 cups of coffee/day) in men (Davis et al., 2013) and women (Gleason et al., 2013). In a prospective cohort study involving more than 65,000 men and women, Jura et al. (2011) reported that a fourth of the cases of urinary incontinence with highest caffeine intake would be eliminated if high caffeine intake were eliminated.
  - b. Intervention studies in which dietary caffeine was eliminated or reduced have reported decreased rates of urinary incontinence (Edelstein et al., 1984; James et al., 1989; Tomlinson et al., 1999).
2. The association between coffee/caffeine and urinary incontinence is consistent with the known diuretic effects of caffeine.

## **IV. Claimed Health Benefits**

### **A. Health Safety**

1. The European Food Safety Authority (EFSA) has rejected separate applications seeking approval for health claims made about coffee and protection of DNA (EFSA, 2011a, b, 2015).

2. The Food and Drug Administration (FDA) has rejected separate applications seeking approval for health claims made about green tea and cardiovascular disease (FDA, 2006) and green tea and cancer (FDA, 2011).

## **B. Antioxidants**

1. The basis of claims of benefit from coffee rests heavily on the presence of polyphenol antioxidants in coffee beverages. Antioxidants may have a role in the prevention of chronic diseases associated with oxidative stress, including cardiovascular diseases, cancers, type 2 diabetes, neurodegenerative diseases, and osteoporosis. Antioxidants are molecules that are believed to inhibit oxidative processes that produce unstable oxygen molecules (free radicals) that damage living cells.
2. The claim that coffee is health-protective due to its antioxidant content is an unproven hypothesis that has yet to be rigorously tested. There are no clinical-trial data showing that coffee is health-protective due to antioxidant content. Accordingly, from the available evidence, claims that antioxidants render coffee health-protective are exaggerated.
3. Coffee solid is a small fraction of a cup of coffee and the antioxidant content is a smaller fraction still. Health authorities advocate moderation in coffee consumption, which necessarily limits the potential of coffee as a source of dietary antioxidants.
4. The main dietary sources of antioxidants include whole fruits, berries, nuts, and vegetables. Coffee consumption has been reported to be associated with reduced dietary intake of fruits and vegetables (Freedman et al., 2012). Rather than being health-protective, coffee may be harmful in proportion to the extent that its consumption encourages lower intake of high-antioxidant whole foods.
5. Coffee consumption is correlated with smoking, alcohol consumption, and less physical activity (Freedman et al., 2012). Accordingly, any health-protective effect from the antioxidant content of coffee would need to exceed the harmful effects of coffee-related smoking and alcohol consumption for there to be a net health-protective effect from coffee.

6. Compared to whole foods in diet, coffee beverages are derived from roasting whole coffee beans, with a potential loss of antioxidant content in the final product. Mullen et al. (2011) reported the antioxidant activity of whole coffee fruit extracts to be up to 25-fold higher than the final product.
7. Despite having antioxidant properties, the aromatic hydrocarbons, cafestol and kahweol, in coffee beverages (Liang & Kitt, 2014) are known to increase serum total cholesterol in consumers (Corrêa et al., 2013; Strandhagen & Thelle, 2003).
8. The *net* health effect, if any, from antioxidant constituents of coffee remains unknown.

## V. Limitations of Epidemiology

### A. Epidemiologic Approaches

1. Epidemiological studies of coffee/caffeine have been mainly of three kinds: cohort studies in which outcomes for participants who have been exposed (or have had more exposure) to coffee/caffeine are compared to outcomes for participants who have had no (or less) exposure; case-control studies that compare the history of exposure among patients who have the disease or outcome of interest to the history of exposure among participants (controls) who do not have the disease or outcome of interest; and cross-sectional studies that compare at a specific point in time levels of disease or outcome of interest and accompanying levels of exposure to coffee/caffeine in a population.
2. Epidemiological studies of coffee/caffeine have been either prospective (participants are recruited before the outcome of interest has occurred) or retrospective (participants are recruited after the outcome of interest has occurred).
3. In common with nutritional epidemiology in general, epidemiological studies of coffee/caffeine share the weakness of not being able to infer causation from observed associations between outcomes and exposure to coffee/caffeine. This contrasts with the causal inferences that may be

derived from experimental intervention studies (randomized controlled clinical trials), in which outcomes (dependent variables) are observed in a systematic relation to controlled exposure (independent variable) (FDA, 1999).

4. The need for caution is possibly greater for studies of coffee/caffeine consumption than for almost any other health-related dietary component. This is because of what has been described as the “etiologic distance” (Turkheimer, 1998) between the putative causal variable (coffee/caffeine in this instance) and outcomes of interest (the common complex diseases that occur in later life). The decades-long consumption characteristic of older-aged coffee consumers is but one of countless potential biobehavioural variables that may or may not covary with coffee/caffeine consumption while simultaneously benefitting or harming health.
5. A pedagogic exercise in introductory epidemiology class is to ask students to imagine a population in which everyone is a smoker. Undoubtedly, cardiovascular diseases, cancers, and other common complex diseases would be rampant in that population due to the high levels of smoking exposure. Ironically, under those circumstances, epidemiologic method would be rendered essentially useless for identifying smoking as the cause of excess death and disability in that population. This is because differences in disease outcomes between individuals are discernible only when there is variation in the relevant exposure variables. Unlike the aforementioned example, smoking in the real world is typically below 50% of the population, creating the variation in exposure needed to identify it as a potential source of harm. Notably, the aforementioned illustration of smoking in a hypothetical population approximates the actual situation for coffee/caffeine with the proportion of coffee/caffeine consumers in the population being consistently high and sometimes close to 100% (de Leon et al., 2003). As such, it is unlikely that current epidemiologic methods are capable of unraveling the complex relationships between coffee/caffeine consumption, myriad other lifestyle and environmental variables, and disease.
6. A further limitation of epidemiologic studies is the acknowledged absence of good methods for measuring exposure, especially lifetime exposure, to coffee/caffeine. Consequently studies are subject to substantial exposure

misclassification, thereby undermining attempts to reliably estimate associations between exposure (coffee/caffeine consumption) and outcome (disease).

## **B. Confounder effects**

1. Epidemiological studies of coffee/caffeine are subject to profound problems of confounding from myriad variables. Confounders are thus “third” variables (e.g., behavioural habits, nutritional patterns, environmental exposures) that are correlated with key exposure and outcome variables, and thereby confound the meaning of the observed association between the principal exposure variable of interest and outcomes. Epidemiological studies typically employ statistical manipulations to adjust for confounder effects, which are subject to extreme limitations in nutritional epidemiology, especially with respect to coffee/caffeine consumption.
2. **Confounder misclassification.** Studies frequently rely on participant self-reports to measure potential confounders, and these are known to be subject to uncontrolled bias, resulting in confounder misclassification.
3. **Over-adjustment.** Schreiber et al. (1988) reported only cigarette smoking and gender as two key potential confounders that require adjustment in studies of associations between caffeine and disease. Yet, studies typically adjust for long lists of “potential” confounders, some of which (e.g., BP, serum cholesterol) are likely to be part of the causal mechanism responsible for coffee/caffeine-induced harmful effects. Not infrequently, harmful effects implicated by unadjusted results disappear or are reversed (i.e., deemed health “protective”) only after extensive statistical adjustment for potential confounders, as was the case in the widely-cited study by Freedman et al. (2012) of coffee/caffeine and mortality.
4. **Unobserved confounders.** Despite extensive adjustment for suspected confounders, no epidemiological study can be confident of having adjusted for all important confounders. In one study of coffee and cardiovascular disease, selenium was found to be an important confounder, but it has not been measured in other studies (Gyntelberg et al., 1995). In a study of age-related cognitive decline, level of intelligence measured

comprehensively in childhood was crucial for understanding the association between coffee consumption and rate of cognitive decline 60+ years later (Corley et al., 2010). This was the Lothian (Scotland) Birth Cohort study, which found that the reputedly protective association between coffee & cognitive decline was an artifact explained entirely by level of childhood intelligence, data that no other study of coffee and age-related cognitive decline has had available.

5. **Hydration.** Level of hydration is a potential confounder that has been overlooked in epidemiological studies of coffee/caffeine and associated health outcomes.
  - a. Hydration is essential for good health (Jequier & Constant, 2010; Lee et al., 2016; Popkin et al., 2010).
  - b. Coffee contains approximately 98-99% water (Lingle, 2011), and is therefore a source of hydration.
  - c. Water is the superior form of hydration compared to alternatives, including coffee (Popkin et al., 2006).
  - d. Acknowledging that adequate hydration is essential for good health and that coffee is inferior to water as a source of hydration, the consumption of coffee is harmful to health to the degree that it discourages consumption of water.

## VI. Summary

- A. Evidence indicates that near-universal lifelong coffee/caffeine consumption is harmful to population health. Adverse outcomes include cardiovascular disease and harm to reproductive health. Additionally, frequent episodes of caffeine withdrawal are disruptive to mood and cognition, coffee/caffeine is directly disruptive of sleep, caffeine interacts adversely with therapeutic drugs, coffee/caffeine is associated with urinary incontinence, and caffeine consumption represents a threat to the health and well-being of children and adolescents.
- B. The claimed benefits of coffee are based primarily on epidemiological studies that are ill-suited to deal with the complex methodological challenges associated with the life-long population-wide exposure that is characteristic of coffee/caffeine.
- C. The occurrence of a syndrome of abstinence-induced withdrawal effects shows that habitual coffee/caffeine consumption encourages the development of physical

dependence, which is a prototypic feature of addictive drugs, and for that reason coffee/caffeine may be said to be addictive.

- D. The population distribution of coffee/caffeine generally lacks a harm-free threshold.

## **VII. Conclusion**

Coffee/caffeine is addictive, harmful, and without an evident safe level of consumption.

# **EXHIBIT “B”**

## **Curriculum Vitae**

**Jack E. James, PhD**

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## Curriculum Vitae

### Jack E. James, PhD

#### Tertiary Qualifications

- Bachelor of Science (First Class Honours), University of New South Wales, Australia, 1971.
- Master of Psychology (Clinical), University of New South Wales, Australia, 1973.
- Doctor of Philosophy, University of Western Australia, 1976.  
Thesis title: *Behavioural Self-control of Stuttering Using Timeout from Speaking.*

#### Current Appointment

2012 (Feb.) - Present Professor, Department of Psychology  
Reykjavík University, Iceland

#### Previous Appointments

1998 - 2012 (Jan.) Professor Emeritus and Head (1998-2011), School of Psychology,  
National University of Ireland, Galway

1991 - 1998 Foundation Professor of Behavioural Health Sciences and Head  
(1993-1998), School of Behavioural Health Sciences  
La Trobe University, Melbourne

1983 - 1991 Senior Lecturer, School of Social Sciences  
Flinders University of South Australia, Adelaide, Australia

1978 - 1983 Lecturer, Department of Psychology  
University of Queensland, Brisbane, Australia

1977 - 1978 Lecturer, Department of Behavioural Sciences  
Lincoln Institute of Health Sciences, Melbourne, Australia

#### Biographical Sketch

Born and raised in Sydney, Australia, Jack completed university studies in psychology, biological sciences, social sciences, and humanities at the University of New South Wales, obtaining a BSc (Applied Psychology) degree with First Class Honours. In addition, he completed a Master's degree in clinical psychology, obtaining certification to practice professionally, and completed a PhD in experimental clinical psychology at the University of Western Australia. Concurrent with his PhD studies, he practiced professionally as a clinical psychologist with the Western Australian Ministry of Community Health.

In Australia, Jack held faculty positions at the Lincoln Institute of Health Sciences (Melbourne, Australia), the University of Queensland (Brisbane, Australia), and the Flinders University (Adelaide, Australia), where he taught psychology at both undergraduate and postgraduate levels. He has contributed extensively to curriculum design, especially in relation to postgraduate professional training. During the period of his academic career in Australia, his teaching and research activities in clinical psychology broadened to include behavioural medicine and health psychology.

In 1991, Jack was appointed Foundation Professor of Behavioural Health Sciences, La Trobe University, Melbourne. He led the development of university-based professional doctoral programs in health psychology. Additionally, he led the development and formation of the national College of Health Psychologists, an arm of the Australian Psychological Society, and was elected the College's Founding National President.

Jack relocated to Ireland in 1998 to take up the post of Professor and Head of the Department (now School) of Psychology, National University of Ireland, Galway, and relocated to Iceland in 2012 to become Professor of Psychology, Reykjavík University.

Jack was Founding Editor-in-Chief (2010 - 2014) of the *Journal of Caffeine Research* (New York: Mary Ann Liebert, Inc. Publishers).

His main research interests include health psychology, behavioural epidemiology, global health, psychophysiology (with particular reference to cardiovascular health), psychopharmacology (with particular reference to dietary caffeine), and applied behaviour analysis. He has been Principal Investigator of numerous research grants awarded by major granting bodies in Australia, Ireland, Iceland, and the European Union.

## PUBLICATIONS

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### **Books**

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