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August 15, 2018

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. 17

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. Jodi D. Stookey regarding unhealthy constituents of coffee beverages and confounding of coffee-cancer epidemiology studies by water:

1. Exhibit A - Opinions of Jodi D. Stookey (2017).

2. Exhibit B - Biosketch of Jodi D. Stookey.

Kindly include these materials of Dr. Jodi D. Stookey in the record for this rulemaking proceeding.

Very truly yours,

Raphael Metzger

RM:ip
encls: as specified

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EXHIBIT “A”

OPINIONS OF DR. JODI STOOKEY

I. The Human Diet

A. The human diet is complex, consisting of thousands of foods and beverages. (USDA Food Composition Database, available at https://ndb.nal.usda.gov/ndb/).

B. There are numerous interactions between dietary components. (Willett, W., *Nutritional Epidemiology* (3d ed. 2012).

C. Dietary component effects cannot be adequately assessed individually. (Willett, W., *Nutritional Epidemiology* (3d ed. 2012).

II. Beverages

A. Beverages are major constituents of the human diet. (Institute of Medicine, "Water," Chapter 4 in *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate*, National Academy of Sciences, 2005).

B. There are various types of beverages, most of which contain water. (USDA Food Composition Database)

C. Water-containing beverages include coffee, tea, milk, juices, sports drinks, soda, and various types of water. (USDA Food Composition Database)

III. Water Intake

A. "Water is the largest single constituent of the human body and is essential for cellular homeostasis and life." (IOM 2005).

B. Adequate Intake (AI) for men is 3.7 liters of total water per day, which includes about 3.0 liters (~13 cups) as total beverages, including drinking water. Adequate Intake for women is 2.7 liters of total water per day, which includes about 2.2 liters (~ 9 cups) as total beverages, including drinking water. (IOM 2005). Thus, most (approximately 80% of) dietary intake of water in the US is from beverages.

C. Humans evolved consuming water as the sole beverage.

D. An individual's water intake is determined by physiological and socio-environmental factors. (Greenleaf JE, "Dehydration-induced drinking in humans," *Fed. Proc.* 41(9):2509-2514 (1982); Greenleaf, JE, "Problem: thirst, drinking behavior, and involuntary dehydration," *Med Sci Sports Exerc.*24(6):645-656 (1992)).

IV. Dietary and Water Intake Assessment

A. Currently, only crude techniques are available for assessing usual dietary intake for population-based research. (Gandy J, "Water Intake: Validity of Population Assessment and Recommendations," *Eur. J. Nutr.* 54(Suppl 2):11-16 (2015)).

B. The available techniques are diet records, diet recalls, food frequency questionnaires, and biomarkers. (Willett 2012).

C. The available techniques may be adequate for comparatively ranking intake between individuals. (Willett 2012).

D. Dietary intake assessment techniques are inadequate to quantify intake of individual foods and beverages for population-based research studies. (Willett 2012).

E. Food frequency questionnaires do not include all sources of water intake and are therefore inadequate to determine total water intake and patterns of intake. (Willett 2012).

F. The available techniques are especially inadequate for assessing water intake. (Gandy 2015).

G. Water intake should be clearly defined as to type of water, absolute intake, and intake relative to other sources and individual water requirements. (Stookey 2008, Stookey 2012).

H. It is important to distinguish types of water including tap water, bottled water, filtered water, mineral water, carbonated water, and water from food and other beverages. (Wang, 1993, Taylor 1999, Stookey 2008, Stookey 2012).

I. It is also important to account for water quality, including both microbiological and chemical contamination of water. (Wang, 1993, Taylor 1999).

J. It is extremely difficult to accurately define and quantify water intake. (Gandy 2015).

V. Limitations of Nutritional Epidemiology

A. Most nutritional epidemiology studies are observational studies that are generally inadequate to determine causality. (FDA 2009; Cochrane GRADE http://training.cochrane.org/path/grade-approach-evaluating-quality-evidence-pathway (Accessed 2017)).

B. The currently available scientific evidence from nutritional epidemiology studies of beverage intake is especially weak and inadequate to make causal assessments. The IOM concluded the evidence was too weak to propose AI for preventing chronic disease. The AI was explicitly designed to prevent adverse effects of acute dehydration (IOM 2005)

C. Limitations to nutritional epidemiology include the need for large and representative populations; imprecise tools for exposure and outcome assessment; age, period and cohort effects (changes in individual consumption, lifestyles and social norms); lengthy followup periods for chronic diseases (decades for cancer effects), ethical constraints on exposing human subjects and privacy rights); the inability to control exposures as in experimental animal studies. (Willett 2012)

D. Nutritional epidemiology is subject to multiple confounders and types of bias, including measurement and selection bias, and effect modifiers (interactions). (Willett 2012)

E. For all these reasons, it is extremely difficult to isolate the effects of a single food or beverage.(Willett 2012)

VI. Coffee

A. Coffee is a beverage that is made by brewing roasted coffee beans, grounds or powder in water. People either buy ready-to-drink coffee or brew the beverage, drinking it "black" or with additives, e.g., creamers and sweeteners.(National Coffee Association of USA Inc., *National Coffee Drinking Trends 2016*)

B. The beverage commonly known as "coffee" is a liquid mixture that contains approximately 98-99% water and about 1-2% soluble constituents of brewed roasted coffee grounds or powder, along with optional additives. (USDA Food Composition Data Base)

C. "Coffee drinkers in the United States consume more than 18 million bags – or approximately 2 billion pounds – of coffee each year. Assuming that each pound of coffee is prepared with about 3 gallons of water, slightly more than 6 billion gallons of water are needed annually to quench the U.S. population's thirst for coffee. [Water] typically represents 98%-99% of the coffee beverage . . . ." [Lingle, T., The Coffee Brewing Handbook, 2nd edition, p. 36 (Specialty Coffee Association of America, 2011)].

D. More American adults drink coffee on a given day than any other beverage. Approximately 60% of Americans drink coffee. Average consumption is about three cups per day among coffee drinkers. (NCA 2016)

E. Gourmet Coffee Beverages include Traditional Coffee - Gourmet (traditional coffee drunk hot or iced, brewed from premium whole bean or ground varieties), Espresso-based beverages (which includes cappuccino, espresso, latte, café mocha, macchiato, flat white and caffè Americano), Iced/Frozen blended coffee (which includes iced and frozen blended coffee), Cold brew coffee (brewed without heat for a long period of time), and Iced coffee infused with Nitrogen (carbonated). (NCA 2016).

F. Coffee can be brewed using a drip coffee maker, an Espresso machine, a French press/plunger, a Moka stove top (octagonal Italian style brewer), a Percolator, a machine that uses a pre-measured, sealed disk or capsule of coffee to make a single cup, a Coffee strainer, a Pour over (e.g. Chemex), and by cold brewing (brewing without heat for a long period of time). (NCA 2016).

G. Coffee can be prepared using instant coffee (adding hot water to coffee granules, powder or syrup in a cup), or coffee concentrate (purchased in a bottle, prepared by adding water or milk). Coffee can also be purchased ready-to-drink in a bottle, can or carton. (NCA 2016).

H. An important factor affecting the constituents (and likely the health effects) of coffee beverages is whether they are prepared using a paper filter, because diterpenes (e.g., cafestol and kahweol), which increase blood cholesterol, are insoluble and do not pass through paper filters. (Urgert 1996, Urgert 1997)

I. Coffee is roasted to different degrees, typically light, medium and dark. 39% of Americans drink dark roast coffee, 63% drink medium roast coffee, 11% drink light roast coffee, and 6% don't know what roast type they drink. (NCA 2016).

J. Coffee contains several acids. (Balzer, H.H., "Acids in Coffee," Chapter 1B (pp. 18-32) in Clarke, R.J. and Vitzthum, O.G., eds., *Coffee: Recent Developments* (Blackwell Science 2001)). Acids impart a bitter taste to coffee beverages.

K. Because coffee beverages are bitter, many consumers add sweeteners and/or creamers (sometimes called "whiteners") to render their coffee more palatable. 47% of American coffee drinkers add sweeteners and whiteners to their coffee, 9% add only sweeteners, and 20% add only whiteners. (NCA 2016).

L. Coffee drinks are often consumed with flavor, whiteners or sweeteners added. When these are added, the coffee beverage contribute calories, fat and/or sugar. (USDA Food Composition Database)

M. To determine the caloric contribution of ready-to-drink coffee to consumers, researchers from the Centers for Disease Control and Prevention examined afternoon beverage purchases in New York City at two major coffee chains and estimated mean caloric content of almost 3,000 beverages (1,127 at Starbucks and

1,830 at Dunkin' Donuts). One-third of all beverage purchases at Starbucks were for brewed coffee or tea. Of the 377 customers who purchased brewed coffee or tea, almost 75% added milk or sugar. Half cream/half milk and whole milk were popular additions. Even minor modifications increased calories, and the mean caloric value of brewed coffee and tea purchases was estimated to be 38 kcal. Two-thirds of Starbucks customers ordered a blended coffee beverage. Milk-based drinks, such as lattes, were the most popular blended coffee beverage. More than half of these customers purchased more than 200 kcal in a single drink. At Starbucks, the category with the most calories (mean = 306) was the ice-blended beverage group, which represented 22% of blended coffee purchases. Only 20% of these customers chose the "light" option. 40% opted for whipped cream, which added 60 to 150 kcal to their beverages. 55% of these drinks had more than 300 calories. At Dunkin' Donuts most customers added milk and sugar to their coffee or tea (55%); only 10% added neither. The most popular blended coffee beverage (ice-blended) had the most calories. All the ice-blended beverages ordered had >200 kcal and 72% had >300 kcal). (Huang 2009). Thus, coffee beverages as consumed often have very high caloric contents due to the sweeteners and creamers or other whiteners added to the brew.

N. "Sugar-sweetened beverages are those that contain caloric sweeteners and include . . . teas and coffees to which caloric sweeteners have been added." (Centers for Disease Control, *The CDC Guide to Strategies for Reducing the Consumption of Sugar-Sweetened Beverages* (CDC 2010).

O. Sugar-sweetened beverages have been associated with multiple adverse health effects, including cardiovascular disease (Malik 2010, Sundborn 2014, Keller 2015, Malik 2015, Xi 2015), type 2 diabetes (Malik 2010, Bray 2014, Sundborn 2014, Imamura 2015, 2016), gout (Merriman 2014, Sundborn 2014), metabolic syndrome (Bray 2013), obesity (Te Morenga 2013, Bes-Rastrollo 2013, Bray 2014, Pereira 2014, Sundborn 2014, Trumbo 2014, Keller 2015, Malik 2015), tooth decay (Bassiouny 2012). Pathways explaining these associations are supported by short-term randomized controlled trials (Stookey 2016).

P. The sweeteners, creamers, and other additives that coffee companies and consumers add to coffee to make coffee palatable greatly increase intake of sugars and fats, which have been associated with multiple adverse health consequences. Coffee with sweeteners and creamers results in excess energy intake and higher glycemic index. Thus, such concoctions are generally not healthy beverage. (Stookey 2016)

Q. Many of the coffee companies in this case sell roasted coffee products that contain natural or artificial sweeteners and creamers that have a high caloric content. (Coffee companies' webpages). Coffee companies that sell ready-to-drink coffee sell coffee beverages that contain sweeteners and creamers. (AM/PM documents).

R. The roasted coffee products and coffee beverages sold by the coffee companies that contain sweeteners and creamers are not healthy beverages. Sound considerations of public health do not support the consumption of such beverages. (Stookey 2016).

VII. Confounding by Water

A. It is especially difficult, perhaps impossible, to determine whether any reductions in risks of cancer and chronic diseases reported in coffee epidemiology studies are due to the roasted coffee bean, as opposed to the manner in which coffee beverages are prepared and consumed. (De Koning Gans 2010). This is so because of the water content of coffee beverages.

B. Since the average coffee drinker consumes about 3 cups of coffee per day (NCA 2016), the average coffee drinker receives more than one-third of daily recommended water intake of 8 servings per day (Grandjean 2005) just from drinking coffee, without taking into account water intake from other beverages or foods. Coffee drinkers who consume 8 or more cups of coffee per day may receive their total daily recommended water intake from coffee alone. Thus, heavy coffee drinkers necessarily consume large volumes of water.

C. Increased consumption of water has been associated with decreased risks of cancer (Bar David 2004) and chronic diseases (Manz 2005, Manz 2007), and decreased water intake (dehydration) has been associated with increased risks of cancer and chronic diseases (Warren 1994, El-Sharkawy 2015).

D. In order to test for or characterize independent effects of coffee, studies must account for total water intake, pattern of beverage intake and individual water requirements. These studies need to check for complex non-linear relationships (U- or J-shaped associations) and interactions between beverage intake and variables that determine water intake requirements (including age, smoking, physical activity and health status). Because of the variability in individual water requirements (IOM 2005), it cannot be assumed that coffee effects will apply uniformly to all groups in the general population.

E. Randomized controlled studies of beverage effects are needed to confirm causality. Other study designs cannot control for the many variables that determine fluid intake or correlate with fluid intake, including unobserved, period- or cohort-specific factors.

F. Epidemiologic studies of coffee consumption have not been designed to determine whether any reductions in cancer or chronic diseases among coffee drinkers is due to the soluble constituents of coffee or is due to increased water intake. While more than a thousand epidemiology studies have been published regarding coffee and cancer, only a few studies have attempted to compare cancer risks from

consumption of coffee with consumption of water or water-containing beverages or control for total fluid (beverage) intake ((e.g. de Koning Gans 2010). No study has tested an effect of coffee, while also simultaneously accounting for total water intake, beverage pattern, and individual water intake requirements. Studies of coffee effects on chronic disease and mortality, to date, have not been designed to distinguish independent causal effects of coffee.

VIII. Confounding by Brewing

A. Almost all coffee beverages undergo a heat treatment process before consumption. The optimal temperature for brewing coffee is 195-205°F. (NCA website). While some consumers drink iced coffee, iced coffee is prepared by dissolving soluble constituents of roasted coffee in hot water and chilling the coffee brew.

B. Drinking water is contaminated to a greater or lesser degree with microbes (Allevi 2013, Ashbolt 2015, Farkas 2013, Ibekwe 2011, Jung 2014, Liu 2016, Rowny 2012, Sokolova 2015), including bacteria (Chao 2015, Furuhata 2015, Won 2013, Zanetti 2014), viruses (Borchardt 2012, Fongaro 2013, Gall 2015), fungi (Kelly 2004, Yamaguchi 2007, Hageskal 2008, Siqueira 2011, Al-Gabr 2014), and protozoa (Crockett 1997).

C. "Slightly more than 20% of the global cancer burden can currently be linked to infectious agents, including viruses, bacteria and parasites." (zur Hausen 2009). "Of these, the majority of the causative agents are viruses, which make up nearly two thirds of the infectious causes." (Caygill 2012, zur Hausen 2009).

D. A recent analysis identified the following types of cancer as having substantial infectious causes: non-cardia gastric carcinoma, cardia gastric carcinoma, carcinoma of liver, cervix uteri, vulva, anus, penis, vagina, oropharynx, oral cavity, larynx, nasopharynx, bladder, Hodgkin's lymphoma, gastric non-Hodgkin lymphoma, Burkitt's lymphoma, HCV-associated non-Hodgkin lymphoma, Adult T-cell leukemia and lymphoma, and Kaposi's sarcoma. (Plummer 2016). The fraction of these cancers combined that was attributable to infectious agents was 56.5%. (Plummer 2016).

E. Boiling water kills or inactivates viruses, bacteria, protozoa and other pathogens by using heat to damage structural components and disrupt essential life processes (e.g. denature proteins) (Sullivan 1971; Thraenhart 1991; Backer, 2002; Brown 2012; Clasen 2008). Boiling is not sterilization and is more accurately characterized as pasteurization, which kills those organisms that cause harm to humans -- not all organisms.

F. "Heat inactivation of microorganisms is exponential and follows the rules of first-order kinetics. Thus, thermal death is reached in less time when higher temperatures are used; lower temperatures are effective when a longer contact

time is used. Pasteurization uses this principle to kill enteric food pathogens and spoiling organisms at temperatures of 60°C-70°C, temperatures that are well below the boiling point. All common enteric pathogens are readily inactivated by heat, although the heat sensitivity of microorganisms varies. . . . [E]nteric pathogens are killed within seconds by boiling water and are killed rapidly at temperatures > 60°C." (Backer 2002).

G. Temperature has the highest effect on virus's survival in water since lower temperatures are the key to longer virus survival. The rate of protein, nucleic acid denaturation and chemical reactions that destroy the viral capsid are increased at higher temperatures, thus viruses will survive best at low temperatures. Hepatitis A, adenoviruses and paroviruses have the highest survival rate in low temperatures amongst enteric viruses. (Bosch 2007). Importantly, enteric viruses are inactivated by heating at 70°C for less than one minute (Sullivan 1971) and Hepatitis A Virus, a waterborne virus, is inactivated by heating at 85°C for less than a minute. (Thraenhart 1991).

H. Since the optimal temperature for brewing coffee is 195-205°F (90.6 - 96°C)(NCA website), most viruses, bacteria and other pathogens in drinking water are destroyed by brewing coffee. Since boiling or brewing coffee destroys most infectious organisms in water and since infectious organisms are major causes of human cancer, reduced risks of cancers reported in coffee epidemiology studies may be due to reduced consumption of microbial-contaminated water rather than coffee. This is especially true for cancers with a high attributable fraction of infectious cause, such as liver cancer (73.4%) and nasopharyngeal cancer (95.5%). (Plummer 2016). Since coffee-cancer epidemiology studies have not evaluated whether statistical reductions in cancer risk are due to coffee constituents or consumption of heat-treated water, it cannot be determined from the coffee-cancer epidemiologic literature whether any statistical reductions in cancer risk associated with consumption of coffee are due to coffee or due to heated water purification in brewing coffee.

IX. Water as a Risk Factor for Cancer

A. Epidemiologic studies have reported increased risks of cancer with decreased consumption of water (dehydration), as well as decreased risks of cancer with increased consumption of water. Studies have investigated such risks for overall cancer mortality, bladder cancer, colorectal cancer (including colon cancer and rectal cancer), breast cancer, gastric cancer, kidney cancer, and prostate cancer.

B. One review summarized this literature as follows: "These studies support the beneficial effect of water drinking on cancer prevention in addition to other lifestyle factors, such as smoking avoidance or cessation, moderation of alcohol consumption, and treatment or prevention of obesity." (Bar David, Y., et al., "Water Intake and Cancer Prevention," *J. Clin. Oncol.* 22(2):383-385 (2004)).

C. A study by government researchers used data from 1991 Medicare files to analyze the contribution of dehydration to mortality. They reported that Medicare beneficiaries hospitalized with dehydration had significantly increased risks of death from cancer compared to those without dehydration. Among those who died within 30 days of hospitalization, the risk of cancer mortality was more than tripled among those hospitalized with dehydration. Among those who died within one month to one year of hospitalization, the risk of cancer mortality was increased more than 1.5 times among those hospitalized with dehydration. (Warren, J.L., et al., "The Burden and Outcomes Associated with Dehydration Among US Elderly, 1991," *Am. J. Public Health* 84(8):1265-1269 (1994)).

D. Eight studies have reported decreased risks of bladder cancer with increased consumption of water. Israeli researchers reported a strong protective effect of tap water on bladder cancer in women. (Bitterman 1991). American researchers reported an 80% reduction of bladder cancer risk from tap water in Hawaiian women, with a significant dose response. (Wilkens 1996). Harvard researchers reported a 50% reduced risk of bladder cancer in men from water consumption, with a highly significant dose-response. (Michaud 1999). Serbian researchers reported a 48% reduced risk of bladder cancer from mineral water in men and women. (Radosavljevic 2003). A 53% reduced risk of bladder cancer with increased water intake was reported among Spanish men and women, with a highly significant dose-response. (Michaud 2007). Researchers from the University of Southern California reported a 10% reduction in bladder cancer in Los Angeles County among those who drank 6 or more glasses of water per day compared those drinking less than 1 glass of water per day. (Jiang 2008). Chinese researchers reported a 57% reduction in bladder cancer risk among those consumed 1500 ml of fluid per day, compared to those who consumed 750 ml of fluid per day. (Zhang 2010). Recently, American researchers reported a 25% reduced risk of bladder cancer in American women, with a statistically significant trend. (Zhou 2014). Increased water intake has been recommended as a means of preventing bladder cancer. (Moore 2009). It should also be noted that some studies have reported increased risks of bladder cancer in association with increased consumption of water, but most of these are studies of drinking water that was contaminated with various toxins, such as arsenic, chlorinated disinfection byproducts, and nitrites (Crump 1982; Morris 1995; Cantor 1997).

E. Several studies have reported decreased risks of colorectal cancer with increased consumption of water. Researchers from Seattle reported reductions in risk of colon cancer of 45% in women ($p = 0.004$) and 32% in men ($p = 0.16$). (Shannon 1996). American researchers reported that "higher consumption of . . . plain water [was] more common among controls" than among those with colon cancer. (Jacobs 1998). American researchers reported a significant 29% reduction in risk of colon cancer for consumption of > 4 to 6 cups of coffee per day (Slattery 1999). Taiwanese researchers reported reductions in risk of colorectal cancer from water consumption of 75% in women and 45% in men, with a highly significant dose-

response. (Tang 1999). American researchers also reported a 30% reduction in risk of colon cancer in men and women with increased consumption of water. (Murtaugh 2004). Spanish researchers reported a 65% reduced risk of colorectal cancer with increased consumption of water. (Solera Albero 2007). Finally, Jordanian researchers reported a 42% reduction in risk of rectal cancer associated with consumption of more than 4 cups per day. (Tayyem 2013).

F. A few studies have reported decreased risks of kidney cancer with increased consumption of water or total fluid intake. In the Nurses' Health Study and the Health Professionals Followup Study, risk of kidney cancer was reduced among those in the highest quartile of exposure to water (≥5 servings per day) (RR 0.83, 95% CI 0.47 - 1.48). (Lee 2006). In a study of the role of fluid and beverage intake, risk of kidney cancer was reduced in those who consumed more than one 8 oz. serving of bottled water per day, which was lower than the risk of those in the highest quartile of exposure to tap water not used to brew coffee or tea (> 4.5 8-oz. servings/day) (Hu 2009). In the Million Women Study, participants in the highest quintile of fluid intake had a reduced risk of kidney cancer on multivariate analysis; no data was provided specifically for water intake. (Allen 2011). In the Netherlands Cohort Study, a prospective cohort study of 120,852 participants aged 55-69, individuals who were in the highest quintile of fluid intake exposure had a reduced risk of kidney cancer on multivariate analysis. (Deckers 2014).

G. Studies have also reported decreased risks of some other cancers in association with water intake. A study from the United Kingdom reported a 79% reduction in the risk of breast cancer in water drinkers vs never water drinkers (Stookey 1997). Chinese researchers reported a 20% reduction in risk of gastric cancer comparing occasional versus never drinkers of water. (Li 1989). Recently, Argentinian researchers reported that subjects diagnosed with prostate cancer drank significantly less water than controls. (Pacheco 2016).

H. A randomized controlled trial was undertaken of healthy French young men who were smokers and drank little water. To be eligible, subjects had to have smoked 15 or more cigarettes per day for the past two years and had to drink no more than 1 liter of fluid and 500 mL water per day. Subjects were excluded if they regularly drank more than 12 grams of alcohol per day, or were taking or addicted to drugs. Eligible subjects were randomized to the test or control group, 31 men per group. Subjects assigned to the test group had to consume three 500 mL bottles daily of Evian mineral water in addition to their usual water intake for 50 days. At baseline and at the end of the study, subjects 24-hour urine samples were obtained. Urinary mutagenicity was significantly decreased in the intervention group, and a slight decrease in DNA adduct formation was observed between the intervention group and the control group, although the difference was not significant. The study provides some mechanistic support for a cancer preventive effect of water intake. (Buendia 2015).

X. Potential Confounding of Coffee Cancer Epidemiology Studies by Water

A. Some coffee epidemiology studies have reported decreased risks of certain cancers, e.g., liver cancer and endometrial cancer.

B. Water intake is a potential confounder of coffee cancer epidemiology studies for three reasons. First, coffee beverages contain approximately 99% water. Second, evidence suggests that water intake may be an independent risk factor for cancer: Third, dehydration has been associated with increased cancer risk.

C. Since increased water consumption has been reported to decrease human cancer risk and since water comprises approximately 99% of coffee beverages, it is essential for coffee cancer epidemiology studies to specify water sources in detail and control for water intake as a potential confounder and to make adjustments for water intake in multivariable logistic regression analyses. It therefore cannot be concluded that reduced rates of human cancer reported in coffee epidemiology studies are due to "coffee," i.e., the soluble coffee components that comprise approximately 1% of coffee beverages, rather than water, which constitutes approximately 99% of coffee beverages.

D. None of the hundreds of coffee cancer epidemiology studies control for total water and pattern of water intake. This is a major flaw in these studies that precludes assessment of cancer effects of coffee. "To provide meaningful results, reliable and valid instruments should be introduced to measure fluid intake in epidemiological studies. (Gofti-Larcohe *et al,* 2001). This is a particularly difficult task, since the fluid component of foods should also be considered. (Frenceschi 1993, 1995; Decarli 1996). Moreover, the separation of the effect of total fluid intake from that of individual beverages is difficult. (Altieri 2003). "No adjustment was made with regard to fluid intake by the cohort. In particular, consumption of tea and other beverages was not considered, even though such information was collected by their food-frequency questionnaire." (Lee 2011) In a multi-site investigation of fluid intake and risk of urothelial cell carcinomas in the European Prospective Investigation into Cancer and Nutrition (EPIC), European researchers "excluded centres that did not assess drinking water intake, because water intake is an important component of total fluid intake." (Ros 2010). In a recent meta-analysis of coffee consumption and urinary incontinence, researchers commented that the results of their study were limited by "several potential confounding factors such as parity, BMI, smoking and water intake." (Sun 2016).

XI. Epidemiology Studies Comparing Cancer Risks of Coffee and Water

A. Some epidemiologic studies compare cancer risks of coffee consumption with water consumption. If coffee were responsible for the reductions in cancer risk in such studies, effects of coffee that do not parallel effects of water intake would be expected. We might expect to see an inverse effect of coffee with no effect of

water. In the few studies that have compared cancer risks of coffee consumption and water intake, the inverse is seen: the risk of cancer associated with higher water intake is lower than the risk of cancer from high coffee consumption. This suggests that reduced risks of cancers observed in coffee epidemiology studies may be due to consumption of water rather than coffee.

B. In a population-based case-control study, the risk of bladder cancer in the highest consumption group of coffee was significantly increased by 60%, whereas risk was not associated with water intake. (Slattery 1988).

C. In a multi-center population-based case-control study involving 1,185 histopathologically confirmed cases of kidney cancer and 1,526 controls, highest coffee consumption more than doubled the risk of kidney cancer in women. The investigators found no association of kidney cancer with either water or total beverage consumption. (Wolk 1996).

D. In the Health Professionals Follow-up Study, total daily beverage intake was inversely associated with risk of bladder cancer. The inverse relationship was strongest for plain water. The investigators concluded that a high fluid intake, especially of plain water, is associated with a decreased risk of bladder cancer in men. (Michaud 1999).

E. In a population-based case-control study, risk of colon cancer was not associated with caffeinated and decaffeinated coffee, but was significantly decreased 19% for water. (OR 0.81, 95% CI 0.68 - 0.97).

F. In a case-control study of bladder cancer in Los Angeles County, consumption of 5 to 6 cups of coffee per day was not associated with bladder cancer risk, but drinking 4 to 5 glasses of water per day significantly reduced the risk of bladder cancer by about 25%. (Jiang 2008).

G. In a population-based case-control study, risk of kidney cancer was significantly increased among Canadians who drank more than 2½ cups of coffee per day, but risk of kidney cancer was not related to consumption of more than 4½ glasses of water per day. Thus, this study suggests that consumption of water confers a lower risk of kidney cancer than consumption of coffee. (Hu 2009).

H. In 2014 Chinese researchers published a meta-analysis of studies regarding total fluid intake and bladder cancer. Seventeen case-control studies and four cohort studies were included in the analysis. Comparing the highest and lowest level of intake, the risk of bladder cancer was significantly increased for consumption of coffee, but not for water. (Bai 2014).

XII. Effects of Coffee and Water Consumption on Cardiovascular Disease

A. Water intake is a potential confounder of coffee cardiovascular epidemiology studies for three reasons. First, coffee beverages contain approximately 99% water. Second, evidence suggests that water intake may be an independent risk factor for cardiovascular effects. Third, dehydration has been associated with increased risk of cardiovascular outcomes.

B. None of the studies that test effects of coffee on cardiovascular risk have controlled for total water intake and beverage pattern, accounting for water intake requirements.

C. In a longitudinal cohort study, adult atrial fibrillation patients with comorbid dehydration had significantly higher risks of ischemic stroke within 20 days post-discharge. (Swerdel 2016).

D. In a multicenter case-control study, those who consumed caffeine-containing medicines had more than double the risk of all hemorragic stroke. (Lee 2013).

E. In a multicenter case-crossover study, consumption of coffee doubled the risk of acute ischemic stroke in the hour after consumption. (Mostofsky 2010).

F. One meta-analysis regarding coffee consumption and coronary heart disease, reported a significantly increased risk of coronary heart disease. (Sofi 2007).

G. In a case-control study, consumption of 5 caffeinated drinks per day significantly increased the risk of intracerebral hemorrhage. (Feldmann 2005).

H. In the Adventist Health prospective cohort study, high versus low daily water intake reduced the risk of coronary heart disease by about half in men and women. A high versus low intake of fluids other than water doubled the risk of coronary heart disease in women. (Chan 2002).

I. In a case-control study, dehydration increased the risk of stroke five-fold among patients hospitalized for stroke. (Nadav 2002).

J. In a cohort study, consumption of 3 cups of coffee per day significantly increased the risk of thromboembolic stroke in Hawaiian men at high risk of cardiovascular disease. (Hakim 1998).

K. In a case-control study, consumption of coffee increased the risk of angina pectoris in a dose-response manner. (Palmer 1995).

L. In a longitudinal study, the risk of angina pectoris was not associated with coffee consumption in men, but was significantly increased in women. (Stensvold 1995).

M. Among Medicare beneficiaries, dehydration more than doubled the risk of cardiac mortality. (Warren 1994).

N. In a meta-analysis of 22 studies, consumption of 5 cups versus no coffee per day significantly increased the risk of myocardial infarction or coronary death. (Greenland 1993).

O. High circulating copeptin levels, a biomarker of dehydration, are associated with pulmonary arterial hypertension (Nickel 2013), coronary artery disease (Tasevska 2015), ischemic stroke (Katan 2009, Dong 2013, Wang 2014, Xu 2016), acute intracerebral hemorrhage (Zweifel 2010), aneurysmal subarachnoid hemorrhage (Zhu 2011), acute myocardial infarction (Khan, 2007).

XIII. Effects of Coffee and Water Consumption on Constipation

A. Water intake is a potential confounder of coffee constipation epidemiology studies for two reasons. First, coffee beverages contain approximately 99% water. Second, evidence suggests that low water intake may be an independent risk factor for constipation.

B. In the Nurses' Health Study, the highest intake of coffee was significantly associated with constipation in women. (Dukas 2003).

C. In the National Health and Nutrition Examination Survey, risk of constipation was increased with coffee and tea intake, but decreased with other beverages. (Sandler 1990).

XIV. Effects of Coffee and Water Consumption on Type 2 Diabetes

A. Water intake is a potential confounder of coffee type 2 diabetes studies for three reasons. First, coffee beverages contain approximately 99% water. Second, low water intake may be an independent risk factor for type 2 diabetes. Third, dehydration has been associated with increased risk of type 2 diabetes.

B. In a controlled trial, postprandial plasma glucose and insulin concentrations were higher after consumption of sugar-sweetened coffee than water. (Li 2017).

C. In the Women's Health Initiative cohort, the risk of Type 2 diabetes was increased for high vs low consumption of sugar-sweetened and artificially sweetened beverages, but substituting water for one serving of sweetened beverages was associated with a significant reduction in incident diabetes. (Huang 2017).

D. In a cross-sectional study, each cup of water consumed per day reduced the Type 2 diabetes risk score. (Carroll 2015).

E. In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, substituting one serving per day of water for sweetened beverages reduced the risk of Type 2 diabetes. (O'Connor 2015).

F. A meta-analysis of prospective cohort studies reported that coffee consumption reduced the risk of Type 2 Diabetes. (Jiang 2013).

G. In a longitudinal cohort study with 9 years followup, water intake was inversely and independently associated with risk of incident hyperglycemia in a dose-response manner. (Roussel 2011).

H. In a longitudinal analysis of community-dwelling older adults, hyperglycemia was found to progress to type 2 diabetes significantly faster in hyperglycemic people with evidence of cell dehydration (plasma hypertonicity). (Stookey 2004).

I. In a study of hospitalized Medicare beneficiaries, dehydration significantly increased risk of death from diabetes. (Warren 1994).

J. High circulating copeptin levels, a biomarker of dehydration, are associated with Type 2 diabetes (Enhörnung 2010, Wannamethee 2015, Guelinckx 2016).

XV. Effects of Coffee and Water Consumption on Metabolic Syndrome

A. "The metabolic syndrome is a cluster of complex metabolic disorders (defined as the presence of three or more of the five following medical conditions: elevated fasting plasma glucose, abdominal obesity, elevated blood pressure, high serum triglycerides, and low high-density lipoprotein (HDL) levels) that affects about 20-25% of the world's adult population." (Shang 2016).

B. Water intake is a potential confounder of coffee metabolic syndrome epidemiology studies for three reasons. First, coffee beverages contain approximately 99% water. Second, evidence suggests that low water intake may be an independent risk factor for metabolic syndrome. Third, dehydration has been associated with increased risk of metabolic syndrome.

C. None of the studies of coffee on metabolic syndrome control for total water intake and pattern of beverage sources, accounting for water intake requirements.

D. A meta-analysis of observational studies reported an inverse association between coffee consumption and risk of metabolic syndrome, but the study omitted a significantly positive study that satisfied the inclusion criteria. (Chiu 2007).

E. A Mendelian randomization study regarding coffee consumption and metabolic syndrome found no genetic evidence to support a causal relationship. (Nordestgaard 2015).

F. In the First National Health and Nutrition Examination Survey Epidemiologic Followup Study, increased consumption of coffee reduced the risk of diabetes, but only in participants who had lost weight. (Greenberg 2005).

G. In the Stanford A To Z weight loss intervention study, increased water intake reduced metabolic syndrome over a period of 12 months, independent of diet composition, activity and weight loss. (Stookey 2008).

H. In a randomized controlled trial, substituting water for sugar-sweetened beverages reduced the prevalence of metabolic syndrome in obese Mexican women. (Hernández-Cordero 2014).

I. High circulating copeptin levels, a biomarker of dehydration, are associated with metabolic syndrome (Saleem 2009, Vintilă 2016).

XVI. Effects of Coffee and Water Consumption on Obesity

A. Water intake is a potential confounder of coffee obesity epidemiology studies for three reasons. First, coffee beverages contain approximately 99% water. Second, evidence suggests that drinking caloric beverages other than drinking water and/or low total water intake may be an independent risk factor for obesity. Third, dehydration has been associated with obesity.

B. Studies of coffee effects on obesity have not specified the total water intake or beverage intake pattern of the participants. In these studies, it is not clear what the non-coffee consumers drank, or if coffee drinking was a flag for other health behaviors or weight loss.

C. Short-term experiments report that caffeinated and caloric beverages increase energy expenditure to a greater extent than plain water. However, the magnitude of increase in energy expenditure can be negated by the amount of calories consumed in the beverage (ie the caloric beverage results in positive energy balance, regardless of the higher rate of energy expenditure). (Stookey 2016)

D. A cohort study of almost 19,000 Norwegians reported a positive association between coffee consumption and BMI in both sexes. (Kamycheva 2002).

E. In the Nurses' Health Study, increased intake of caffeinated and decaffeinated coffee, and caffeine were inversely associated with weight gain over a 12-year period. (Lopez-Garcia 2006).

F. In a cross-sectional study, weight loss maintainers reportedly consumed significantly more cups of coffee and caffeinated beverages than participants in the general population. (Icken 2016).

G. Systematic reviews of studies of water intake and weight loss have concluded that increased water intake yields small, but significant weight loss, among dieters. (Dennis 2009, Daniels 2010, Muckelbauer 2013, Stookey 2016).

H. In a Mediterranean cohort study, the consumption of water instead of caffeinated coffee decreased the risk of obesity. Replacing one serving of coffee with one serving of water per day was related to a lower incidence of obesity and to greater weight loss over four years. (Fresán 2016).

I. In population-representative data (NHANES), obesity is associated with higher plasma tonicity (biomarker of dehydration). (Stookey 2007).

XVII. Effects of Coffee and Water Consumption on Parkinson's Disease

A. Water intake is a potential confounder of coffee Parkinson's epidemiology studies for two reasons. First, coffee beverages contain approximately 99% water. Second, evidence suggests that low water intake may be an independent risk factor for Parkinson's.

B. In a cross-sectional study, water intake was significantly lower in Parkinson's disease patients than controls. (Ueki 2004).

XVIII. Effects of Coffee and Water Consumption on Frailty

A. "Frailty is theoretically defined as a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday or acute stressors is compromised. In the absence of a gold standard, frailty has been operationally defined by Fried et al. as meeting three out of five phenotypic criteria indicating compromised energetics: low grip strength, low energy, slowed walking speed, low physical activity, and/or unintentional weight loss. (Xue 2011)

B. "Gradually diminishing physiological reserve in older adults, leading to presymptomatic and eventually symptomatic frailty, is associated with a range of adverse outcomes, including functional dependence and mortality. Multiple intermediates and pathways are thought to link fraily with disability and death." (Stookey 2004).

C. Water intake is a potential confounder of coffee frailty epidemiology studies for two reasons. First, coffee beverages contain approximately 99% water. Second, evidence suggests that dehydration is associated with frailty.

D. In a multi-center cross-sectional study, the risk of frailty was significantly reduced among elderly women in the highest quintile of coffee intake. (Kobayashi 2014).

E. In a longitudinal study, plasma hypertonicity was significantly associated with disability and mortality. (Stookey 2004).

F. Dehydration is a recognized risk factor for frailty. (McCrow 2016).

XIX. Effects of Coffee and Water Consumption on Mortality

A. Water intake is a potential confounder of coffee mortality studies for two reasons. First, coffee beverages contain approximately 99% water. Second, dehydration is consistently associated with mortality.

B. Variation in water intake and/or hydration status has not been considered as possible explanation for inconsistent effects of coffee on mortality across studies. For example, the inverse association reported by Freedman 2012 and the adverse association reported by (Kahn 1984).

C. In a prospective cohort study, low water intake was associated with increased mortality in nursing home residents. (Szafara 2012).

D. Many studies report increased mortality associated with dehydration (Stookey 2004; Darmon 2010; El-Sharkawy 2015; Figuero 2014; Funk 2010; Hoorn 2008; Johnson 2015; Martinot 2010; O'Neil 1990; Sylla 2015; Teno 2013; Wakefield 2009; Warren et al 1994; Weinburg 1994; van der Steen 2007; Uematsu 2014; Wilson 2013; Moudouni 2012; Wolff 2015).

XX. Copeptin as a Prognostic Marker for Mortality and Chronic Disease Risk

A. Hypertonicity, dehydration and copeptin have been recognized as diagnostic and prognostic markers to risk-stratify patients for many outcomes. (Stookey 2004; Katan 2008, Katan 2009).

B. "Copeptin and arginine vasopressin (AVP) are derived from a common precursor molecule and have equimolar secretion and response to osmotic, haemodynamic and stress-related stimuli. Plasma concentrations of copeptin and AVP in relation to serum osmolality are highly correlated. The physiological functions of AVP with respect to homeostasis of fluid balance, vascular tonus and regulation of the endocrine stress response are well known . . . . Quantification of AVP can be difficult, but copeptin is stable in plasma and can be easily measured with a sandwich immuno-assay. For this reason, copeptin has emerged as a promising marker for the diagnosis of AVP-dependent fluid disorders." (Christ-Crain 2016).

C. High circulating copeptin levels, a surrogate marker of arginine vasopressin, have been associated with numerous chronic diseases, including Type 2 diabetes (Enhörnung 2010, Wannamethee 2015, Guelinckx 2016), metabolic syndrome (Saleem 2009, Vintilă 2016), pulmonary arterial hypertension (Nickel 2013),

coronary artery disease (Tasevska 2015), ischemic stroke (Katan 2009, Dong 2013, Wang 2014, Xu 2016), acute intracerebral hemorrhage (Zweifel 2010), aneurysmal subarachnoid hemorrhage (Zhu 2011), acute myocardial infarction (Khan 2007), heart failure (Kelly 2008, Balling 2012, Balling 2014, Enhörnung 2015, Zabarovskaja 2017, Zhang 2017), decreased kidney function (Boertien 2013, Ponte 2015), chronic kidney disease (Zittema 2012, Tasevska 2016, Zittema 2017), cirrhosis (Moreno 2013), cancer (Belting 2012), and death (Zweifel 2010, Zhang 2012, Zhang 2013, Wang 2014, Enhörnung 2015, Ristagno 2015, Tasevska 2015, Guelinckx 2016, Krychtiuk 2017, Zhang 2017).

D. Decreasing water intake increases copeptin levels (Szinnai 2007) and increasing water intake decreases copeptin levels. (Sontrop 2015, Melander 2016, Lemetais 2017).

E. Since elevated copeptin is an independent risk factor for multiple chronic cardiovascular and metabolic diseases as well as mortality, since dehydration increases copeptin, and since increased hydration decreases copeptin, increased water intake among coffee drinkers is a biologically plausible explanation for the apparent reduction of chronic disease risk among coffee drinkers.

XXI. CONCLUSIONS

A. Studies have not established any independent causal or preventive effects of coffee on cancer, other chronic disease and mortality.

B. Coffee epidemiology studies have not accounted for water intake. This is a major limitation of these studies that precludes causal assessment and inference.

C. Inverse associations between coffee intake and chronic disease outcomes in observational epidemiologic studies may be attributable to increased water intake among coffee drinkers, rather than any effect of the roasted coffee bean, or to low water intake in non-coffee drinkers.

D. Some of the inverse associations between coffee intake and chronic disease outcomes may also be due to the boiling or brewing of water for coffee, which reduces microbiological contamination of water.

E. According to the Surgeon General, chronic diseases are the leading cause of death and disability in the United States, causing 7 out of 10 deaths each year, with heart disease, cancer, and stroke alone causing more than 50 percent of all deaths. (Healthy People 2020, https://www.healthypeople.gov/2020/about/foundation-health-measures/General-Health-Status, citing Heron MP, et al., “Deaths: Final Data for 2006. *Natl Vital Stat. Rep.* 57(14) (2009).

F. The excess calories, fat and sugar in many coffee beverages increase risk for the leading causes of death for consumers.

G. In the absence of any proven preventive effect of coffee on cancer or chronic disease, no appreciable health benefit can be attributed to coffee.

H. Therefore, coffee consumption is not supported by sound considerations of public health.

EXHIBIT “B”

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Stookey, Jodi J.D.	Epidemiologist
eRA COMMONS USER NAME JSTOOKEY	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of California, San Diego, CA	BA	1992	Anthropology
University of Sheffield, Ctr. For Human Nutrition, UK	MSc	1994	Human Nutrition
University of North Carolina, Chapel Hill, NC	PhD	2002	Nutrition & Epidemiology
Ctr. For the Study of Aging & Human Development, Duke University, Durham, NC	---	2003	Postdoctoral Training
Stanford Prevention Research. Ctr., Stanford, CA	---	2004	Postdoctoral Training

A. Positions and Honors

1992	Phi Beta Kappa, University of California, San Diego
1994 – 1996	Research Assistant, Center for Human Nutrition, University of Sheffield, UK
1994	Caroline Walker Trust Bursary Recipient, University of Sheffield, UK
1996 – 2002	Postdoctoral Trainee, Carolina Population Center, UNC Chapel Hill
1996 – 2000	NRSA support, UNC Chapel Hill
1996	Member American Society of Nutrition
1999	Instructor, Masters level introduction to Nutrition Epidemiology, UNC Chapel Hill
2000 – 2002	Research Assistant, Carolina Population Center, UNC Chapel Hill
2000	Institute of Nutrition, Nutritional Graduate Fellowship for 2000/2001
2001	A. Hughes Bryan Outstanding Doctoral Award, UNC Chapel Hill
2002	Theta Chapter, Delta Omega Society, UNC Chapel Hill
2002 – 2003	NRSA Postdoctoral Fellow, Center for the Study of Aging and Human Development, Duke University
2003 – 2005	NRSA Postdoctoral Fellow, Stanford Prevention Research Center
2006	Assistant Staff Scientist, Children's Hospital of Oakland Research Institute
2006	Sigma Xi, The Scientific Research Society
2009	Danone Research & Development, Waters Scientific Advisory Board
2011	Epidemiologist, Maternal, Child & Adolescent Health, San Francisco Department of Public Health
2013	Member American Physiological Society
2013	Editorial Board, Beverages

B. Selected peer reviewed publications (in chronological order).

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