Comments to the 2015 Dietary Guidelines Advisory Committee

Submitted by: Center for Science in the Public Interest 1220 L Street, N.W., Suite 300 Washington, D.C. 20036

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The Center for Science in the Public Interest (CSPI) thanks the 2015 Dietary Guidelines Advisory Committee (DGAC) for the opportunity to submit comments on the **Subcommittee** (SC) request 5-1: Food safety. We respectfully submit the following comments on the safety of coffee and caffeine to the DGAC.

CSPI is a non-profit consumer education and advocacy organization that has been working to improve the public's health through better nutrition and food safety policies since 1971. CSPI's work is supported primarily by its 900,000 subscribers to its *Nutrition Action Healthletter*, the nation's largest-circulation health newsletter. CSPI is an independent organization that does not accept any government or corporate funding. We would be pleased to provide more information to the DGAC upon request. Please contact Laura MacCleery, Chief Attorney for Regulatory Affairs, at 202-777-8343 or lmaccleery_at_cspinet.org.

CSPI applauds the DGAC for considering the safety of coffee and caffeine. However, we have several concerns about the DGAC's statements regarding coffee and caffeine, both in general and as they pertain to risks during pregnancy. We will submit a separate comment regarding high dose caffeine, such as that contained in energy drinks, as well as the need for warnings and limitations regarding caffeine that is marketed in pure form. The issues addressed in the current comment are categorized as the DGAC has divided the topic.

1) Moderate consumption of coffee/caffeine in healthy adults: Careful communication about benefits of coffee and caffeine is essential.

We concur with the serious concerns voiced at the public meeting in July 2014 that pronouncements by the DGAC regarding the health benefits of coffee/caffeine may be used by industry to promote consumption of caffeine-containing foods and beverages where the scientific record does not justify such claims.

As we noted in our previous comments, there has been a proliferation of foods and beverages (including waffles and fruit juice¹) that contain added caffeine. We are concerned that the DGAC's message of moderation will not be an effective counter-weight to over-consumption if caffeine is permitted to be marketed as healthful. Claims on packages of caffeine-containing foods and beverages would have no reason to include appropriate disclaimers, and some consumers may wrongly assume that if a little caffeine is beneficial, lots of caffeine must be even better.

This risk is heightened by the fact that caffeine is mildly addictive, and habitual users become dependent, sometimes causing consumers to increase the amount consumed over time to achieve a similar effect in terms of alertness.² Thus, the DGAC must be careful not to encourage excess

consumption of caffeine, particularly in vulnerable populations. In addition, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) states that caffeine intoxication can occur "with low doses (e.g., 200 mg) in vulnerable individuals such as children, the elderly, or individuals who have not been exposed to caffeine previously."³

Pronouncements related to the benefits of coffee or caffeine should receive extraordinarily careful consideration prior to being publicly communicated. We urge the DGAC to exercise absolute precision when discussing health benefits of caffeine or coffee for each health outcome reviewed and to be clear when the scientific record is limited to either coffee or caffeine or when the data are confounded as to a particular health outcome. Coffee is a complex substance with many constituents, and the DGAC should not assume that particular health outcomes are related to caffeine. For example, as Committee member Frank Hu indicated, different health outcomes may be related to coffee versus caffeine – reduced risk of Type 2 diabetes and cardiovascular disease may be related to constituents of coffee, while reduced risk of neuro-degenerative diseases may be due to caffeine. In addition, as the slides note, coffee consumption can include high-calorie sweetened drinks with unhealthful components.

Moreover, several recent reviews suggest that caffeine consumption is disruptive of sleep.⁴ A 2011 review notes that "caffeine may produce detrimental effects on subsequent sleep, resulting in daytime sleepiness [following a period of enhanced alertness]" and that this "justifies a careful consideration of risks related to sleep deprivation in combination with caffeine consumption, especially in adolescents." Another 2008 review reports that "[1]arge sample and population-based studies indicate that regular daily dietary caffeine intake is associated with disturbed sleep and associated daytime sleepiness." The Committee should consider how to balance impacts on sleep and sleep consistency, and any consequent impacts on overall health, against the specifically demonstrated benefits as part of its message to the public. More investigation into the impacts on sleep is warranted, and patterns of sleep disturbance or sleep deprivation may countermand some of the demonstrated benefits in ways that are not now measured by research.

In sum, the Committee should carefully consider whether the benefits are sufficiently demonstrated for either coffee or caffeine regarding a particular health outcome, with full awareness that its public communication of these benefits could lead to additional marketing claims and excessive consumption of either coffee or caffeine. Any benefits that are sufficiently well demonstrated to be specifically enumerated in public statements should be couched in terms that clearly emphasize appropriate moderation in either caffeine or coffee consumption and should be clear that the information applies only to a subset of healthy, non-pregnant adults. The Committee should also consider whether the current literature regarding the impact of caffeine on healthy sleep and sleep patterns should be part of its public message favoring moderation.

The Committee's statements should also make clear that there is a wide variation in how people metabolize and react to caffeine, and what is "moderate" for one is not moderate for another. For example, some people feel anxious or experience insomnia after consuming only 150 mg of caffeine, whereas others do not experience caffeine-induced anxiety until consuming 450 mg; that difference in the impact of caffeine has been linked to polymorphisms in the ADORA2A gene.⁷

2) Moderate consumption of coffee/caffeine by pregnant women: The Committee is badly off-track.

CSPI is deeply concerned that the Committee may approve the following draft implication regarding caffeine and coffee consumption during pregnancy, as was proposed at the DGAC's meeting in September 2014: "Based on existing evidence, pregnant women, or women planning to become pregnant, should be cautious and adhere to current recommendations of the ACOG regarding caffeine consumption, and consume no more than 200 mg per day."

In fact, the evidence actually indicates that following that recommendation could increase the risk of adverse pregnancy outcomes and childhood leukemia. We urge the committee to instead adopt language similar to the clearer, stronger language that FDA did several decades ago in its 1981 brochure on "Caffeine and Pregnancy," which urged women to avoid consuming caffeine while pregnant.⁸

A. The data show that there is an incremental risk of adverse pregnancy outcomes associated with "moderate" levels of caffeine, not a safe threshold under which there is no effect.

The recently published meta-analysis by Greenwood, *et al*, concluded that there is evidence across multiple studies for an incremental dose-response curve for caffeine and multiple serious birth outcomes:

An increment of 100 g [sic: mg] caffeine was associated with a 14% (95% CI 10–19%) increase in risk of spontaneous abortion, 19% (5–35%) stillbirth, 2% (-2 to 6%) preterm delivery, 7% (1–12 %) low birth weight, and 10% (95% CI 6–14%) SGA [small for gestational age]."

As that states, for miscarriage and stillbirth, and only slightly less so with low birth weight and SGA, there is a consistent positive association across virtually all of the studies included in the meta-analysis.

While some of the underlying studies, as noted in the DGAC slides, do not adequately distinguish the effects of smoking and caffeine, the overall associations are troubling. As the authors note, adjustment for smoking and other differences among studies were not consistently associated with the observed differences in the results; the heterogeneity in results "mostly reflected variation in the size of the association, rather than whether there was an association."

The study authors also note the possibility that the associations may not be causal; it could be that women who are experiencing a healthy pregnancy are likely to consume less caffeine, and that caffeine has nothing to do with adverse outcomes among women who consume more caffeine. Among non-smokers at least, it seems equally plausible that coffee drinkers, overall, may also be healthier than the general population, as they tend to be employed and somewhat younger, according to the discussion at the DGAC July meeting. As women have been told by the influential public health authorities at the American College of Obstetricians and Gynecologists (ACOG) that 200 mg or less of caffeine per day while pregnant is "safe," many

women may be consuming caffeine out of habit or because they are working and fatigued, rather than less healthy overall or less healthy in their pregnancy.

Regardless, it is convincing that the association is causal, given, as the authors acknowledge, the plausible biological mechanisms, the evidence from animal studies, the mounting evidence from different observational human studies, and the dose-response slopes. Therefore pregnant women should be informed of the risks, and advice should err on the side of caution.

Furthermore, the authors note that there is no identifiable threshold below which the associations are not apparent. Although the authors state that the size of the associations are modest and might be explained by bias in study design or publication, the results of the meta-analysis for miscarriage in particular are striking in that the lowest estimated effect at the 95 percent confidence interval is a 10 percent increase in risk of miscarriage per 100 mg/caffeine.

That means that associations exist within the range for normal, even low, consumption of coffee, which contains on the order of 100 mg/cup, though the associations are stronger above 300 mg/day. In plain terms, however, the data show that for each cup of coffee consumed, there is a significantly increased risk of miscarriage, stillbirth, low birth weight and SGA.

There is some confusion about this in the slides presented at the September DGAC meeting. While Slide 15 indicates a Key Finding is that "Consumption of caffeine from various sources was associated with a small increased risk of miscarriage, stillbirth, low birth weight and small for gestational age births within the typical range of consumption (up to 300 mg per day)," Slide 16 says "**Higher caffeine intake** is associated with a small increased risk of miscarriage, stillbirth, low birth weight, and small for gestational age births." (*Emphasis added*.) Yet 100–200 mg is hardly "higher" intake.

To compound the confusion, the final slide says: "Based on existing evidence, pregnant women, or women planning to become pregnant, should be cautious and adhere to current recommendations of the ACOG regarding caffeine consumption, and consume no more than 200 mg per day." This conclusion is misleading. It implies that the recommendation is out of an excess of caution and not based on the numerical risks as analyzed by Greenwood, *et al*.

The DGAC's conclusion is also far too vague. Women should be informed of the increase in risks associated with 100 mg of caffeine, rather than being referred to a general policy by ACOG that is widely understood, on pregnancy advice sites, as indicating that there are *no* risks to pregnancy or pregnant women at levels of consumption of 200 mg/day or lower.¹¹

In reality, there is variability due to genetic polymorphisms and other factors in how different people metabolize and react to caffeine. In studies that pool both more and less susceptible women together, the risks to those women who are most susceptible can be missed. For example, one study found that without consideration of polymorphisms in CYP1A2, there were no significant differences in the risk of recurrent pregnancy loss, but the risk was significantly increased among women who had homozygous CYP1A2*1F alleles. 12

While in absolute terms the risk of adverse pregnancy outcomes may remain small, the magnitude of incremental risk being increased by a purely voluntary activity (*i.e.*, 14 percent for

miscarriage per 100 mg of caffeine, or 28 percent per two cups of coffee) is not. Consumption of coffee may confer some benefit to some pregnant women, however, some women may only be drinking coffee while pregnant out of longstanding habit or an addiction to caffeine – and those women might choose to act differently if they are advised of the risks.

In either case, the risk curves for miscarriage, stillbirth, low birth weight and SGA lacks a "threshold" as suggested by the current advice. These are all serious consequences: while the impact of having a miscarriage or stillbirth is obviously devastating, it is also the case that low birth weight and SGA are now known to carry serious health consequences, some of them lifelong, for children as well, as noted in the Greenwood meta analysis. SGA has been associated with "increased risk of perinatal mortality and morbidity, including perinatal asphyxia," as well as "increased incidence of obesity, hypertension, hypercholesterolemia, cardiovascular disease and type 2 diabetes." Furthermore, it only makes sense to include a safety factor in recommending a dose of caffeine well below the lowest observed effect level.

Pregnant women should be better informed of the risks of consuming caffeine. Therefore, a wiser, more protective approach given the increased risks for devastating health outcomes like miscarriage and stillbirth would be for the DGAC to indicate that "Pregnant women should avoid caffeine-containing foods and beverages."

We would also like to emphasize the inappropriateness of a DGAC endorsement of the ACOG statement regarding the risks to pregnant women. ACOG's document summarizes the issue as follows: "Moderate caffeine consumption (less than 200 mg per day) does not appear to be a major contributing factor in miscarriage or preterm birth. The relationship of caffeine to growth restriction remains undetermined. A final conclusion cannot be made at this time as to whether there is a correlation between high caffeine intake and miscarriage." ¹⁵

In fact, while the contribution of caffeine to the overall miscarriage rate may be small, that hardly disposes of the issue in how its risks should be communicated to pregnant women. For both moderate and high caffeine intake, the discussion in ACOG's analysis regarding the risk of miscarriage is remarkably thin. They consider only two recent studies, weighing only one positive study¹⁶ of the 25 identified in the Greenwood meta-analysis, against *the only negative study on miscarriage identified in the Greenwood meta-analysis*. That is hardly careful science or a weight-of-the-evidence approach. In addition, because the Greenwood analysis was so recently published, the ACOG guideline is out-of-date.

The bottom line is that the DCAG has no basis to conclude that the women shouldn't worry about a problem until they consume *more than* 200 mg/day, or to indicate that such concerns are based on mere "precaution." The data show an incremental dose-response risk at each 100 mg increase for serious consequences, like miscarriage, stillbirth, low birth weight, and having a baby who is small for their gestational age. Pregnant women deserve more careful consideration – and risk communication – than the Committee's approach currently reflects.

B. The DGAC must consider new research regarding the risk of childhood leukemia related to *coffee* consumption during pregnancy.

In order to fully address the relationship between coffee consumption and health, the subcommittee needs to consider the issue of a pregnant woman's coffee consumption and the resulting impact on the risk to her child of developing childhood leukemia. At the fourth meeting of the DGAC, a bibliography listing systematic reviews considered by Subcommittee 5 was provided, ¹⁷ but none of the readings address this issue.

The bibliography does not include the 2014 meta-analysis by Cheng, *et al.*, ¹⁸ which found a dose-related increased risk of childhood acute leukemia (both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) associated with maternal coffee consumption, nor does it include a 2011 meta-analysis by Milne, *et al*, ¹⁹ which also found an increased risk of childhood acute leukemia associated with maternal coffee consumption, especially among non-smoking mothers.

Dr. Peter Infante, a distinguished epidemiologist and former Director of the Office of Standards Review Health Standards Program at the Occupational Safety and Health Administration, has analyzed the literature on this issue and provided comments to the subcommittee. He concludes that "[e]pidemiologic studies and meta-analysis provide strong evidence of an association between maternal coffee consumption during pregnancy and CAL [childhood acute leukemia]."

Furthermore, Dr. Steven Bayard, a distinguished biostatistician with over 30 years of government experience, conducted a quantitative risk analysis that he submitted in separate comments to the committee. He calculated that the increased lifetime childhood acute leukemia risk due to maternal coffee drinking of 1–2 cups per day during pregnancy as 19 per 100,000. This is a substantial increase in risk well above the recognized threshold of concern of one additional cancer per million people.

Both of those eminent scientists have urged the Committee to consider the results of the metaanalyses and studies on maternal coffee consumption and childhood leukemia.

CSPI strongly agrees. We recommend that both Dr. Infante and Dr. Bayard be consulted as invited experts to SC 5. We are transmitting their CVs with this comment.

Notes

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¹ For example, Frava, a new drink which is 40 percent juice, contains 200 mg of caffeine in a 16-ounce bottle, or double the limit for cola-type beverages of 71 mgs of caffeine per 12 ounces. *See* http://www.drinkfrava.com/about-us/ (visited Nov. 12 2014); http://www.caffeineinformer.com/caffeine-content/frava-caffeinated-juice (providing caffeine content; visited Nov. 12, 2014).

² As FDA notes, "[s]ome studies show that caffeine causes a physical dependence or addiction." http://www.fda.gov/downloads/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandingover-the-countermedicines/ucm205286.pdf (visited Nov. 1, 2014).

³ The Diagnostic and Statistical Manual of Mental Disorders [hereinafter DSM-5] § 305.90. Am. Psychiatric Ass'n 5th ed. 2013.

⁴ See, e.g., Roehrs, T., Roth T. "Caffeine: Sleep and Daytime Sleepiness," Sleep Med Rev, 2008 Apr; 12 (2); 153-62; Snel, J., Lorist, MM. "Effects of Caffeine on Sleep and Cognition," Prog Brain Res, 2011; 190; 105-17; DOI 10.1016/B978-0-444-53817-8.

⁵ Snel, *ibid*.

- ¹¹ See Committee Opinion, American College of Obstetricians and Gynecologists, "Moderate Caffeine Consumption During Pregnancy," Number 462, August 2010, Reaffirmed 2013. http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Moderate-Caffeine-Consumption-During-Pregnancy (visited Nov. 1, 2014).
- ¹² See Fumihiro, S., et al. "Caffeine Intake, CYP1A2 Polymorphism and the Risk of Recurrent Pregnancy Loss," Mol. Hum. Reprod. 2005; 11(5): 357-360. DOI: 10.1093/molehr/gah175.
- ¹³ Greenwood, Darren C., et al.., at 732.
- ¹⁴ *Id*.
- ¹⁵ See http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Moderate-Caffeine-Consumption-During-Pregnancy (visited Nov. 1, 2014).
- ¹⁶ Weng, X., Odouli, R. and De-Kun, L. "Maternal Caffeine Consumption during Pregnancy and the Risk of Miscarriage: a Prospective Cohort Study." Amer J Obst Gyn. 2008; 198(3): 279.e1–279.e8. http://www.ajog.org/article/S0002-9378%2807%2902025-X/fulltext (visited Nov. 2, 2014).
- ¹⁷ See http://www.health.gov/dietaryguidelines/2015-BINDER/meeting4/sc5-lit-list.aspx.
- ¹⁸ Cheng J., Su H., Zhu R., *et al.* "Maternal Coffee Consumption during Pregnancy and Risk of Childhood Leukemia: a Metaanalysis." Am J Obst Gyn. 2014; 210: 151.e1-151.e10.
- ¹⁹ Milne E., Royle J., Bennett L., *et al.* "Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: results from an Australian case-control study." Cancer Causes Control. 2011; 22: 207-218.

⁶ Roehrs, *ibid*.

⁷ Rogers, PJ, *et al.* "Association of the Anxiogenic and Alerting Effects of Caffeine with ADORA2A and ADORA1 Polymorphisms and Habitual level of Caffeine Consumption," Neuropsychopharmacology, 2010 Aug 35(9); 1973-83. DOI 10.1038/npp.2010.71 Epub 2010 Jun 2.

⁸ "Caffeine and Pregnancy," HHS Publication No. (FDA) 81-1081 (1981).

⁹ Greenwood, Darren C., *et al.* Caffeine Intake during Pregnancy and Adverse Birth Outcomes: A Systematic Review and Dose-Response Meta-Analysis. Eur J Epidemiol. 2014; 29:725.