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August 28, 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 SUBMISSION NO. 18

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):

1. Comments of the Council for Education and Research on Toxics (CERT), to the Initial Statement of Reasons for Title 27, California Code of Regulations: Adoption of New Section 25704: Exposures to Listed Chemicals in Coffee Posing No Significant Risk

2. Exhibit A: Summary of IARC Coffee Working Group Meeting -- July 2016: Loomis D, Guyton KZ, Grosse Y, Lauby-Secretan B, El Ghiassassi F, Bouvard V, Benbrahim-Taallaa, L, Guha N, Mattock H, Straif K, "Carcinogenicity of drinking coffee, mate, and very hot beverages," *Lancet Oncol.* 17:877-878 (July 2016).

3. Exhibit B: International Agency for Research on Cancer: Q&A on Monographs Volume 116: Coffee, maté, and very hot beverages, from IARC website (July 2016).

4. Exhibit C: U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition, Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims (January 2009).

5. Exhibit D: Jiang W, Wu Y, Jiang X, "Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies," (2013) *Gynecol Oncol.* 129(3):620-629.

6. Exhibit E: *CERT v. Starbucks* Statement of Decision on Trial (Phase 1), September 11, 2015.

7. Exhibit F: *CERT v. Starbucks* Statement of Decision on Trial (Phase 2), May

8. Exhibit G: *CERT v. Starbucks* Order Declassifying and Unsealing Documents regarding the Relationship between Grocery Manufacturers' Association and its Members, February 16, 2018, with unsealed industry documents attached.

Kindly include CERT's Comments regarding the Initial Statement of Reasons and exhibits supporting CERT's Comments in the record for this rulemaking proceeding.

Very truly yours,

Raphael Metzger

RM:ip
encls: as specified

COMMENTS OF THE COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS (CERT) TO THE INITIAL STATEMENT OF REASONS FOR TITLE 27, CALIFORNIA CODE OF REGULATIONS: ADOPTION OF NEW SECTION 25704: EXPOSURES TO LISTED CHEMICALS IN COFFEE POSING NO SIGNIFICANT RISK

August 2018

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I. EXECUTIVE SUMMARY

The proposed regulation that would declare all heat-formed carcinogens in coffee to present no significant risk of cancer is ill-conceived, is unnecessary, is contrary to sound public health policy, is based on a misinterpretation of the IARC monograph on coffee, is contrary to accepted principles of science and causality, is contrary to OEHHA's own scientific determination that the NSRL for acrylamide is exceeded for all coffee drinkers, is contrary to the Voters' Intent in adopting Proposition 65, and would violate the Agency's own agreement in settling the *Duke II* case and set a bad precedent for future regulatory decisions.

Public health policy favors reducing carcinogens in the human diet, which is responsible for more than a third of human cancers. Acrylamide levels in coffee can easily be reduced so that the NSRL for acrylamide is not exceeded, while still maintaining good flavor and taste. The coffee industry should reduce acrylamide levels in coffee in lieu of giving Proposition 65 warnings, just as the potato chip industry reduced acrylamide in potato chips. [Declaration of Dr. Ronald L. Melnick].

The proposed regulation is not supported by quantitative risk assessments for any heat-formed carcinogens in coffee and therefore lacks scientific basis and rigor. Worse yet, the regulation is contrary to OEHHA's own scientific determination that the NSRL for acrylamide is exceeded for all coffee drinkers. [OEHHA, "Characterization of Acrylamide Intake from Certain Foods" (2005)].

The proposed regulation is based almost entirely on the IARC monograph on coffee. However, OEHHA misinterprets IARC's conclusions in the monograph in three critical respects.

First, contrary to OEHHA's Initial Statement of Reasons, IARC did not conclude that "coffee . . . has not been found to increase the risk of any cancers." [ISOR at p. 11] In fact, the IARC monograph reports significantly increased risks for some human cancers, especially childhood leukemia from maternal consumption of coffee during pregnancy. Further, significantly increased risks of cancer from consumption of coffee have been reported for many cancers, including bladder cancer, esophageal cancer, gastric cancer, laryngeal cancer, lung cancer, non-Hodgkin's lymphoma,

ovarian cancer, pancreatic cancer, prostate cancer, and total cancer. [Report of Dr. Peter Infante]

Second, OEHHA assumes that the inverse associations noted by IARC between coffee consumption and some cancers in observational studies are causal. However, IARC made no such determination. In fact, IARC concluded that "the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer . . . ." [Preamble to the IARC Monograph on Coffee]. Additionally, several high-quality epidemiological studies specifically designed to assess causality using a Mendelian randomization design – all of which were published after IARC completed its literature review of coffee and cancer – indicate that the inverse associations between coffee consumption and certain cancers are ***not*** causal, but are more likely the result of confounding and reverse causation.

Additionally, in the *CERT v. Starbucks* trial, the coffee industry's nutritional epidemiology expert, Dr. Dominik Alxeander, acknowledged that "given the considerable degree of exposure misclassification from self-reported dietary intake, correlation of certain foods with other dietary and lifestyle factors and the impact of bias and confounding, there is significant uncertainty surrounding the epidemiologic evidence for foods and cancer," including coffee; that "despite billions of research dollars and decades of research, few if any foods have been clearly causally associated with increasing or decreasing the risk of cancer;" that "[t]he interdependency of food consumption with other dietary and lifestyle factors, socioeconomic characteristics, clinical variables and genetic traits makes it difficult to isolate the independent effects of a specific food or food group . . . on disease risk"; and that he was unaware of any international organization, governmental authority, or any peer-reviewed article in a reputable journal that has concluded that coffee consumption prevents any chronic disease or cancer. Indeed, Dr. Alexander questioned whether it is possible to isolate in individual food component to determine causality for that food component, and admitted that "there's a big distinction between association and causation," that "[a]n association indicating a decreased risk of disease is not a health benefit unless the association is causal," that he had no

opinions on causation of health effects from consumption of coffee" and that he therefore was "not making a conclusion of causation regarding a health benefit" of coffee consumption. [Testimony of Dr. Dominik Alexander in the *CERT v. Starbucks* trial, September 7, 2017 a.m. at pp. 46-55].

Third, OEHHA relies upon IARC's discussion of antioxidants in coffee to implicitly conclude that this large class of diverse chemicals of widely differing biological activities and toxicities prevents human cancer and mechanistically explains the inverse associations between coffee consumption and certain cancers reported in some observational epidemiological studies. However, the antioxidant-cancer prevention hypothesis is extremely controversial and neither IARC nor any reputable scientific organization has concluded that antioxidants prevent human cancer. In fact, meta-analyses of randomized controlled trials of antioxidants and cancer show that antioxidants increase the risk of cancer, rather than reducing it. Moreover, the mechanism by which antioxidants are hypothesized to prevent cancer (destruction of free radicals) is not relevant to the mechanism by which acrylamide causes cancer. Thus, the lengthy discussion by OEHAA in the Initial Statement of Reasons regarding the supposed chemopreventive effects of antioxidants in coffee constitutes a hypothetical mechanism in search of a recently disproven effect.

Based on its erroneous assumption that coffee consumption causally reduces human cancer, OEHHA also erroneously concludes that drinking coffee would prevent three cancers in women: endometrial cancer, liver cancer, and breast cancer. However, the inverse association between coffee consumption and endometrial cancer is due to negative confounding by cigarette smoking due to its anti-estrogenic properties, as well as many other factors that reduce the risk of this cancer. Similarly, the inverse association between coffee consumption and liver cancer is largely due to confounding by liver disease (especially Hepatitis viruses) as well as reverse causation, and is therefore likely spurious, as many of the authors of the epidemiological studies have indicated. Likewise, the inverse association between coffee consumption and breast cancer is likely due, in part, to negative confounding by cigarette smoke due to its anti-estrogenic properties, as well as numerous other confounding factors that have been reported to reduce the risk of breast cancer in meta-analyses.

OEHHA's assertion that "[c]offee is unique in that it shows reductions in certain human cancers, has not been shown to increase any cancers, and is particularly rich in cancer chemopreventive compounds," (ISOR at page 11), is incorrect, because the same is true of tobacco. Indeed, just as coffee has been shown to significantly decrease the risk of endometrial cancer, breast cancer, melanoma, and thyroid cancer in some observational epidemiological studies, meta-analyses of observational studies have reported inverse associations for these cancers and cigarette smoking. Additionally, just like consumption of tobacco, the consumption of coffee has been shown to increase the risk of several cancers, identified above. Further, just as coffee contains "cancer chemopreventive compounds," so too does tobacco. Indeed, tobacco "contains significant concentrations of polyphenols and carotenoids, which are important naturally occurring anti-oxidants." Rodu B, Ou B, "The Antioxidant Properties of Tobacco," *Tobacco Sci.* (2000) 44:71-73.

OEHHA's assertion that coffee is unique "because it has been the subject of very high scientific interest for many years," (ISOR at pp. 11-12) is also incorrect , because more studies have been published regarding tobacco than coffee and it is only to be expected that the most widely consumed beverage in the world other than water would be extensively studied. Curiously, OEHHA does not mention the most important characteristic of coffee – that people drink coffee due to their addiction to caffeine, just as smokers smoke cigarettes due to addiction to nicotine in cigarettes.

In its zeal to tout the supposedly beneficial effects of coffee, OEHHA ignores many of coffee's proven adverse health effects, including known adverse psychological and physiological effects (caffeine intoxication, caffeine withdrawal, anxiety, sleep disorders, and problematic caffeine use), adverse pregnancy outcomes (reduced fetal weight and growth, pregnancy loss (including spontaneous abortion and stillbirth), and infertility; adverse effects in children and adolescents, and chronic diseases, including bone disease (osteoporosis and fractures), cardiovascular diseases (coronary heart disease, myocardial infarctoin, stroke, heart failure, and angina pectoris),, autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes), gastrointestinal disorders (constipation, gallstones, and gastroesophageal reflux disease), urological

conditions, (urolithiasis, lower urinary tract symptoms, urinary incontinence, and urinary tract infections), as well as mortality and acute cardiovascular events within 1 hour of consumption.

Nor does the Dietary Guidelines Advisory Committee Report prove the safety of coffee. It indicates coffee should not be consumed by susceptible individuals (e.g. pregnant women, children), that it can be consumed by healthy people only "in moderation," and it recommends that "individuals who do not consume caffeinated coffee should not start to consume it for health benefits alone."

Lastly, that coffee has been consumed by millions of people for many years cannot establish safety, as is readily shown by the butter flavoring diacetyl, whose extreme toxicity to the human respiratory system was coincidentally discovered the same year acrylamide was discovered in coffee.

The proposed regulation would also contravene the intent of the Voters, who, in adopting Proposition 65, intended it to apply to carcinogens in coffee. Indeed, pre-election materials of both proponents and opponents of the Initiative asserted that the Act would apply to carcinogens in coffee.

The proposed regulation is also unlawful, because it creates a categorical exemption for heat-formed carcinogens in coffee in the absence of quantitative cancer risk assessments supporting such. Indeed, both Judge Ronald Robie (who was the trial court judge in the *Duke II* case who invalidated former section 12721 on this ground and is now an appellate justice of the Third District Court of Appeal) and Judge Elihu Berle (who has tried the *CERT v. Starbucks* case), opined that Proposition 65 does not allow any categorical exemptions from the warning requirement of Health & Safety Code § 25249.6 based on a conclusion of no significant risk in the absence of a quantitative cancer risk assessment showing that the No Significant Risk Level for the listed carcinogen is not exceeded.

Finally, the proposed regulation violates the Settlement Agreement in the *Duke II* case, pursuant to which the Agency agreed, on December 23, 1992, "that any provision which is adopted after the date of this agreement to define the term 'no significant risk' of the Act for any food . . . shall be based upon specific numeric standards for the chemical . . . ."

For all of these reasons, the Council for Education and Research on Toxics and its Scientific Advisory Board respectfully urge OEHHA to withdraw its ill-conceived proposed regulation.

II. PRELIMINARY COMMENTS

A. CERT's Interest in the Proposed Regulation

The Council for Education and Research on Toxics (CERT) has long been at the forefront of protecting California consumers from the carcinogenic hazard of acrylamide in the human diet. CERT filed the first case to enforce Proposition 65 regarding acrylamide in french fries in 2002 - the very year that the carcinogen and neurotoxin known as acrylamide was first reported to be present in cooked foods. CERT co-litigated the next case regarding acrylamide in potato chips with the California Attorney General. Those cases were both successful and conferred substantial benefits to California consumers. In the former case, french fry manufacturers agreed to provide legally required cancer hazard warnings and in the latter case, potato chip manufacturers reduced acrylamide levels in potato chips in lieu of warning, which is, of course, the best result for public health. Since 2010 CERT has been litigating a case against the coffee industry regarding acrylamide in coffee (*CERT v. Starbucks, et al.,* Los Angeles Superior Court Case No. BC 435759), with the goal of persuading companies that produce coffee (i.e. coffee roasters) to reduce acrylamide levels in coffee, which is the largest source of acrylamide in the adult diet. CERT recently prevailed in this case and has settled with some small coffee companies, resulting in payments of civil penalties to OEHHA.

B. Contrary to Media Reports, the Judge in the *CERT v. Starbucks* Case Has Not Required Coffee Companies to Give Proposition 65 Warnings Regarding Coffee

On Page 5 of its Initial Statement of Reasons, OEHHA writes that "the effect of th[e] ruling [in the *CERT v. Starbucks* case] is that exposures to acrylamide in coffee may require Proposition 65 warnings." Contrary to countless media reports that the trial court ordered coffee companies to provide cancer warnings for coffee, the court has not ordered any of the numerous coffee companies that are defendants in the case to provide Proposition 65 warnings. Moreover, at no time since the court issued its Phase 2 Statement of Decision in the Spring of 2018 has CERT filed a motion seeking an injunction that would require any of the defendants to provide Proposition 65 warnings.

In fact, CERT recognizes that Proposition 65 warnings would unlikely be effective for coffee, because coffee is an addictive beverage due to its caffeine content, so consumers who do not want to consume acrylamide in coffee would likely be unable to stop drinking coffee. Indeed, cancer hazard warnings on coffee would probably be as effective in deterring consumers from drinking coffee as such warnings on packs of cigarettes were effective in deterring smokers from smoking.

For this reason, CERT's primary goal is not to have the coffee company defendants provide Proposition 65 warnings for coffee, but rather that they reduce the levels of acrylamide in their products to a degree that exposure of coffee drinkers to acrylamide would not exceed the No Significant Risk Level for this potent carcinogen. Thus, CERT only seeks Proposition 65 warnings for acrylamide in coffee from coffee roasters as a means of persuading them to reduce the acrylamide levels in their products in lieu of providing Proposition 65 warnings.

There is precedent for such action by product manufacturers, because potato chip manufacturers settled the Proposition 65 case brought against them by the California Attorney General by reducing the acrylamide content of potato chips in lieu of giving Proposition 65 warnings. CERT also believes that reduction of acrylamide levels in coffee would better serve public health than a proliferation of warnings to coffee drinkers who cannot heed such warnings due to their addiction to caffeine in the defendants' coffee products.

Shortly after the trial court issued its Phase 2 Statement of Decision, CERT filed a motion for a permanent prohibitory injunction against the defendants which, if granted, would enjoin them from continuing to violate Proposition 65 with respect to acrylamide in their products. However, that motion does not seek any order requiring the defendants to provide Proposition 65 warnings. Indeed, in that motion CERT explained that it did not seek to require Proposition 65 warnings:

> How Defendants choose to comply with Proposition 65 with respect to acrylamide in coffee is up to them. Defendants can either provide warnings that their products contain acrylamide, a chemical known to the State to cause cancer in compliance with OEHHA's warning regulations, or Defendants can get the acrylamide out of their coffee to avoid giving such cancer hazard warnings.

As previously mentioned, CERT would much prefer that the defendants exercise the latter option.

C. The Coffee Industry Can Easily Reduce Acrylamide Levels in Roasted Coffee

CERT considers it especially important to recognize that the coffee industry can easily reduce the acrylamide content of coffee to a degree that the No Significant Risk Level for acrylamide will not be exceeded. Indeed, numerous technologies have been developed that can be used to substantially reduce acrylamide levels in coffee without negatively affecting flavor or taste, just as the potato chip industry was able to reduce acrylamide levels in potato chips while maintaining taste.

The various technologies for reducing acrylamide in coffee that have been published in the peer-reviewed literature or that are the subject of patents and/or patent applications were comprehensively reviewed by Dr. Ronald L. Melnick, formerly Senior Toxicologist and Director of Special Programs in the Environmental Toxicology Program at the National Institute of Environmental Health Sciences and a senior scientist within the National Toxicology Program, who holds a Ph.D. in Food Science. In a declaration, Dr. Melnick concluded that the coffee industry could easily reduce acrylamide levels in coffee by at least 90% while maintaining good palatability. (Declaration of Dr. Ronald L. Melnick in Support of Plaintiff's Motion for Summary Adjudication of Defendants' Alternative Significant Risk Level ("ASRL") Defense, dated May 14, 2016).

Dr. Melnick also prepared a more recent report regarding technologies for reducing acrylamide in coffee in which he reviewed not only the published, peer-reviewed studies and patent applications/patents, but in which he also evaluated confidential internal reports of major coffee companies that conducted experiments assessing different technologies for reducing acrylamide in coffee. Dr. Melnick was able to review those confidential internal reports of the major coffee companies by signing a confidentiality agreement that he would not disclose any aspects of the defendants' confidential internal acrylamide reduction reports. Unfortunately, neither CERT nor its counsel can provide OEHHA with Dr. Melnick's report that discusses the confidential internal acrylamide reduction reports of the major coffee companies, because doing so would violate the protective order that the coffee companies obtained in the *CERT v. Starbucks* case, thereby

subjecting CERT and its counsel not only to monetary sanctions, but also to contempt charges.

As Dr. Melnick explains in his reports and as he testified at trial, the coffee industry can easily reduce acrylamide levels in coffee, because most of the acrylamide in coffee can be eliminated without changing the process by which coffee beans are roasted – a simpler solution than the potato chip industry's use of asparaginase to prevent the formation of acrylamide in potato chips (which is also viable for coffee). As Dr. Melnick testified at trial, after roasting coffee beans and packaging them in sealed foil bags or cans, the coffee industry need only "cure" the coffee by storing it at room temperature to reduce acrylamide levels. As Dr. Melnick explained at trial, so long as the containers are sealed and vacuum-packed, the coffee has a shelf life of up to two years and it will not stale because the air-tight bags and cans prevent oxidation from occurring. Studies have shown that simply by storing roasted coffee for 9 months yields a 40-50% reduction of acrylamide content, without negatively affecting coffee's favorable sensorial properties. Acrylamide is reduced simply by storing roasted coffee at room temperature in airtight containers, because the chemical reactions initiated during roasting continue during storage, resulting in degradation of acrylamide and the formation of additional flavor compounds.

D. The European Commission Regulates Acrylamide in Coffee

In 2017 the European Commission adopted Regulation 2017/2158, establishing measures and benchmark levels for the reduction of acrylamide in food, requiring Food Business Organizations to (1) identify the critical roast conditions to ensure minimal acrylamide formation within the target flavour profile; (2) incorporate control of roast conditions into a Pre-requisite Program as part of Good Manufacturing Practice and (3) consider the use of asparaginase treatment, insofar possible and effective to reduce the presence of acrylamide. [Commission Regulation (EU) 2017/2158, *Official J. EU* (November 20, 2017) L 304/24, available online at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2017.304.01.0024.01.ENG&toc=OJ:L:2017:304:TOC]

E. The Coffee Industry Concealed Information About the Feasibility of Acrylamide Reduction From the U.S. Food and Drug Administration

The coffee industry has long claimed that acrylamide cannot be reduced in coffee without negatively affecting palatability. However, this claim is belied by the industry's confidential reports.

The coffee industry claims that its position that acrylamide cannot be reduced in coffee has been accepted by the FDA, noting that the FDA's report *Guidance for Industry: Acrylamide in Foods* (March 2016), states that "a viable commercial process is not yet available." However, the only reference that the FDA provides in support of this conclusion is a report prepared by the European food and beverage industry: FoodDrinkEurope (FDE). 2013. Acrylamide Toolbox 2013; http://www.fooddrinkeurope.eu/uploads/publications_documents/AcrylamideToolbox_2013.pdf. The section of this report by the European food and beverage industry regarding coffee was written by Nestle, which is, of course, one of the largest coffee roasters in the world. Worse yet, the FDA's conclusion that there is no viable commercial process for reducing acrylamide in coffee was based on false representations by Nestle and Nestle's intentional concealment of acrylamide reduction information from the FDA. Fortuitously, the document which shows that Nestle intentionally concealed acrylamide reduction information from the FDA was recently declassified by the court in the *CERT v. Starbucks* case, so CERT and its counsel can provide OEHHA a copy of the document. The document was declassified by the court along with a few other confidential industry documents which show that the American coffee industry presented its position through the Grocery Manufacturers Association, so that coffee would not be the target of acrylamide reduction efforts. (The declassification order and the confidential industry documents are attached as Exhibit "G").

The critical document was produced by Nestle USA, Inc. and is titled "Progress and Development Guide." This document shows that Nestle was on notice of the unacceptable acrylamide content of its coffee products, and that the company made concerted efforts to conceal information regarding technologies for reducing acrylamide in coffee from the FDA. The document was authenticated by Mark F. Nelson, Ph.D., who was Nestle's Director of Regulatory and Scientific

Affairs. The document was a "Progress and Development Guide" for Nestle employee, Dr. John Mwangi, who was Nestle's Manager of Technical Regulator Affairs. The Progress and Development Guide was authored mostly by Dr. Mwangi himself, although some portions were either authored or approved by Dr. Nelson. The document was prepared in February 2011, as a review of events that had occurred during the just-completed year 2010. The first portion of the document is in two columns: an "Objectives" column listing Dr. Mwangi's objectives that had been laid out at the beginning of the year and a "Results" column consisting of text entries entered by Dr. Mwangi describing the activities that he had recently pursued relative to those objectives.

One of the objectives that Dr. Mwangi recorded in the Guide was to "Determine the impact of the safe harbor level MADL/ASRL on our products and advise the business accordingly." In the "Results" column, Dr. Mwangi reported that "The NSRL set for acrylamide as a carcinogen in California of .2 ug/day is so low that all our products will need a warning under Prop. 65." Another objective was to "Start a monitoring program for our products for acrylamide levels to get a baseline level for acrylamide." However, Dr. Mwangi reported in the "Results" column that Nestle delayed in testing any products at all, in order "to protect the data from discovery under Prop. 65."

It was decided that Dr. Mwangi would make a visit to the FDA in order to influence the FDA's regulatory position with regard to acrylamide. One of Nestle's goals was to encourage the FDA not to set guidance values for acrylamide in Nestle's products, which would have involved specific limitations on the level of acrylamide permitted. Instead, Nestle wanted the FDA to use the CIA Toolbox approach, which allowed coffee companies to measure acrylamide levels on their own, and to apply such methods to reduce it as they could. In other words, a regulatory framework that implemented the CIA Toolbox approach would not have involved any formal requirement that Nestle actually take steps to reduce the high levels of acrylamide it knew were in its coffee products.

Dr. Mwange made a trip to the FDA in May 2010 with Dr. Richard Stadler, who headed up the Contaminants and Biomarkers Group at the Nestlé Research Center from 1998 to 2003 and who, since 2004, has served as Head of the Quality Management Department at the Nestlé Product

Technology Centre in Orbe, Switzerland. See, Editorial announcing the appointment of Dr. Stadler as Editor of the journal *Food Additives and Contaminants.* Gilbert J, Phillips T, Anklam E, "Editorial," *Food Additives Contam.* (2009) 26(1):1. When they visited the FDA in May of 2010, Dr. Mwange and Dr. Stadler met with Dr. Nega Baru, Director of the Office of Food Safety in the Center for Food Safety and Applied Nutrition at the FDA.

In summarizing his meeting with the FDA, Dr. Mwange reported that although Nestle had initially offered to provide its data to the FDA, the company elected ***not*** to disclose its data "because of the risk of the data being discovered in the event of a lawsuit under Prop. 65." Dr. Mwangi also discussed Nestle's decision to withhold its acrylamide data from the FDA, writing that Nestle had generated most of the data on acrylamide, but that "we would not divulge any data that would be damaging to us rather we would be perceived [by FDA] as being proactive . . . ." Lastly, Dr. Mwangi reported that Nestle had retained a post-doctoral student to write a paper on acrylamide, but that he personally reviewed the paper, and stated that "The original draft contained data that would have played into the hands of the anti acrylamide lawyers." As a result, Dr. Mwangi altered the research paper to "correct the [e]rroneous impression created by the data."

Thus, the Progress and Development Guide clearly shows that Nestle USA's Manager of Technical Regulator Affairs, Dr. John Mwange, and its Nestle's Head of the Quality Management Department at the Nestlé Product Technology Centre in Orbe, Switzerland, Dr. Richard Stadler, concealed information from the FDA regarding the company's ability to reduce acrylamide, in order to deter the FDA from adopting regulatory limits for acrylamide in foods including coffee, all with the approval of Nestle USA's Director of Regulatory and Scientific Affairs, Dr. Mark Nelson.

It is regrettable that Nestle intentionally concealed information about reduction of acrylamide from the FDA and instead asserted (via the FDE Acrylamide Toolbox) the false claim that there is no viable commercial process for reducing acrylamide in coffee. By so doing, the coffee industry not only misled the FDA into believing that there is no viable commercial process for reducing acrylamide in coffee, but also deterred it from regulating acrylamide levels in food, including coffee.

III. GENERAL COMMENTS REGARDING THE PROPOSED REGULATION

A. Import of the IARC Monograph on Coffee

It appears that the primary source upon which OEHHA relies for the proposed regulation is the recently published monograph of the International Agency for Research on Cancer (IARC) on the Evaluation of Carcinogenic Risks to Humans: Drinking Coffee, Mate, and Very Hot Beverages," which provides information supporting IARC's conclusion reached in 2016 that coffee is not classifiable as to its carcinogenicity to humans.

It is important to consider what IARC does and what IARC does not do. Although the IARC monographs are titled "Evaluation of Carcinogenic Risks to Humans," IARC does ***not*** quantify risks of cancer to humans. There are two types of risk assessments: qualitative risk assessments and quantitative risk assessments. The IARC monographs are qualitative risk assessments, i.e., they identify cancer hazard rather than quantify cancer risk. IARC acknowledges this in its Monograph on Coffee in a Note to the Reader which states:

> The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

IARC has recently been subjected to much criticism by the chemical industry because IARC does not assess risks of human cancer, but rather assesses only whether chemicals can cause cancer. A recent response to these criticisms was prepared by the IARC Director and posted on IARC's website in January 2018. It states:

"IARC Monographs identify carcinogenic hazards and do not include a risk assessment

- The IARC monographs identify carcinogenic hazards i.e. those agents having the potential to cause cancer under some circumstances. This has led some to downplay the relevance of hazard identification and even to suggest the exercise is without value.

- The IARC Monographs program is explicit about the difference between hazard identification and risk assessment on its website.

- In fact, identifying carcinogenic hazards is a crucially important and necessary first step in risk assessment and management; it should be a "red flag" to those charged with protecting public health.

* * *

- In contrast to hazard identification, the specific exercise of risk assessment typically involves extrapolation beyond the observed data, employs a variety of statistical models and is based on anticipated levels of exposure and background cancer incidence rates that are often specific to a population or region.

- Following risk assessment, decisions on managing risk

encompass social, economic and political considerations. For the above reasons, IARC defers risk assessment and risk management to national and international bodies, restricting itself to provision of hazard identification as a scientific foundation to those subsequent steps.

- This area of debate brings into sharp relief the different and often imprecise ways the word risk is used and understood. A quantitative examination of the elevated risk associated with a given exposure is an integral part of hazard identification, as a support to causal inference. But this differs from the statistical exercises of quantitative risk assessment described above.

IARC Director, "IARC response to criticisms of the Monographs and the glyphosate evaluation," (January 2018), available online at: http://www.iarc.fr/en/media-centre/iarcnews/pdf/IARC_response_to_criticisms_of_the_Monographs_and_the_glyphosate_evaluation.pdf.

IARC is one of the authoritative bodies that OEHHA relies on in determining whether a chemical causes cancer and should be included on the Governor's List of Carcinogens, but OEHHA does not rely on IARC for determining risks of cancer, because IARC does not do quantitative cancer risk assessment. These analyses are done by the U.S. EPA and other agencies, including OEHHA. Thus, it is totally unreasonable for OEHHA to rely almost exclusively on the IARC monograph to propose a change to a health-based regulation by simply declaring that "exposures to listed chemicals in coffee created by and inherent in the processes of roasting coffee beans or brewing coffee do not pose a significant risk of cancer." While the IARC monographs are considered authoritative for identifying cancer hazard, they are clearly not reliable matter for determining risks of cancer.

B. Misinterpretation and Mischaracterization of IARC's Conclusions

The Initial Statement of Reasons (ISOR) acknowledges that IARC concluded that coffee is "not classifiable as to its carcinogenicity to humans," but fails to explain what this language means, although it is specifically defined in the IARC monograph. Further, the ISOR states that "IARC concluded there was inadequate evidence of an association between coffee drinking and [some] types of cancers," but fails to explain what this language means, although it too is specifically defined in the IARC monograph. The effect of these and other misleading statements in the ISOR suggest that IARC concluded that coffee does not cause human cancer, which is not what IARC concluded at all.

IARC's overall conclusion regarding the carcinogenicity of coffee is that coffee "is not classifiable as to its carcinogenicity to humans (Group 3)." The Preamble to the Monograph explains what this means: "An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations." Nowhere does the ISOR explain that IARC's conclusion "is not a determination of non-carcinogenicity." Rather, the ISOR provides the erroneous impression that coffee does not cause cancer, while not addressing the fact that a genotoxic carcinogen, such as acrylamide, is present at levels above the OEHHA-established NSRL.

Moreover, IARC's conclusion that coffee is not classifiable as to its carcinogenicity to humans is not news. IARC announced this overall conclusion after the meeting of the IARC Working Group on coffee two years ago, at which time IARC published a summary of the meeting in *Lancet Oncology*. (Exhibit "A") To be sure that its conclusion would not be misinterpreted, IARC posted a Q & A regarding its coffee evaluation on IARC's website at the time. (Exhibit "B") Item No. 10 posed the question: "Does the IARC classification mean that coffee is safe in terms of a potential link to cancer?" IARC answered this question as follows: "A Group 3 evaluation does not mean that a substance has been proven to be safe. It means that the existing scientific data do not enable a conclusion to be made about whether it causes cancer. . . ." (Exhibit "B")

Thus, contrary to the implication of the Initial Statement of Reasons, IARC has not concluded that coffee does not cause cancer. Nor did IARC conclude that coffee probably does not cause cancer, because had IARC done so, it would have classified coffee as "probably not carcinogenic to humans (Group 4)," rather than as unclassifiable as to its carcinogenicity to humans (Group 3).

As mentioned above, the Initial Statement of Reasons also states that "IARC concluded there was inadequate evidence of an association between coffee drinking and [certain] types of cancers," but fails to explain what this language means, thereby again giving the impression that coffee does not cause certain types of cancer. However, the Preamble explains that "Inadequate evidence of carcinogenicity" means that "the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer . . . ." Absent this explanation, the statement is misinterpreted to mean that coffee doesn't cause certain cancers, which is contrary to the definition in the Preamble.

C. Absence of Quantitative Cancer Risk Assessments for Carcinogens in Coffee

The Initial Statement of Reasons (ISOR) is more notable for what it doesn't contain than what it does contain. Glaringly absent from the ISOR is any data or discussion of the quantitative risk of cancer from exposure to heat-formed contaminants in coffee. The absence of any quantitative risk assessment for any of the listed chemicals in coffee renders the proposed regulation unscientific and unsupported by any of the data that is essential to support a regulation that purports to conclude no significant cancer risk. Indeed, the absence of any supporting quantitative cancer risk assessment grossly fails to satisfy the requirement that "the determination of whether a level of exposure to a chemical known to the state to cause cancer poses no significant risk for purposes of Section 25249.10(c) of the Act shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer." 27 C.C.R. § 25701(a). Thus, OEHHA's new and precedent-setting position is contrary to the objectives of Proposition 65 and could adversely affect future evaluations.

D. Omission of Quantitative Cancer Risk Assessment of Acrylamide in Coffee

Worse yet, the Initial Statement of Reasons ignores substantial scientific evidence that the No Significant Risk Level for exposure to at least one heat-formed listed carcinogen in coffee (acrylamide) is exceeded among coffee drinkers. In 2005 OEHHA published a report titled "Characterization of Acrylamide Intake from Certain Foods" in which the Agency evaluated whether consumption of coffee results in exposure to acrylamide above its No Significant Risk Level. In this report, OEHHA concluded:

> In all cases the lower bound on acrylamide intake (population-based intake) exceeded 1.0 µg/day. . . . Based on the lower end of the range of consumption . . . , average consumption of coffee with 4.1 ppb or more acrylamide concentration would exceed the NSRL. Since actual consumption by coffee drinkers is greater, a lower concentration would also exceed the ... NSRL. The lower bound on what this would be is 1.9 ppb. Of the individual brewed coffee samples tested by FDA, 19 of 20 had levels higher than 4.1 ppb. All were above 1.9 ppb. Thus, OEHHA is fairly confident that the NSRL is exceeded for coffee drinkers.

Thus, the proposed regulation that declares no significant risk for any listed carcinogen in coffee is contrary to OEHHA's own scientific findings and determination that the No Significant Risk Level (NSRL) for acrylamide is exceeded in coffee drinkers. In other words, the proposed regulation is not merely unsupported by any quantitative cancer risk assessment; it is contrary to OEHHA's own scientific determination!

E. Quantitative Assessments of the Risk of Cancer from Consumer Exposure to Acrylamide in Coffee By Experts for the Parties in the *CERT v. Starbucks* Case

The major issue litigated in the Phase 1 trial in *CERT v. Starbucks* was whether exposure to acrylamide in coffee exceeds the No Significant Risk Level for acrylamide. Expert testimony was proffered regarding the type of risk assessment necessary to make this determination and whether the risk assessment had to be of acrylamide, exposure to acrylamide from coffee, or of coffee as a mixture. Upon hearing testimony from highly qualified experts, the Honorable Elihu M. Berle correctly determined that quantitative cancer risk assessment is the only type of risk assessment that can properly be used to quantify the risk of cancer from exposure to a carcinogen in a mixture (e.g., acrylamide in coffee) and that the risk assessment had to be of exposure to the carcinogen in the mixture (acrylamide in coffee) rather than of the carcinogen alone or of the mixture (coffee). *CERT v. Starbucks* Statement of Decision on Trial (Phase 1), September 11, 2015. (Exhibit "E"))

OEHHA's determination that the No Significant Risk Level for acrylamide in coffee is exceeded for coffee drinkers was confirmed by a quantitative cancer risk assessment conducted by Dr. Steven Bayard for CERT and was presented in the Phase 1 trial of the *CERT v. Starbucks* case. On behalf of the coffee industry, Dr. Lorenz Rhomberg presented a quantitative cancer risk assessment of acrylamide in the Phase 2 trial of the *CERT v. Starbucks* case. Although Dr. Rhomberg's risk assessment was based on assumptions more favorable to the coffee industry than Dr. Bayard's analysis, Dr. Rhomberg's analysis also confirmed that the No Significant Risk Level for exposure to acrylamide from consumption of coffee is exceeded. Thus, the risk assessment experts for both CERT and the coffee industry agreed that the No Significant Risk Level for exposure to acrylamide from consumption of coffee is exceeded for coffee consumers, just as OEHHA concluded in its 2005 risk assessment. Thus, it appears that all quantitative assessments of the risk of cancer from exposure to acrylamide in coffee that have been undertaken uniformly show that the No Significant Risk Level for exposure to acrylamide is exceeded in coffee drinkers.

Expert testimony regarding risk assessment was presented during the Phase 1 trial by Dr. Steven P. Bayard and Dr. Ronald L. Melnick for CERT, and by Dr. F. Jay Murray for the defendants.

1. Testimony of CERT's Risk Assessment Experts Regarding Risk Assessment

When risk assessors determine the risk of cancer in the context of a chemical mixture, they identify the carcinogen(s) in the mixture and quantify the risk of human cancer presented by the carcinogen(s) in the mixture, unless the mixture itself has been deemed to be carcinogenic. [Testimony of Dr. Steven P. Bayard, October 27, 2014 a.m. at 12:12 - 23:14 (Exhibit "26"); Phase 1 Statement of Decision ¶ 40 (Exhibit "137")].

When Dr. Bayard has been tasked with quantifying the risk of cancer with respect to a chemical mixture, he always identified the carcinogen(s) in the mixture and quantified the risk of human cancer of the carcinogen(s) in the mixture. [Testimony of Dr. Steven Bayard, October 27, 2014 a.m. at 13:10-13 and 23:9-14 (Exhibit "26")].

A cancer risk assessment of a chemical in water or in another medium must be done of the carcinogen in the mixture (unless the mixture itself is itself carcinogenic), because the risk of cancer is due to exposure to the carcinogen. [Testimony of Dr. Steven Bayard, October 27, 2014 a.m. at 14:1-15:17, 23:9-14 (Exhibit "26"); Testimony of Dr. Ronald Melnick, October 7, 2014 a.m. at 11:2 - 12:2 (Exhibit "17")]

The only evidence of cancer risk assessments done by governmental agencies to assess the risk of cancer in the context of a chemical in water or in another medium is that they were all done as quantitative risk assessments, not as qualitative risk assessments. [Testimony of Dr. Steven Bayard, October 27, 2014 a.m. at 20:23 - 21:28 (Exhibit "26")].

All the cancer risk assessments of mixtures that Dr. Steven Bayard conducted throughout his years of service to federal governmental agencies as a risk assessor were quantitative cancer risk assessments of carcinogens, not qualitative risk assessments. [Testimony of Dr. Steven Bayard, October 27, 2014 a.m. at 12:12 - 20:22 and 22:1 - 23:14 (Exhibit "26")].

2. Testimony by the Coffee Industry's Expert Regarding Risk Assessment

Dr. Murray was unable to identify any cancer risk assessment of a chemical in water or another medium published by a governmental agency that was not a ***quantitative*** cancer risk assessment. [Testimony of F. Jay Murray, September 9, 2014 a.m. at 82:12-23 (Exhibit "3")].

Dr. Murray could not identify any risk assessment for a chemical in water or another medium that was published in a peer-reviewed journal that was not a ***quantitative*** cancer risk assessment. [Testimony of F. Jay Murray, September 9, 2014 a.m. at 82:17-23 (Exhibit "3")].

Dr. Murray could not identify any risk assessment for a chemical in water that had been commissioned by the EPA that was not a ***quantitative*** cancer risk assessment. [Testimony of F. Jay Murray, September 9, 2014 a.m. at 83:2-6 (Exhibit "3")].

3. Testimony of CERT's Experts Regarding Risk Assessment Science

It is not scientifically valid to assess the degree of cancer risk of a chemical in a mixture without quantifying the risk of cancer of the chemical in the mixture. [Testimony of Dr. Steven Bayard, October 27, 2014 a.m. at 19:19 - 20:8 (Exhibit "26"); Testimony of Dr. Ronald Melnick, October 7, 2014 a.m. at 11:2-12:2 (Exhibit "17")].

When a chemical mixture is not known to cause cancer, it is scientifically invalid to assume that a carcinogen in that chemical mixture does not increase the risk of cancer. One must calculate the quantitative risk from the carcinogen in the mixture in order to make this determination. [Testimony of Dr. Steven Bayard, October 27, 2014 a.m. at 27:7-15 (Exhibit "26"); Testimony of Dr. Steven Bayard, October 27, 2014 a.m. at 19:19 - 20:8 (Exhibit "26")].

4. Judge Berle's Conclusion Regarding Risk Assessment Science

After hearing the testimony of the parties' respective risk assessment experts during the Phase 1 trial, Judge Berle found that CERT's experts were correct. Judge Berle concluded:

> Since the level of exposure to a chemical listed as causing cancer (.e.g., acrylamide) must be determined by multiplying the level in question (stated in terms of a concentration of a chemical in a given medium) times the reasonably anticipated rate of exposure for an individual to the given medium of exposure measured over a lifetime of seventy years (CCR 25721(c)), the focus on the level of risk in this case must be based on the concentration of acrylamide in coffee. [Phase 1 Statement of Decision ¶ 41. (Exhibit "137")].

5. Dr. Bayard's Quantitative Risk Assessment of Acrylamide in Coffee

Dr. Steven Bayard has extensive experience in performing risk assessments, including conducting risk assessments for the U.S. Occupational Safety and Health Agency, the U.S. Environmental Protection Agency, the National Cancer Institute, and the Consumer Products Safety Commission. [Testimony of Dr. Steven P. Bayard, October 27, 2014 a.m. at 6:26-13:27 (Exhibit "26)].

Dr. Bayard did a quantitative cancer risk assessment in accordance with Proposition 65's regulations to determine whether the average rate of exposure to acrylamide from consumption of coffee by an average coffee drinker results in more than 1 case of cancer in an exposed population of 100,000, assuming lifetime exposure at such a level of dietary consumption. [Testimony of Dr. Steven P. Bayard, October 27, 2014 a.m. at 46:8-11 (Exhibit "26")].

Dr. Bayard used linearized multistage models without a threshold to extrapolate cancer effects from the higher doses of acrylamide in the National Toxicology Program's chronic rat and mouse bioassays to the levels of acrylamide to which consumers are exposed from consumption of coffee; he used the same method that the EPA used in its 2010 acrylamide risk assessment. [Testimony of Dr. Steven P. Bayard, October 27, 2014 a.m. at 62:2-27 and 63:5-8 (Exhibit "26")].

Dr. Bayard's use of a linear model without a carcinogenic threshold for his quantitative cancer risk assessment was appropriate because acrylamide is a genotoxic carcinogen that is metabolized to glycidamide and all of their toxicokinetic processes are linear, including formation of hemoglobin and DNA adducts, chromosome aberrations and tumor response. [Testimony of Dr. Stephen Rappaport, September 30, 2014 a.m. at 39:11-25, 62:10-23 and 65:20-27 (Exhibit "13"); Testimony of James L. Huff, October 22, 2014 a.m. at 82:14 - 83:18 (Exhibit "24"); Testimony of Dr. Steven P. Bayard, October 27, 2014 a.m. at 43:6-20, 44:10-28, 45:5-7, 45:21 - 46:4, 62:2-27 and 63:5-8 (Exhibit "26")].

Pursuant to Dr. Bayard's exposure analysis using data compiled by the FDA, the average concentration of acrylamide in brewed coffee was 7.35 parts per billion (ppb) or 7.35 micrograms per kilogram (ug/kg). [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 185:16 - 187:2 (Exhibit "27")].

Pursuant to Dr. Bayard's exposure analysis based on data published by the National Coffee Association, the average consumer drinks 3.08 cups of coffee per day. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 188:17-28 (Exhibit "27")].

Pursuant to Dr. Bayard's exposure analysis, the average size of a cup of coffee consumed is 10.66 ounces. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 189:1-19 (Exhibit "27")].

Pursuant to Dr. Bayard's exposure analysis, there are 2.22 micrograms of acrylamide per 10.66 ounce cup of coffee. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 190:13-27 (Exhibit "27")].

Dr. Bayard converted the 2.22 micrograms of acrylamide per cup of coffee into micrograms per kilogram body weight of human, because his cancer potency estimates were in units of micrograms per kilogram body weight of human, yielding 0.03 micrograms of acrylamide per kilogram body weight in one cup of coffee. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 191:4-14 (Exhibit "27")].

Dr. Bayard also determined percentiles of consumption based on NCA data, calculating that consumption of 1 cup of coffee per day represents the 9th percentile, consumption of 3.1 cups of coffee per day represents the 49th percentile, consumption of 5 cups of coffee per day represents the 71st percentile, and consumption of 7 cups of coffee per day represents the 85th percentile of consumption. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 194:4 - 195:3 (Exhibit "27")].

Pursuant to Dr. Bayard's quantitative cancer risk assessment, the amount of acrylamide from consumption of coffee by the average consumer that would result in one excess case of cancer per 100,000 exposed people is 0.26 micrograms of acrylamide per day assuming lifetime exposure. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 196:27 - 197:11 (Exhibit "27")].

Pursuant to Dr. Bayard's analysis, the amount of acrylamide from consumption of coffee by the average consumer that would result in one excess case of cancer per 100,000 people exposed is 0.34 micrograms of acrylamide per day, assuming exposure for 54 years (consumption from age 17 to age 70). [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 197:21 - 198:5 (Exhibit "27")].

Dr. Bayard calculated cancer risks based on the acrylamide risk assessment done by Cal-EPA in 2005 for average consumers drinking 3.1 cups of coffee per day to be 5 excess cancers per 100,000 for lifetime exposure, for consumers drinking 5 cups of coffee to be 8.6 excess cancers per 100,000, for consumers drinking 7 cups of coffee per day to be 12 excess cancers per 100,000, and for consumers drinking 9 cups of coffee per day to be 15.4 excess cancers per 100,000. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 199:11 200:2 (Exhibit "27")].

Dr. Bayard also calculated excess cancer risks based on the acrylamide risk assessment done by the United State Environmental Protection Agency in 2010 for consumers drinking 1 cup of coffee per day to be 1.2 excess cancers per 100,000 assuming lifetime consumption, for consumers drinking 3.1 cups of coffee per day to be 3.8 excess cancers per 100,000, for consumers drinking 5 cups of coffee to be 6.1 excess cancers per 100,000, for consumers drinking 7 cups of coffee per day to be 8.6 excess cancers per 100,000, and for consumers drinking 9 cups of coffee per day to be 11 excess cancers per 100,000, assuming lifetime exposure. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 200:17 - 201:9 (Exhibit "27")].

Dr. Bayard calculated the No Significant Risk Level of acrylamide for 54 years of coffee drinking based on Cal-EPA 2005 to be 1.3 ug/day. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 200:5-8 (Exhibit "27")].

Dr. Bayard calculated the No Significant Risk Level of acrylamide for 54 years of coffee drinking based on US-EPA 2010 to be 1.8 ug/ day. [Testimony of Dr. Steven P. Bayard, Oct. 27, 2014 p.m. at 201:9-15 (Exhibit "27")].

Dr. Bayard concluded that, assuming 70 years of exposure per the California standard, the amount of acrylamide from consumption of coffee that would produce one excess cancer per 100,000 is 0.26 micrograms per day. [Testimony of Dr. Steven P. Bayard, Oct. 27, 2014 p.m. at 204:25 - 205:5 (Exhibit "27")].

Dr. Bayard concluded that, based on his approach which excluded childhood consumption of coffee and therefore assumes 54 years of exposure, the amount of acrylamide from consumption of coffee that would result in one excess cancer per 100,000 is 0.34 micrograms per day. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 204:25 - 205:8 (Exhibit "27")].

Dr. Bayard concluded, for people drinking more than one cup of coffee per day from age 17 to 70, using his figures and human cancer potency values of governmental agencies, they would predict a greater than 1 in 100,000 cancer risk for acrylamide in coffee. [Testimony of Dr. Steven P. Bayard, Oct. 27, 2014 p.m. at 206:11 - 207:6 (Exhibit "27")].

Based on Dr. Bayard's risk assessment, exposure to acrylamide from consumption of just one half-cup of coffee per day would produce more than 1 excess cancer in an exposed population of 100,000 assuming lifetime exposure at such a low level of coffee consumption. [Testimony of Dr. Steven P. Bayard, October 27, 2014 p.m. at 207:7-25 (Exhibit "27")].

6. Dr. Rhomberg's Quantitative Risk Assessment of Acrylamide

In the Phase 2 trial, the coffee industry presented a quantitative cancer risk assessment of acrylamide by Dr. Lorenz Rhomberg.

Dr. Rhomberg calculated a No Significant Risk Level for acrylamide. [Testimony of Dr. Lorenz Rhomberg, Sept. 7, 2017 p.m. at 51:16-25 (Exhibit "110")].

Dr. Rhomberg did not calculate a No Significant Risk Level (NSRL) for exposure to acrylamide from drinking coffee. [Testimony of Dr. Lorenz Rhomberg, September 7, 2017 p.m. at 51:16-25 (Exhibit "110")].

Dr. Rhomberg did not calculate an Alternative Risk Level based on sound considerations of public health for exposure to acrylamide from consumption of coffee. Dr. Rhomberg does not consider himself qualified to do a risk assessment that quantitatively compares health benefits and health detriments. [Testimony of Dr. Lorenz Rhomberg, September 7, 2017 p.m. at 51:16-25 (Exhibit "110"); Testimony of Dr. Lorenz Rhomberg, September 8, 2017 a.m. at 65: 17-28 (Exhibit "111")].

Rather than calculating an Alternative Significant Risk Level (ASRL) based on sound considerations of public health, Dr. Rhomberg did a quantitative risk assessment for acrylamide and applied it to calculate the 10^{-4} (1 in 10,000) risk level for humans, because he was asked to do that. [Testimony of Dr. Lorenz Rhomberg, September 7, 2017 p.m. at 50:3-10 (Exhibit "110")].

In his final analysis Dr. Rhomberg excluded from his risk assessment pituitary gland adenomas, tunica vaginalis mesotheliomas, mammary gland benign fibroadenomas, uterine

adenocarcinomas, harderian gland tumors, central nervous system tumors of glial origin, forestomach papillomas in rats, heart schwannomas for one sex, pancreas islet cell adenomas, mononuclear cell leukemias, and clitoral gland tumors. [Testimony of Dr. Lorenz Rhomberg. September 8, 2017 a.m. at 4:11 - 8:19 and 72:28 - 75:9 (Exhibit "111")].

Data from all animal tumor sites should be evaluated for purposes of human cancer risk assessment. Since acrylamide induces carcinogenic responses at multiple sites in animals, a true evaluation of the potential cancer risk to humans is not to single out one target site, but to combine them to give an overall view or an estimate of the true carcinogenic risk to humans. [Testimony of Dr. James Huff, October 22, 2014 p.m. at 152:22 - 153:4 (Exhibit "25")]

Analyses of all tumor sites in animals should be combined for estimating cancer risk, because a more true response in an animal is gathered by combining all tumor sites to get a better estimate of the total carcinogenic effect of a chemical. This is an opinion that Dr. Huff and others have published. [Testimony of Dr. James Huff, Oct. 22, 2014 p.m. at 154:18 - 155:5 (Exhibit "25")].

Of those tumors that have been reported in animals exposed to acrylamide or its genotoxic metabolite glycidamide, tumors of the clitoral gland, the epididymis (testicular mesotheliomas), the forestomach, the heart, the testes, and the thyroid gland are all rare tumors. [Testimony of Dr. James Huff, October 22, 2014 a.m. at 86:10-15 (Exhibit "24")]. That acrylamide and glycidamide induced so many rare tumors in animals is significant with respect to human carcinogenic potential, because the occurrence of so many rare tumors in animals indicates that acrylamide would likely be carcinogenic in humans. [Testimony of Dr. James Huff, October 22, 2014 a.m. at 86:16-21 (Exhibit "24")]. The rare tumors induced by acrylamide in animals add to the evidence of a likely cancer hazard to humans. [Testimony of Dr. James Huff, October 22, 2014 a.m. at 69:3-9 (Exhibit "24")]. Dr. Huff has published articles to this effect along with his colleagues at the National Toxicology Program. [Testimony of Dr. James Huff, October 22, 2014 a.m. at 69:11-15 (Exhibit "24")].

Brain cancer (central nervous system cancer) is one of the rare tumors induced by glycidamide in rats. [Testimony of Dr. James Huff, October 22, 2014 a.m. at 76:26 - 77:6 (Exhibit

"24")]. That glycidamide induced central nervous system tumors in rats is significant, because this response is almost invariably induced by genotoxic chemicals such as acrylamide. Dr. Huff observed this from the many cancer bioassays that he directed when he was the head of the National Toxicology Program. This fact is also the subject of a publication by Dr. Jerry Rice, who concluded that acrylamide must be a genotoxic carcinogen because it is an animal neurocarcinogen. [Testimony of Dr. James Huff, Oct. 22, 2014 a.m. at 76:26 - 77:6 (Exhibit "24")]

The harderian gland is a sebaceous gland in the eye of animals that humans have a counterpart in their tear duct glands. [Testimony of Dr. James Huff, October 22, 2014 a.m. at 78:21-25 (Exhibit "24")]. The harderian gland of mice had the highest tumor rate of all the tumor sites. There was also concordance between this finding in the NTP bioassay studies and earlier cancer bioassays of acrylamide. [Testimony of Dr. James Huff, October 22, 2014 a.m. at 78:26 - 79:5 (Exhibit "24")]. Although humans don't have an exact counterpart of the harderian gland, the strong tumor response of the harderian gland of mice is relevant to humans because there is not strict concordance between the sites in animals and humans that cancers develop in response to carcinogenic exposure. For instance, benzene causes tumors of the zymbal gland in animals rather than leukemias it causes in humans. Additionally, a number of human carcinogens cause harderian gland tumors in animals. [Testimony of Dr. James Huff, October 22, 2014 a.m. at 83:28 - 84:14 (Exhibit "24")].

The most recent cancer risk assessment of acrylamide was published in 2015 by the European Food Safety Authority (EFSA), which based its cancer risk assessment exclusively on harderain gland tumors. [Testimony of Dr. Ronald Melnick, October 2, 2017 p.m. at 155:1-12 (Exhibit "108")]. In support of its exclusive use of mouse harderian gland tumors as the basis of its human cancer risk assessment, EFSA cited an article published by Dr. Melnick which observed that the harderian gland is a common target for epoxide-forming chemicals like acrylamide and therefore should not be disregarded in assessing human cancer risk. [Testimony of Dr. Ronald Melnick, October 2, 2017 p.m. at 157:9-159:27(Exhibit "108")].

Regardless of the tumor site, whether it is unique to rodents or not, the response of these organs to a chemical are indicative of a carcinogenic effect in humans and should not be ignored when attempting to protect the public health from a cancer hazard. [Testimony of Dr. James Huff, October 22, 2014 p.m. at 153:26 - 154:9 (Exhibit "25")]. This is an opinion that Dr. Huff published before this case. [Testimony of Dr. James Huff, October 22, 2014 p.m. at 154:10-12 (Exhibit "25")]. Governmental and other authorities support Dr. Huff's opinion, including the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), and the Environmental Protection Agency (EPA). [Testimony of Dr. James Huff, Oct. 22, 2014 p.m. at 154:13-17 (Exhibit "25")]

Dr. Rhomberg claimed that he excluded some animal tumors from his cancer his cancer risk assessment because they are benign, rather than malignant, tumors. However, benign tumors induced by chemicals in animals are relevant for judging human carcinogenicity, because most carcinogens rarely induce only benign tumors and benign tumors typically progress to malignancy. This is an opinion that Dr. Huff published before the *CERT v. Starbucks* case; it is also an opinion that is held by governmental and international agencies, including the NTP, FDA, EPA, IARC and others. [Testimony of Dr. James Huff, October 22, 2014 p.m. at 155:6 - 25 (Exhibit "25")]

In its 2005 cancer risk assessment, OEHHA included tumors from all sites, including the mammary gland (the fibroadenomas and adenocarcinomas), the thyroid gland, and the tunica mesotheliomas (the peritesticular mesotheliomas). [Testimony of Dr. Ronald Melnick, October 2, 2017 p.m. at 154:9-16 (Exhibit "108")].

In its 2010 cancer risk assessment the U.S. EPA also included the mammary fibroadenomas and adenocarcinomas and thyroid tumors in female rats, and the tunica vaginalis mesothelioma and thyroid gland tumors in male rats. [Testimony of Dr. Ronald Melnick, October 2, 2017 p.m. at 154:17-23 (Exhibit "108")].

7. Dr. Rhomberg's Misuse of Pharmacokinetic Factors

Under Proposition 65, "[h]uman cancer potency shall be derived from data on human or animal cancer potency" and "interspecies conversion of animal cancer potency to human cancer potency shall be determined by multiplying by a scaling factor equivalent to the ratio of human to animal bodyweight, taken to the one-fourth power." [27 C.C.R. §25703(a)(6) (Exh. "40")].

"When available data are of such quality that physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence, they may be used in the risk assessment for inter-species, inter-dose, and inter-route extrapolations." [27 C.C.R. § 25703(a)(7) (Exhibit "40"); Testimony of Dr. Ronald Melnick, Oct. 2, 2017 pm at 174:24-26. (Exh. "108")].

In lieu of using the default body weight scaling factor, Dr. Rhomberg used pharmacokinetic factors that could not be taken into account with confidence. [Testimony of Dr. Ronald Melnick, October 2, 2017 p.m. at 175:14-16 (Exhibit "108")].

Dr. Rhomberg relied on a pharmacokinetic model that had been proposed by Young et al, but that had not been validated. [Testimony of Dr. Ronald Melnick, October 2, 2017 p.m. at 181:9-12 (Exhibit "108")]. Dr. Rhomberg acknowledged that the pharmacokinetic model he relied on had not been independently validated. [Testimony of Dr. Lorenz Rhomberg, September 8, 2017 p.m. at 12:10-21 (Exhibit "112")].

The model that Dr. Rhomberg used was totally unreliable for determining a pharmacokinetic factor; it produced parameter values that are uncertain or unknown or not well characterized to fit available data. [Testimony of Dr. Ronald Melnick, October 2, 2017 p.m. at 170:22-24; 183:11-18 (Exhibit "108")].

The EPA determined that the Young pharmacokinetic model was not ready for use in risk assessment because it had multiple parameters to fit multiple data sets and no sensitivity analysis had been done. The EPA therefore rejected the model for rats and did not use it when the EPA did its risk assessment of acrylamide. [Testimony of Dr. Ronald Melnick, Oct. 2, 2017 p.m. at 175:14 -

178:5, 177:13-27 (Exh. "108")].

Dr. Rhomberg used data for acrylamide administered to animals by gavage as the basis for a pharmacokinetic adjustment factor when more appropriate data was available in animals from dietary consumption of acrylamide in drinking water, which is more like drinking coffee than having a single bolus of liquid injected into the stomach by gavage. [Testimony of Dr. Ronald Melnick, October 2, 2017 p.m. at 176:3-22, 180:1 - 181:1 (Exhibit "108")] Dr. Rhomberg's use of a pharmacokinetic factor was improper because the default factor had to be used in the absence of scientifically more appropriate information. [27 C.C.R. § 25703(a) (Exh. "40"); Testimony of Dr. Ronald Melnick, Oct. 2, 2017 p.m. at 183:19-184:2 (Exh. "108")].

Despite all the assumptions that he made and the exclusion of much animal tumor data that Dr. Rhomberg did to decrease cancer potency and thereby generate a higher level of acceptable risk, Dr. Rhomberg's quantitative cancer risk assessment of acrylamide yielded an increased risk of 1 cancer in 10,000 people exposed to acrylamide (1×10^{-4} risk) of 19 micrograms per day. This equates to a No Significant Risk Level for acrylamide in 100,000 people exposed to acrylamide (1×10^{-5} risk) of 1.9 micrograms of acrylamide per day. [Testimony of Dr. Lorenz Rhomberg, September 8, 2017 at 50:16 - 51:8, 63:1 - 67:11].

Thus, even Dr. Rhomberg's quantitative risk assessment (which was based on assumptions and exclusions that were much more favorable to the coffee industry than the assumptions used in the acrylamide cancer risk assessments of Dr. Bayard, OEHHA, and EFSA) indicated an increased risk of cancer for exposure to acrylamide from consumption of coffee that was almost 10 times OEHHA's Safe Harbor level of 0.2 micrograms per day.

Accordingly, all of the quantitative cancer risk assessments of acrylamide, including those of OEHHA, EFSA, Dr. Bayard and Dr. Rhomberg establish that the No Significant Risk Level for acrylamide is greatly exceeded among coffee drinkers.

F. Specious Scientific Reasoning

The Initial Statement of Reasons appears to conclude that exposure to heat-formed carcinogens in coffee cannot pose a significant risk of cancer, because coffee does not cause cancer. However, this conclusion is fallacious for at least two reasons.

First, IARC has not concluded that coffee does not cause cancer. Indeed, IARC has not even concluded that consumption of coffee probably does not cause cancer. Epidemiological studies do not have sufficient power to detect 10^{-5} cancer risk--the level established by OEHHA as the NSRL.

Second, merely because a substance (e.g. coffee) may not have been demonstrated to be carcinogenic does not establish that carcinogenic constituents or contaminants in that substance do not significantly increase the risk of cancer. U.S. Environmental Protection Agency, *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (US EPA, 2000). This is readily demonstrated by arsenic in water. Reasonable scientists would agree that uncontaminated water is not carcinogenic. However, it is equally true that reasonable scientists would agree that arsenic-contaminated water may significantly increase the risk of cancer, depending on the extent of arsenic contamination and the frequency and duration of consumption of such arsenic-contaminated water. OEHHA would not exempt arsenic-contaminated water from the no significant risk requirement of Proposition 65 absent a quantitative risk assessment demonstrating no significant cancer risk based on the level of arsenic contamination. Likewise, there is no scientifically valid basis to exempt heat-formed carcinogens in coffee from the no significant risk requirement of Proposition 65 absent quantitative risk assessments demonstrating that individual heat-formed carcinogens in coffee do not significantly increase the risk of cancer.

G. Epidemiological Studies Regarding Coffee Are Not Suitable to Evaluate the Risk of Cancer to Humans from Acrylamide and Other Carcinogens in Coffee

Acrylamide has no known human health benefit. Therefore, any positive health effect that has been associated with consumption of brewed coffee in epidemiological studies must therefore be due to constituents other than acrylamide. There is no evidence that acrylamide, which is classified by the International Agency for Research on Cancer as a probable human carcinogen, loses its carcinogenic potential when present in coffee.

The effect of coffee consumption on certain types of cancers has not been well studied, including adult leukemia and lymphoma. This is a critical gap in the scientific evidence, because exposures to other chemicals that are metabolized to epoxide intermediates by CYP2E1, the same human enzyme that metabolizes acrylamide to the DNA-reactive epoxide intermediate glycidamide, are associated with increased risk of leukemia and/or lymphomas in humans. Some of these known human carcinogens include 1,3-butadiene, ethylene oxide, trichloroethylene, and benzene. Melnick RL, "Carcinogenicity and mechanistic insights on the behavior of epoxides and epoxide-forming chemicals," *Ann. N. Y. Acad. Sci.* (2002) 982:177-189; International Agency for Research on Cancer, "Chemical Agents and Related Occupations," *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* Vol. 100F (IARC 2012); International Agency for Research on Cancer, "Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents," *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* Vol. 106 (IARC 2014).

Three fundamental issues that must be addressed when evaluating the carcinogenic effects of an agent in animals or in humans are: (1) reliable characterization of exposure, (2) the comparison of responses in exposed groups to an appropriate control or reference group, and (3) duration of exposure and follow-up. Food based questionnaires used to estimate past exposures are known to suffer from recall bias; this issue is especially problematic for cancer epidemiological studies, because cancer can take many years or even decades to manifest into a clinically recognized disease.

The most critical limitation in drawing conclusions about the cancer risk of acrylamide from epidemiological studies of coffee is the fact the reference group is also exposed to acrylamide. Because acrylamide is known to be present in several types of foods, including breads, cereals, potato chips, and french fries, as well as in cigarette smoke and roasted coffee, acrylamide exposure in the reference group may be similar to acrylamide exposure among coffee drinkers. The exposure of control or reference groups to acrylamide from sources other than coffee is a serious confounding factor in evaluating cancer risk of acrylamide in coffee. Consequently, it is not possible to make any reliable conclusion about cancer risk of acrylamide in coffee from available epidemiological studies of coffee drinkers. The only way the latter situation could be addressed is by quantifying levels of acrylamide intake among all comparison groups included in coffee epidemiological studies. In the absence of such data, the conclusion that if coffee does not increase cancer risk in epidemiological studies then exposure to acrylamide in coffee does not increase cancer risk lacks scientific credibility.

The duration of exposure and follow-up of epidemiological studies are critical issues because of the long latency needed for tumor development. To reach a conclusion that there is no carcinogenic hazard based on well-conducted epidemiologic studies, IARC requires multiple, mutually consistent, adequately powered studies covering the full range of human exposures that exclude with reasonable certainty bias, confounding, and chance and provide individual and pooled estimates of risk near unity with narrow confidence intervals. In particular, IARC cautions that "latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity." Because the California NSRL is based on 70 years of exposure, evaluations of cancer risks from coffee consumption must be based on epidemiological studies of long exposure duration and follow-up.

Epidemiological studies lack power to evaluate an excess lifetime cancer risk of one per 10^5 or even one per 10^4. For example, the mortality rate for leukemia or NHL among men in the US is about 70 per 100,000 by 70 years of age. For these cancers, the relative risk for acrylamide in coffee

at the NSRL (an excess of one case per 100,000 for a person exposed for 70 years) would be 71 x 10^{-5}/70 x 10^{-5} = 1.014, a level too low to detect an effect that might actually exist. The chance of developing an invasive cancer in the US by age 70 is approximately 5,000 per 100,000. For all cancer sites, the relative risk for acrylamide in coffee at a risk level of $1x10^{-4}$ would be 501 x 10^{-4}/500 x 10^{-4} = 1.002. In addition, most epidemiological studies on coffee drinkers are not based on 70-year lifetime exposures. Thus, current epidemiological data on coffee drinkers are not suitable for assessing a cancer risk of $1x10^{-5}$ or of $1x10^{-4}$ for acrylamide in coffee.

"An epidemiological study would require a cohort of more than two million to detect such a small relative risk [1.006 to 1.05 for exposure to >70 µg of acrylamide per day] given such a small proportion of the population exposed [less than 1.5% to this level]. Epidemiology lacks "the scientific means to detect such a small effect." Mucci L, Adami HO, "The role of epidemiology in understanding the relationship between dietary acrylamide and cancer risk in humans," *Adv. Exp. Med. Biol.* (2005) 561:39-47.

"Cancer risk from an evenly distributed risk factor in the population could hardly be detected and assessed by standard epidemiological methods, even if it contributes to the overall cancer incidence. It is prerequisite for performing conclusive epidemiological studies that there is enough exposure contrast with the population." "From a purely statistical point of view about 470,000 cases with half as many controls are needed in order to show a relative risk of 1.05 in a statistically significant way (P<0.05)." Hagmar L, Törnqvist M, "Inconclusive results from an epidemiological study on dietary acrylamide and cancer," *Br. J. Cancer* (2003) 89(4):774-775.

"Existing epidemiological studies do not have the statistical power to detect cancer risk from acrylamide exposure at the levels suggested by toxicology studies." Joint Institute for Food Safety and Applied Nutrition (JIFSAN), *Exposure and Biomarkers Working Group White Paper* at p. 4 (JIFSAN 2004); See also Dybing E, Sanner T, "Risk assessment of acrylamide in foods," *Toxicol. Sci.* (2003) 75(1):7-15.

Based on a NSRL for acrylamide of 0.2-1 μg/day (i.e., the level of acrylamide that is calculated to result in no more than one excess case of cancer in an exposed population of 100,000 assuming exposure over a 70-year lifetime) and that measured levels of acrylamide in brewed coffee are approximately 10 parts per billion (10 μg/l), US FDA http://www.fda.gov/food/foodborneillnesscontaminants/chemicalcontaminants/ucm053549.htm), it is rather obvious that consumption of only one 8-ounce cup of coffee (0.23 l) results in exposure to 2.3 μg of acrylamide. This amount of acrylamide is above the NSRL for this carcinogen, while greater consumption of coffee far exceeds the NSRL. Interestingly, consumption of one cup of coffee results in greater daily uptake of acrylamide than from drinking water sources where the maximal allowable concentrations are 0.5 μg/l according to WHO guidelines for drinking water quality (1 μg/day) and 0.1 μg/l in European countries (0.2 μg/day). Agency for Toxic Substances and Disease Registry, *Toxicological Profile for Acrylamide* (ATSDR, 2012). Similarly, the FDA would not approve the use in food of an additive with the level of cancer risk in brewed coffee due to acrylamide.

Null results from epidemiologic studies alone do not prove the absence of carcinogenic effects, because of inadequate statistical power, inadequate study design, inadequate followup, confounding, misclassification of exposure, and other factors. U.S. Environmental Protection Agency, *Guidelines for Carcinogen Risk Assessment* (March 2005). A preference for human data, simply because it is available, may not provide the most appropriate basis for the conduct of a risk assessment. Cal. Health & Welfare Agency, "Final Statement of Reasons: 22 California Code of Regulations Division 2: Sections 12701, et seq. - No Significant Risk Levels," at p. 17 (June 1989).

Thus, the epidemiological studies regarding consumption of coffee and cancer are inadequate to quantify risks of cancer from acrylamide and other carcinogens in coffee, as was explained by Dr. Ronald L. Melnick in his report and testimony during the Phase 1 trial. (CERT's Submission No. 11).

H. Failure to Distinguish Between Association and Causation

The Initial Statement of Reasons selectively identifies some observational epidemiologic studies and meta-analyses of observational epidemiologic studies that report statistically significant decreased risks of certain cancers in association with consumption of coffee. However, the Initial Statement of Reasons does not address whether any of these associations are actually causal. This is a critical omission, because most statistical associations reported in observational epidemiological studies are not causal and it is especially difficult to conclude that associations regarding a single dietary component are causal, due to innumerable confounding factors in the diet, as well as innumerable non-dietary known and unknown confounding factors, as well as measurement error and innumerable other biases that plague observational epidemiology studies. Certainly, IARC has not made any such causal conclusion. Nor does OEHHA do so in its Initial Statement of Reasons. Critically, in the absence of any determination that any of the inverse associations reported in the observational epidemiologic studies of coffee and cancer are actually causal, it cannot be scientifically concluded that coffee does not cause cancer, let alone that it prevents cancer. Yet, this is what OEHHA appears to implicitly conclude in its Initial Statement of Reasons. In his recent decision in *CERT v. Starbucks*, Judge Berle noted that "Defendants' medical and epidemiology experts [Drs. David Kessler and Dominik Alexander] testified that they had no opinion on causation," that the "Defendants' proffered evidence that coffee itself confers some benefit to human health was not persuasive," and that "Defendants failed to prove that coffee confers any human health benefits."

All of the epidemiologic studies that have investigated risks of cancer from coffee consumption are observational epidemiologic studies or meta-analyses of such studies. However, such studies are wholly inadequate to determine causality.

"In contrast to intervention studies, observational studies cannot determine whether an observed relationship represents a relationship in which the substance caused a reduction in disease

risk or is a coincidence." U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition, *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims* (January 2009) (Exhibit "C")

Indeed, the authors of epidemiologic studies regarding coffee and cancer themselves acknowledge that their studies do not establish causation. This includes some of the very studies upon which OEHHA relies in its Initial Statement of Reasons. For example, on page 5 of the Initial Statement of Reasons, OEHHA writes that IARC "reported that studies either showed no association or a statistically significant inverse association for coffee intake and breast cancer." The reference for this statement is page 417 of the monograph, which states: "The most recent meta-analysis of about one million women and more than 50 000 breast cancer cases reported a modestly decreased risk for the highest compared with lowest levels of coffee consumption, with an indication of an inverse dose-response relationship." This meta-analysis is identified on page 241 of the monograph as Jiang 2013, the complete citation of which appears on page 320 of the monograph: Jiang W, Wu Y, Jiang X, "Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies," (2013) *Gynecol Oncol.* 129(3):620-629. (Exhibit "D"). In this meta-analysis, based on 20 case-control studies and 17 cohort studies, the authors acknowledged: "Observational studies cannot prove causality." (Exhibit "D" at p. 629).

I. The Coffee Industry's Own Expert Explained Why Associations Between Coffee Consumption and Cancer in Observational Studies Cannot Be Deemed Causal

In the Phase 2 trial in the *CERT v. Starbucks* case, the coffee industry offered testimony of its nutritional epidemiology expert Dr. Dominik Alexander, who testified that consumption of coffee was associated with decreased risks of some cancers and chronic diseases in observational studies. However, on cross-examination, Dr. Alexander acknowledged that "given the considerable degree of exposure misclassification from self-reported dietary intake, correlation of certain foods with other dietary and lifestyle factors and the impact of bias and confounding, there is significant

uncertainty surrounding the epidemiologic evidence for foods and cancer," including coffee. [Testimony of Dr. Dominik Alexander in *CERT v. Starbucks,* September 7, 2017 at pp. 46 - 47].

Dr. Alexander testified that "[i]n fact, despite billions of research dollars and decades of research, few if any foods have been clearly causally associated with increasing or decreasing the risk of cancer," and that he even questioned whether there is a causal relationship between consumption of fruits and vegetables and cancer. *Id.* at p. 47.

He further acknowledged that "[t]he interdependency of food consumption with other dietary and lifestyle factors, socioeconomic characteristics, clinical variables and genetic traits makes it difficult to isolate the independent effects of a specific food or food group . . . on disease risk." *Id.* at p. 49.

Dr. Alexander also acknowledged that "[d]oing a lot of work in nutritional epidemiology and being very familiar with the food frequency questionnaire for diet and cancer, those studies should not be viewed as a good measuring stick for reliability. *Id.* at pp. 51-52.

Dr. Alexander also acknowledged that he was unaware of any international organization, governmental authority, or any peer-reviewed article in a reputable journal that has concluded that coffee consumption prevents any chronic disease or cancer. *Id.* at p. 52.

Indeed, Dr. Alexander admitted that he even questioned whether it is possible to isolate in individual food component to determine causality for that food component. *Id.* at p. 53.

Dr. Alexander also conceded that "there's a big distinction between association and causation." *Id.* at p. 54.

Finally, Dr. Alexander acknowledged that "[a]n association indicating a decreased risk of disease is not a health benefit unless the association is causal," that he had no opinions on causation of health effects from consumption of coffee" and that he therefore was "not making a conclusion of causation regarding a health benefit" of coffee consumption. *Id.* at p. 55.

J. Randomized Controlled Trials

"In randomized controlled trials, subjects are assigned to an intervention group by chance. Individual subjects may not be similar to each other, but the intervention and control groups should be similar after randomization." U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition, *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims* (January 2009) (Exhibit "C")

"Randomized controlled trials offer the best assessment of a causal relationship between a substance and a disease because they control for known confounders of results (i.e., other factors that could affect risk of disease). Through random assignment of subjects to the intervention and control groups, these studies avoid selection bias – that is, the possibility that those subjects most likely to have a favorable outcome, independent of an intervention, are preferentially selected to receive the intervention. Potential bias is also reduced by 'blinding' the study so that the subjects do not know whether they are receiving the intervention, or 'double blinding,' in which neither the subjects nor the researcher who assesses the outcome knows who is in the intervention group and who is in the control group. By controlling the test environment, including the amount and composition of substance consumed and all other dietary factors, these studies also can minimize the effects of variables or confounders on the results. Therefore, randomized controlled intervention studies provide the strongest evidence of whether or not there is a relationship between a substance and a disease." *Id.* (Exhibit "C"). Randomized controlled trials "can provide convincing evidence of a cause and effect relationship between an intervention and an outcome." U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition, *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims* (January 2009) (Exhibit "C"), citing Kraemer HC, Lowe KK, Kupfer DJ, *To Your Health: How to Understand What Research Tell Us About Risk* (2005) Oxford University Press. Randomized controlled trials have been considered essential to determining causality, because

associations reported in observational epidemiological studies and meta-analyses of observational epidemiological studies are often not confirmed by randomized controlled trials. Thus, in a study that compared 19 meta-analyses with 12 large randomized, controlled trials addressing the same questions, the outcomes of the controlled trials were not predicted accurately 35 percent of the time by the meta-analyses published previously on the same topics. LeLorier J, Grégoire G, Benhaddad A, Lapierre J, Derderian F, "Discrepancies between Meta-Analyses and Subsequent Large Randomized, Controlled Trials," *New Engl. J. Med.* (1997) 337:536-642.

Regrettably, none of the hundreds of epidemiologic studies regarding coffee consumption and cancer are randomized controlled trials. See, Henderson G, "Coffee consumption and health: we need randomised controlled trials," *BMJ* (2018) 360:k132.

If randomized controlled trials confirmed the inverse associations in the substantially confounded observational studies regarding coffee consumption and cancer, IARC might well have classified coffee as probably not carcinogenic to humans (Group 4), rather than deeming it unclassifiable, because "the existing scientific data do not enable a conclusion to be made about whether it causes cancer." (Exhibit "B") However, merely because randomized controlled studies are not available to determine whether associations between coffee consumption and cancer are causal does not justify assuming that coffee does not cause human cancer, let alone all cancers. Moreover, several Mendelian randomization studies published since IARC completed its review can determine causality and are thus a useful alternative to randomized controlled studies.

K. Mendelian Randomization Studies

"Observational epidemiological studies are prone to confounding, measurement error, and reverse causation, undermining robust causal inference. Mendelian randomization (MR) uses genetic variants to proxy modifiable exposures to generate more reliable estimates of the causal effects of these exposures on diseases and their outcomes. MR has seen widespread adoption within

cardio-metabolic epidemiology, but also holds much promise for identifying possible interventions for cancer prevention and treatment." Yarmolinsky J, Wade KH, Richmond RC, Langdon RJ, Bull CJ, Tilling KM, Relton CL, Lewis SJ, Smith GD, Martin RM, "Causal inference in cancer epidemiology: what is the role of Mendelian randomization?" *Cancer Epidemiol. Biomarkers Prev.* (June 25, 2018) pii: cebp.1177.2017 doi: 10.1158/1055-9965.EPI-17-1177 [Epub ahead of print].

"Part of the difficulty in translating observational findings into effective cancer prevention and treatment strategies lies in the susceptibility of conventional observational designs to various biases, such as residual confounding (due to unmeasured or imprecisely measured confounders) and reverse causation. These biases frequently persist despite energetic statistical and methodological efforts to address them, making it difficult for observational studies to reliably conclude that a risk factor is causal . . . ." *Id.*

"MR uses germline genetic variants as instruments (i.e., proxies) for exposures (e.g., environmental factors, biological traits, or druggable pathways) to examine the causal effects of these exposures on health outcomes (e.g., disease incidence or progression). The use of genetic variants as proxies exploits their random allocation at conception (Mendel's first law of inheritance) and the independent assortment of parental variants at meiosis (Mendel's second law of inheritance). These natural randomization processes mean that, at a population level, genetic variants that are associated with levels of a specific modifiable exposure will generally be independent of other traits and behavioural or lifestyle factors . . . ." *Id.*

"Analyses using genetic variants as instruments to examine associations with outcomes have a number of advantages: i) effect estimates should be less prone to the confounding that typically distorts conventional observational associations, ii) because germline genetic variants are fixed at conception, they cannot be modified by subsequent factors, thus overcoming possible issues of reverse causation, and iii) measurement error in genetic studies is often low as modern genotyping technologies provide relatively precise measurement of genetic variants, unlike the substantial (and

at times differential) exposure measurement error which can accompany observations studies (e.g., due to self-report)." *Id.*

"Due to the random allocation of alleles at conception it can be useful to compare the structure of a MR analysis to the design of a randomized trial, where individuals are randomly allocated at baseline to an intervention or control group. Groups defined by genotype should be comparable in all respects (e.g., approximately equal distribution of potential confounding factors) except for the exposure of interest. It follows that any observed differences in outcomes between these genotypic groups can be attributed to differences in long-term exposure to the trait of interest." *Id.* "Given long latency periods for many cancers, spurious findings resulting from reverse causation are an important concern in cancer epidemiology. Reverse causation has been suspected in several instances of ambiguous or paradoxical findings in the cancer literature." *Id.*

"The advantages of exploiting the fixed nature of germline genotype extends beyond addressing reverse causation in observational studies. Large cancer prevention trials are often constrained to examining interventions over a limited duration in time and over a particular period in the life-course (e.g., middle and/or late adulthood). Given the length of time required for solid tumor development, randomized trials will often not allow sufficient follow-up for the effect of an intervention to be detected. In turn, long-term chemoprevention trials that are conducted may suffer from issues of non-compliance in the intervention arm, contamination in the control arm, and attrition during follow-up." *Id.*

"Mendelian randomization is a strategy for evaluating causality in observational epidemiological studies. MR exploits the fact that genotypes are not generally susceptible to reverse causation and confounding, due to their fixed nature and Mendel's First and Second Laws of Inheritance. MR has the potential to provide information on causality in many situations where randomized controlled trials are not possible." Zheng J, Baird D, Borges M-C, Bowden J, Hemani G, Haycock P, Evans DM, Smith GD, "Recent Developments in Mendelian Randomization Studies," *Curr. Epidemiol. Rep.* (2017) 4:330-345. "Associations between modifiable exposures and disease

seen in observational epidemiology are sometimes confounded and thus misleading.... Mendelian randomization – the random assortment of genes from parents to offspring that occurs during gamete formation and conception – provides one method for assessing the causal nature of some environmental exposures. The association between a disease and a polymorphism that mimics the biological link between a proposed exposure and disease is not generally susceptible to the reverse causation or confounding that may distort interpretations of conventional observational studies. Several examples where the phenotypic effects of polymorphisms are well documented provide encouraging evidence of the explanatory power of Mendelian randomization." Smith GD, Ebrahim S, "'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease?" *Int. J. Epidemiol.* (2003) 32:1-22.

Mendelian randomization studies have been undertaken to investigate whether the inverse associations that have been consistently reported for coffee consumption and certain chronic diseases (e.g., Type 2 Diabetes, Alzheimer's disease, and cardiovascular disease) are causal. These studies have not confirmed the findings of risk reduction that have been reported in observational studies, thereby showing that the inverse associations of coffee consumption and such chronic diseases are not causal, but are most likely the result of confounding and/or reverse causation.

IV. MENDELIAN RANDOMIZATION SHOWS ASSOCIATIONS ARE NON-CAUSAL

A. Type 2 Diabetes

In 2015 researchers from Denmark published a Mendelian randomization study of 93,179 individuals from two large general population cohorts to test the hypothesis that genetically high coffee intake is associated with low risk of type 2 diabetes, metabolic syndrome and obesity. They tested whether five genetic variants near the CYP1A1, CYP1A2 and AHR genes that are associated with coffee intake are also associated with type 2 diabetes, metabolic syndrome and obesity. They

noted that "a large body of observational studies support a protective role of coffee consumption on risk of type 2 diabetes and possibly obesity, metabolic syndrome and related outcomes." However, in their study genetically derived high coffee intake was not associated with Type 2 diabetes or metabolic syndrome or obesity. There were no significant increases or decreases in odds ratios or trends for risk of obesity, metabolic syndrome, or type 2 diabetes in relation to increases in the number of coffee-intake alleles. Hence, the authors concluded that their genetic analyses suggested that the inverse associations between coffee consumption and these diseases reported in observational epidemiological studies "could be explained by confounding and/or reverse causation, rather than by direct biological mechanisms." Nordestgaard AT, Thomsen M., Nordestgaard BG, "Coffee intake and risk of obesity, metabolic syndrome and type 2 diabetes: a Mendelian randomization study," *Int. J. Epidemiol.* (2015) 44(2):551-565.

In 2016, researchers affiliated with the University of Hong Kong published a study in which they evaluated whether type 2 diabetes, Alzheimer's disease, depression, and ischemic heart disease was associated with genetically predicted coffee consumption using two-sample Mendelian randomization applied to large extensively genotyped case-control and cross-sectional studies. They noted that observationally, coffee is inversely associated with type 2 diabetes, depression and Alzheimer's disease, but not ischemic heart disease. They found that genetically predicted coffee consumption was not associated with type 2 diabetes, Alzheimer's disease, depression, or ischemic heart disease (odds ratios were 1.02, 0.89, 1.17, and 0.96, respectively, and all 95% confidence intervals overlapped 1.0) and concluded that "contrary to observational findings, coffee may not have beneficial effects on T2DM [type 2 diabetes mellitus], depression or Alzheimer's disease." They reasoned that their findings "suggest interventions to prevent these complex chronic diseases should be sought elsewhere." Kwok MK, Leung GM, Schooling CM, "Habitual coffee consumption and risk of type 2 diabetes, ischemic heart disease, depression, and Alzheimer's disease: a Mendelian randomization study," *Sci. Rep.* (November 15, 2016) 6:36500.

In 2017, researchers from Singapore published an abstract of a Mendelian randomization study that they conducted to test the hypothesis that the observationally inverse association between coffee intake and type 2 diabetes risk is causal. In a nested case-control study within the Singapore Chinese Health Study cohort, they included 2,436 type 2 diabetes cases and an equal number of matched controls. They tested the association of nine single-nucleotide polymorphisms (SNPs) with coffee intake or risk of type 2 diabetes and used the instrumental variable estimators to assess causality. Coffee intake was observationally associated with lower risk of type 2 diabetes (OR 0.93, 95% CI 0.88 - 0.98) in the multivariate adjusted model. They found three SNPs that were significantly associated with higher coffee intake. They concluded that while the results of their study showed that high coffee intake was observationally associated with lower type 2 diabetes risk, their gene allege-based findings do not support a causal association. Pashiri MT, Huang T, Koh W-P, "Coffee Intake Was Not Causally Associated With Type 2 Diabetes Risk in Asians: a Mendelian Randomization Based on the Singapore Chinese Health Study," *Circulation* (2017) 135:AP206.

Thus, all three Mendelian randomization studies published to date regarding consumption of coffee and type 2 diabetes show that the inverse association that has been reported in some observational epidemiological studies of coffee and type 2 diabetes is not causal.

B. Alzheimer's Disease

In addition to the Hong Kong study, two other Mendelian randomization studies have been published regarding coffee consumption related to Alzheimer's disease and cognitive function.

In 2017 European researchers published a Mendelian randomization study using genetic variants associated with modifiable risk factors as instrumental variables to determine risk factors associated with Alzheimer's disease. The study was sponsored by the International Genomics of Alzheimer's Project and included 17,008 cases of Alzheimer's disease and 37,154 controls. Although coffee consumption has consistently been inversely associated with Alzheimer's disease

in observational studies, these researchers found that genetically predicted higher consumption of coffee significantly increased the risk of Alzheimer's disease in their study (OR 1.26, 95% CI 1.05 - 1.51, $p = 0.01$). In fact, of all 24 potentially modifiable risk factors investigated, only genetically predicted higher coffee consumption significantly increased the risk of Alzheimer's disease. Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS, "Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis," *Br. Med. J.* (December 6, 2017) 359:j5375.

In 2018 a team of international researchers published a study in which they used Mendelian randomization to investigate whether the relationship between habitual coffee consumption and cognitive function in mid- to later life is causal. The study included up to 415,530 participants and 300,760 coffee drinkers from 10 meta-analyzed European ancestry cohorts. In each cohort, composite cognitive scores that capture global cognition and memory were computed. A genetic score derived using CYP1A1/2 (rs2472297) and SHR (rs6968865) was chosen as a proxy for habitual coffee consumption. Null associations were observed when examining the associations of the genetic score with global and memory cognition. The researchers concluded that despite their study's power to detect very small effects, their meta-analysis provided no evidence for causal long-term effects of habitual coffee consumption on global cognition or memory. Zhou A, Taylor AE, Karhunen V, Zhan Y, Rovio SP, Lahti J, Sjögren P, Byberg L, Lyall DM, Auvinen J, Lehtimäki, Kähönen M, Hutri-Kähönen N, Perälä MM, Michaëlsson K, Mahajan A, Lind L., Power C, Eriksson JG, Raitakari OT, Hägg S, Pedersen NL, Veijola J, Järvelin MR, Munafò MR, Ingelsson E, Llewellyn DJ, Hyppönen E, "Habitual coffee consumption and cognitive function: a Mendelian randomization meta-analysis in up to 415,530 participants," *Sci. Rep.* (2018) 8(1):7526.

Thus, all three Mendelian randomization studies published to date regarding coffee consumption and Alzheimer's disease indicate that the inverse association that has been reported in multiple observational studies is not causal.

C. Cardiovascular Disease

In 2016, Danish researchers published observational and Mendelian randomization analyses in 95,000 to 223,000 Danes to determine whether the inverse associations that had been reported between coffee consumption and cardiovascular disease and all-cause mortality in observational studies is causal. They used multivariable adjusted Cox proportional hazard regression models with restricted cubic splines to examine observational associations and estimated coffee intake according to five genetic variations near the *AHR* (rs4410790; rs6968865) and *CYP1A1/2* genes (rs2470893, rs2472297; rs2472299). In observational analyses, they found U-shaped associations between coffee intake and cardiovascular disease and all-cause mortality, consistent with prior observational studies. However, genetic coffee intake was not associated with the risk of cardiovascular disease or all-cause mortality. The researchers therefore concluded that their study does not support the hypothesis that coffee intake influences the risk of cardiovascular disease and all-cause mortality. Nordestgaard AT, Nordestgaard BG, "Coffee intake, cardiovascular disease and all-cause mortality: observational and Mendelian randomization analysis in 95 000 - 223 000 individuals," *Int. J. Epidemiol.* (2016) 45(6):1938-1952.

Thus, the inverse association between consumption of coffee and cardiovascular disease that has been reported in some observational epidemiologic studies is likely artifactual rather than causal and is more likely the result of confounding and perhaps reverse causation.

D. Parkinson's Disease

Parkinson's disease is another chronic disease that has often been inversely associated with coffee consumption. To date, no Mendelian randomization study of coffee consumption and Parkinson's disease has been published. However, a Mendelian randomization study of three genes known to modify iron levels and Parkinson's disease was undertaken in a meta-analysis of 20,809

Parkinson's disease cases and 88,892 controls. The combined Mendelian randomization estimate showed a statistically significant protective effect of iron, with a relative risk reduction for Parkinson's disease of 3% (95% CI 1% - 6%; $p = 0.001$) per 10 μg/dl increase in serum iron. The investigators concluded that their study indicated that increased iron levels are causally associated with a decreased risk of developing Parkinson's disease. Pichler I, Del Greco FM, Gögele M, Lill CM, Bertram L, Do CB, Eriksson N, Foroud T, Myers RH, PD GWAR Consortium, Nalls M, Keller MF, International Parkinson's Disease Genomics Consortium, Wellcome Trust Case Control Consortium 2, Benyamin B, Whitfield JB, Genetics of Iron Status Consortium, Pramstaller PP, Hicks AA, Thompson JR, Minelli C, "Serum Iron Levels and the Risk of Parkinson's Disease: A Mendelian Randomization Study," *PLoS Med.* (2013) 10(6):e1001462.

This study is relevant to the issue whether consumption of coffee causally reduces the risk of Parkinson's disease, because coffee is known to inhibit the intestinal absorption of iron. Morck TA, Lynch SR, Cook JD, "Inhibition of food iron absorption by coffee," *Am. J. Clin. Nutr.* (1983) 37:416-420; Zijp IM, Korver O, Tijburg LB, "Effect of tea and other dietary factors on iron absorption," *Crit. Rev. Food Sci. Nutr.* (2000) 40:371-398.

Since increased iron levels causally reduce the occurrence of Parkinson's disease, and since consumption of coffee reduces iron absorption, it is likely that the inverse association between coffee consumption and Parkinson's disease reported in observational epidemiologic studies is not causal.

E. Osteoarthritis

A recent Mendelian randomization study, using inverse-variance weighted and weighted median estimated, provided evidence supporting a causal association between coffee consumption and osteoarthritis. Lee YH, "Investigating the possible causal association of coffee consumption with osteoarthritis risk using a Mendelian randomization analysis," *Clin. Rheumatol.* (August 3, 2018) doi: 10.1007/s10067-018-4252-6 [Epub ahead of print].

F. Cancer

The consistently null Mendelian randomization studies regarding coffee intake and type 2 diabetes, Alzheimer's disease, and cardiovascular disease/mortality – all of which have been inversely associated with coffee consumption in observational studies -- suggest that the inverse associations between coffee consumption and certain cancers reported in some observational studies would likely also be non-causal. To date, only two Mendelian randomization studies have been published regarding coffee consumption and cancer - regarding prostate cancer and ovarian cancer.

In 2017 a large group of researchers published a Mendelian randomization study to investigate whether inverse associations between coffee consumption and prostate cancer reported in some observational studies is causal. They used two genetic variants robustly associated with caffeine intake (rs4410790 in AHR and rs2472297 near CYP1A1/CYP1A2) as proxies for coffee consumption in a sample of 46,687 men of European ancestry from 25 studies. They found no association between these genetic variants and prostate cancer risk, but a small significantly increased risk of nonlocalized prostate cancer compared to localized stage disease (OR 1.03, 95% CI 1.01 - 1.06). The researchers concluded that their study results, do not support a causal role of coffee consumption in prostate cancer incidence and suggest that observational findings that coffee consumption is associated with a reduce risk for prostate cancer may be due to confounding by other lifestyle factors. Taylor AE, Martin RM, Geybels MS, Stanford JL, Shui I, Eeles R., Easton D, Kote-Jarai Z, Amin Al Olama A, Benlloch S, Muir K, Giles GG, Wiklund F, Gronberg H, Haiman CA, Schleutker J, Nordestgaard BG, Travis RC, Neal D, Pashayan N, Khaw KT, Blot W, Thibodeau S, Maier C, Kibel AS, Cybulski C, Cannon-Albright L, Brenner H, Park J, Kaneva R, Batra J, Teixeria MR, Pandha H, Donovan J, Munafò MR, "Investigating the possible causal role of coffee consumption with prostate cancer risk and progression using Mendelian randomization analysis," *Int. J. Cancer* (2017) 140(2):322-328.

In 2018 Australian researchers published a Mendelian randomization study using single nucleotide polymorphisms associated with coffee and caffeine consumption (SNPs in the AHR gene and in the CYP1A2 gene) to determine whether reported associations between coffee consumption and epithelial ovarian cancer in observational studies are causal. They conducted a two-sample Mendelian randomization using genetic data on 44,062 individuals of European ancestry from the Ovarian Cancer Association Consortium, and combined instrumental variable estimates using a Wald-type ratio estimator. The causal odds ratios for ovarian cancer and genetically predicted consumption of both coffee and caffeine were not significantly different. The researchers concluded that the results of their study found no evidence of an association between epithelial ovarian cancer risk and genetically predicted coffee or caffeine levels. Ong, JS, Hwang LD, Cuellar-Partida G, Martin NG, Chenvix-TGrench G, Quinn MCJ, Cornelis MC, Gharahkhani P, Webb PM, MacGregor S, "Assessment of moderate coffee consumption and risk of epithelial ovarian cancer: a Mendelian randomization study," *Int. J. Epidemiol.* (2018) 47(2):450-459.

Thus, both Mendelian randomization studies regarding coffee and cancer published to date reflect no causal relationship between coffee consumption and cancer.

In its "new" monograph on coffee, IARC does not discuss any Mendelian randomization studies regarding coffee and cancer. This is not surprising, because the first Mendelian randomization study regarding coffee and cancer was published in 2017, after the IARC Working Group on Coffee had met in May 2016 and reviewed the epidemiological literature then available. The IARC Working Group therefore should not be faulted for being impressed with the inverse relationships that had been reported in observational studies regarding coffee and several cancers. However, the several Mendelian randomization studies regarding coffee and chronic diseases and cancer that have been published since the May 2016 meeting of the IARC Working Group on Coffee are consistent in demonstrating that the inverse associations in the observational epidemiological studies of coffee and chronic diseases and cancer are not causal, but are most likely the result of confounding. IARC's conclusions are therefore already out of date with the current literature.

The Initial Statement of Reasons states that "OEHHA has determined that exposure to listed carcinogens in coffee that are produced as part of and inherent in the processes of roasting and brewing coffee does not pose a significant cancer risk under Proposition 65." The critical basis for OEHHA's conclusion is "the reductions of specific cancers resulting from coffee drinking." However, the Mendelian randomization studies published since IARC's literature review indicate that the reduction in cancer risk in observational studies is artefactual rather than causal, thereby undermining the essential basis for IARC's conclusion and the basis for its new proposed regulation.

Although OEHHA based its conclusion primarily on the inverse associations between coffee consumption and several cancers in observational studies, OEHHA also relied on two other factors in reaching its conclusion: OEHHA's assertion that coffee "has not been found to increase the risk of any cancers" and allegedly "beneficial effects of coffee . . . related to chemoprevention." As will be explained, the former ground is factually incorrect and the latter ground is unsubstantiated.

V. COFFEE CONSUMPTION INCREASES THE RISK OF SEVERAL CANCERS

In the first paragraph of page 11 of the ISOR, OEHHA asserts that "coffee . . . has not been found to increase the risk of any cancers." In the next paragraph OEHHA writes that "coffee . . . has not been shown to increase the risk of any cancer." The only reference given for these assertions is footnote 86, which references page 425 of the IARC monograph. This page of the monograph sets forth IARC's overall conclusion regarding coffee and cancer, but does not state that the assertion that "coffee has not been found/shown to increase the risk of any cancers." Indeed, a word-search of the entire IARC monograph for both formulations of OEHHA's assertion establishes that IARC made no such conclusion in the Monograph and OEHHA's assertion that IARC determined that "coffee has not been found/shown to increase the risk of any cancers" appears to be fabricated. In fact, coffee has been found to increase the risk of certain cancers and IARC has so concluded. IARC also lists several sites with too few studies to draw any conclusions regarding cancer risk.

A. Childhood Cancers

The two major types of childhood cancer are childhood leukemia and childhood brain cancer.

1. Childhood Leukemia

For example, IARC noted increased risks of childhood leukemia in association with maternal consumption of coffee during pregnancy. In its Monograph, IARC identified "[s]even case-control studies reporting results of the association between maternal coffee consumption during pregnancy and risk of childhood leukaemia in the offspring." (Monograph at p. 294). "The Working Group considered that the earliest two studies were of limited quality due to low participation fractions and uninformative categories." (Monograph at p. 418). Of the five studies that IARC considered to be of sufficient quality for analysis, all reported significantly increased risks of childhood leukemia in association with maternal consumption of coffee during pregnancy. (Monograph at pp. 295-296).

IARC also noted that "three meta-analyses of the association between maternal coffee consumption and childhood leukaemia have been conducted, and all reported elevated risks with higher levels of maternal coffee intake." (Monograph at p. 296). The meta-analyses reported statistically significant increased risks of both types of childhood leukemia. IARC noted that in the most recent meta-analysis (Thomopoulos TP, Nouvelis E, Diamantaras AA, Tzanoudaki M, Baka M, Hatzipantelis E, Kourti M, Polychronopoulou S, Sidi V, Stiakaki E, Moschovi M, "Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis," *Cancer Epidemiol.* (2015) 39(6):1047-1059) that "included all studies published to date," "high maternal coffee intake during pregnancy was positively associated with AL [acute leukemia] overall, ALL and AML, with summary odds ratios (95% CI) of 1.57 (1.16 - 2.11), 1.42 (1.22 - 1.68), and 1.81 (0.93 - 3.53), respectively." (Monograph at p. 296).

Since IARC reviewed the studies regarding maternal consumption of coffee during pregnancy and childhood leukemia when the Working Group on Coffee met in 2016, an important study regarding the association has been published. In 2018 researchers from the Childhood Leukemia International Consortium published a study in which they investigated the effects of maternal consumption of coffee and tea during pregnancy on childhood acute lymphoblastic leukemia by pooling data from eight case-control studies. Data on maternal coffee intake were available for 2,552 cases and 4,876 controls. Data on genetic variants in *NAT2, CYP1A1,* and *NQO1* were also available in a subset. Pooled odds ratios and 95 confidence intervals were estimated using unconditional logistic regression and linear trends across categories were assessed. They found evidence of a positive exposure-response; the pooled odds ratio for consumption of coffee of more than 2 cups/day versus none was 1.27 (95% CI 1.09 - 1.43), with a highly significant dose-response (p trend = 0.005). No associations were observed with tea consumption. The investigators of this large study concluded that their "findings suggest that high coffee intake during pregnancy may increase risk of childhood ALL." The researchers further concluded that "current advice to limit caffeine intake during pregnancy to reduce risk of preterm birth may have additional benefits." Milne, E, Greenop KR, Petridou E, Bailey HD, Orsi L, Kang AY, Baka M, Bonaventure A, Kourti M, Metayer C, Clavel J, "Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: a pooled analysis from the Childhood Leukemia International Consortium," *Cancer Causes Control* (2018) 29(6):539-550. Thus, this well-designed and well-conducted international study confirms the observation of IARC in its monograph that maternal consumption of coffee during pregnancy does increase the risk of childhood leukemia. These findings run counter to OEHHA's statement that coffee "has not been found to increase the risk of any cancers."

Thus, epidemiological study results consistently demonstrate statistically significant associations between maternal consumption of coffee and the development of childhood leukemia (ALL and AML). Based on one of these studies, a quantitative estimate of the increased risk of childhood leukemia from maternal coffee drinking during pregnancy was calculated by Dr. Steven

P. Bayard, formerly Director of the Office of Risk Assessment in the Directorate of Health Standards Programs within the U.S. Occupational Safety and Health Administration and a risk assessment expert at the U.S. Environmental Protection Agency and Consumer Product Safety Commission. Dr. Bayard estimated an increased risk of childhood leukemia from maternal consumption of just 1 cup of coffee per day during pregnancy of 19.5 cases per 100,000 – a substantial risk of childhood leukemia indeed. (Statement of Steven Bayard: Calculation for the Increased Risk of Two Acute Childhood Leukemias Due to Maternal Coffee Drinking During Pregnancy).

Regrettably, in its Monograph on Coffee IARC does not discuss the biological mechanisms that would explain the association between maternal consumption of coffee and childhood leukemia. However, biologically plausible mechanisms for the development of childhood leukemia from maternal consumption of coffee during pregnancy do exist. During the Phase 1 trial in *CERT v. Starbucks,* Professor Martyn T. Smith, one of the world's leading researchers regarding the causes of childhood leukemia, testified that "the most probable mechanism to explain [the association] is that the clastogenic chemicals within coffee, including acrylamide, cross into the fetus and cause genetic damage in the fetus of the type where there's chromosome breakage, which leads to chromosome translocations, which then develops into leukemia." (Testimony of Dr. Smith, October 14, 2014 at 42:23-28; Report of Dr. Infante regarding maternal consumption of coffee and childhood leukemia); See also Milne E, Royle JA, Bennett LC, de Klerk NH, Bailey HD, Bower C, Miller M, Attia J, Scott RJ, Kirby M, Armstrong BK, "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; Sörgel F, Weissenbacher R, Kinzig-Schippers M, Hofmann A, Illauer M, Skott A, Landeersdorfer C, "Acrylamide: increased concentrations in homemade food and first evidence of its variable absorption from food, variable metabolism and placental and breast milk transfer in humans," *Chemother.* (2002) 48(6):267-274; Annola K, Karttunen V, Keski-Rahkonen P, Myllynen P, Segerbäck D, Heinonen S, Vähäkangas K, "Transplacental transfer of acrylamide and glycidamide are comparable to that of antipyrine in perfused human placenta," *Toxicol. Lett.* (2008) 182:50-56.

2. Childhood Brain Cancer

Childhood leukemia is not the only childhood cancer whose risk is increased by maternal consumption of coffee during pregnancy. In its Monograph IARC observed: " Three population-based case–control studies have reported findings for prenatal exposure to coffee and risk of childhood brain tumours. All reported non-significant positive associations, with odds ratios (95% CI) of 1.9 (0.9–3.9) for any coffee (Cordier S, Iglesias MJ, Le Goaster C, Guyot MM, Mandereau L, Hemon D, "Incidence and risk factors for childhood brain tumors in the Ile de France," *Int. J. Cancer* (1994) 59(6):776-82), 1.4 (0.8 - 2.4) for > 3 cups/day (Plichart M, Menegaux F, Lacour B, Hartmann O, Frappaz D, Doz F, Bertozzi AI, Defaschelles AS, Pierre-Kahn A, Icher C, Chastagner P, "Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy and childhood malignant central nervous system tumours: the ESCALE study (SFCE)," *Eur. J. Cancer Prev.* (2008) 17(4):376-383); 1.35 (0.90 - 2.04) for ≥ 2 cups/day (Greenop et al., 2014)." Further, "[i]n a subgroup analysis of cases of age < 5 years at diagnosis, Greenop et al. observed significantly elevated odds ratios (95% CI) of 1.76 (1.09 - 2.84) for any maternal coffee intake, 1.55 (0.92 - 2.63) for > 0 =2 cups/day, and 2.52 (1.26 - 5.04) for ≥ 21 cups/day (Greenop et al., 2014). A significant trend (P = 0.007) was also observed in this age group." IARC Monograph at pp. 296-297, citing Greenop KR, Miller M, Attia J, Ashton LJ, Cohn R, Armstrong BK, Milne E, "Maternal consumption of coffee and tea during pregnancy and risk of childhood brain tumors: results from an Australian case–control study," *Cancer Causes Control* (2014) 25(10):1321-1327.

Subsequent to IARC's 2016 review, French investigators published a study of 510 mothers of childhood brain tumor cases and 3,102 controls in which they pooled data from two French national population-based case-control studies with similar designs (the Estelle and Escale studies) conducted in 2003-2004 and 2010-2011. They also reported risks of childhood brain tumors for maternal consumption of one or more cups of coffee per week during pregnancy that were nonsignificantly increased in the pooled data (OR 1.15, 95% CI 0.94 - 1.40) but that were

significantly increased in the Estelle study (OR 1.29, 95% CI 1.00 - 1.67). Bailey HD, Lacour B, Guerrini-Rousseau L, Bertozzi A-I, Leblond P, Faure-Conter C, Pellier I, Freycon C, Doz F, Puget S, Ducassou S, Orsi L, Clavel J, "Parental smoking, maternal alcohol, coffee and tea consumption and the risk of childhood brain tumors: the ESTELLE and ESCALE studies (SFCE, France)," *Cancer Causes Control* (2017) 28(7):719-732.

Thus, maternal consumption of coffee during pregnancy appears to be associated with an increased risk of childhood brain cancer.

B. Meta-Analyses

One means of evaluating the association between coffee and cancer is to consider meta-analyses regarding coffee and individual cancers. Meta-analyses of coffee-cancer epidemiology studies have reported increased risks of the following cancers: bladder cancer, childhood leukemia, esophageal cancer, gastric cancer, laryngeal cancer, lung cancer, non-Hodgkin lymphoma, ovarian cancer, pancreatic cancer, and prostate cancer. Report of Dr. Peter Infante, July 16, 2017 at p. 6.

1. Bladder Cancer

Eight meta-analyses have been published regarding coffee consumption and bladder cancer.

In 2000 European investigators published a pooled analysis of 10 case-control studies regarding consumption of coffee and bladder cancer among nonsmokers in European countries. A statistically significant increased risk was seen for subjects who drank 10 or more cups of coffee per day (OR 1.8, 95% CI - 3.3). The excess risk of bladder cancer among heavy coffee drinkers was observed in both men and women. Sala M, Cordier S, Chang-Claude J, Donato F, Escolar-Pujolar A, Fernandez F, González CA, Greiser E, Jöckel KH, Lynge E, Mannetje A, Pohlabeln H, Porru S, Serra C, Tzonou A, Vineis P, Wahrendorf J, Boffetta P, Kogevinas M, "Coffee consumption and

bladder cancer in nonsmokers: a pooled analysis of case–control studies in European countries," *Cancer Causes Control* (2000) 11(10):925-931.

In a meta-analysis, based on 37 case-control studies, that compared coffee drinkers with nondrinkers, researchers from the Netherlands found the risk of bladder cancer to be increased in men and women combined (OR 1.18, 95% CI 1.01 - 1.38), with the risk being greater among men (OR, 1.26, 95% CI 1.09 - 1.46) than women (OR 1.08, 95% CI 0.79 - 1.46). Zeegers MP, Tan FE, Goldbohm RA, van den Brandt PA, "Are coffee and tea consumption associated with urinary tract cancer risk? A systematic review and meta-analysis," *Int. J. Epidemiol.* (2001) 30(2):353-362;

In a meta-analysis of 9 cohort studies published by Chinese researchers in 2011, the risk of bladder cancer was decreased comparing coffee drinkers with non-lowest drinkers (RR 0.83, 95% CI 0.73 - 0.94). Yu X, Bao Z, Zou J, Dong J, "Coffee consumption and risk of cancers: a meta-analysis of cohort studies," *BMC Cancer* (2011) 11:96.

In a meta-analysis of 23 case-control studies and 5 cohort studies, the pooled smoking-adjusted risk of bladder cancer was increased in the case-control studies, but not in the cohort studies. Compared with nondrinkers, the risk of bladder cancer increased monotonically with coffee consumption in the case-control studies: 1 cup per day (RR 1.07, 95% CI 1.02 - 1.13), 2 cups per day (RR 1.15, 95% CI 1.05 - 1.26), 3 cups per day (RR 1.22, 95% CI 1.08 - 1.38), 4 cups per day (RR 1.29, 95% CI 1.12 - 1.48). Zhou Y, Tian C, Jia C, "A dose–response meta-analysis of coffee consumption and bladder cancer," *Prev. Med.* (2012) 55(1):14-22.

In a meta-analysis meta-analysis of 21 epidemiological studies regarding fluid intake and bladder cancer published by Chinese investigators, of nine different beverages studied, comparing highest and lowest consumption, only coffee significantly increased the risk of bladder cancer (OR 1.17, 95% CI 1.03 - 1.33), based on 14 studies. Bai Y, Yuan H, Li J, Tang Y, Pu C, Han P, "Relationship between bladder cancer and total fluid intake: a meta-analysis of epidemiological evidence," *World J. Surg. Oncol.* (2014) 12(1):223.

In a meta-analysis of 5 cohort studies published by Chinese researchers, comparing highest and lowest consumption of coffee, a small, nonsignificant increased risk of bladder cancer was observed in men and women combined (OR 1.08, 95% CI 0.71 - 1.66). Comparing highest and lowest consumption, risk of bladder cancer was increased in men (OR 1.34, 95% CI 0.99 - 1.80), but not in women (OR 0.55, 95% CI 0.25 - 1.18). Huang TB, Guo ZF, Zhang XL, Zhang XP, Liu H, Geng J, Yao XD, Zheng JH, "Coffee consumption and urologic cancer risk: a meta-analysis of cohort studies," *Int. Urol. Nephrol.* (2014) 46(8):1481-1489.

In a meta-analysis of 34 case-control studies and 6 cohort studies by Chinese investigators, the risk of bladder cancer was increased when comparing coffee consumption with non-consumption (RR 1.33, 95% CI 1.19 - 1.48). These researchers also observed a statistically significant high risk of bladder cancer among non-smokers (RR 1.72, 95% CI 1.25 - 2.35), but not among smokers (RR 1.24, 95% CI 0.91 - 1.70). Wu W, Tong Y, Zhao Q, Yu G, Wei X, Lu Q, "Coffee consumption and bladder cancer: a meta-analysis of observational studies," *Sci. Rep.* (2015) 5:9051.

In the most recent meta-analysis of cohort studies of coffee consumption and bladder cancer, Chinese researchers reported a nonsignificant increased risk of bladder cancer when comparing coffee consumption with non-consumption (RR 1.12, 95% CI 0.94 - 1.34). However, comparing consumption with non-consumption, they observed a significantly increased risk of bladder cancer based on the 5 cohort studies in the United States (RR 1.38, 95% CI 1.02 - 1.85). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and cancer risk: A meta-analysis of prospective observational studies," *Sci Rep.* (2016) 6:33711.

2. Childhood Leukemia

Four meta-analyses have been published regarding maternal consumption of coffee during pregnancy and childhood leukemia.

The earliest meta-analysis published in 2011 and based on three case-control studies, reported a statistically significant greater than 2-fold increased risk of childhood leukemia from maternal consumption of more than 3 cups of coffee per day in nonsmoking mothers (OR 2.32, 95% CI 1.51 - 3.57), with a dose-response relationship. Interestingly, the authors observed no change in risk for equivalent consumption of coffee among smoking mothers (OR 1.01, 95% 0.77 - 1.33), indicating that the greater than doubling of the risk of childhood leukemia from high maternal consumption of coffee during pregnancy is unlikely the result of confounded by smoking. Milne E, Royle JA, Bennett LC, De Klerk NH, Bailey HD, Bower C, Miller M, Attia J, Scott RJ, Kirby M, Armstrong BK, "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(2):207-218.

A meta-analysis published by Chinese investigators in 2014, based on seven case-control studies, also reported an increased risk of childhood leukemia in association with high maternal coffee consumption (OR 1.72, 95% CI 1.37 - 2.16). Comparing the highest level of consumption with non-lowest consumption of coffee, significantly increased risks wee observed for both childhood acute lymphoblastic leukemia (OR 1.65, 95% CI 1.28 - 2.12) and acute myeloid leukemia (OR 1.58, 95% CI 1.20 - 2.08). Cheng J, Su H, Zhu R, Wang X, Peng M, Song J, Fan D, "Maternal Coffee Consumption During Pregnancy and Risk of Childhood Acute Leukemia: A Meta-Analysis," *Am. J. Obstet. Gynecol.* (2014) 210(2):151.e1-e10

A meta-analysis published in 2015 by Greek researchers, based on eight case-control studies, reported a greater than 50% increased risk of childhood leukemia comparing highest verses never-lowest maternal consumption of coffee during pregnancy (OR 1.57, 95% CI 1.16 - 2.11). Thomopoulos TP, Nouvelis E, Diamantaras AA, Tzanoudaki M, Baka M, Hatzipantelis E, Kourti M, Polychronopoulou S, Sidi V, Stiakaki E, Moschovi M, "Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis," *Cancer Epidemiol.* (2015) 39(6):1047-1059.

The most recent meta-analysis, published by Chinese researchers after IARC completed its review, reported an increased risk of childhood acute lymphoblastic leukemia in association with maternal consumption of coffee during pregnancy (OR 1.44, 95% CI 1.07 - 1.92). Yan K, Xu X, Liu X, Wang X, Hua S, Wang C, Liu X, "The Associations Between Maternal Factors During Pregnancy and the Risk of Childhood Acute Lymphoblastic Leukemia: A Meta-Analysis," *Pediatr. Blood Cancer* (2015) 62(7):1162-1170, Corrigendum, *Pediatr. Blood Cancer* (2016) 63(5):953-954.

As IARC noted, the meta-analyses regarding maternal consumption of coffee and childhood leukemia "all reported elevated risks with higher levels of maternal coffee intake" as well as statistically significant increased risks of both major types of childhood leukemia. *Id.* at p. 296.

3. Esophageal Cancer

Four meta-analyses regarding coffee consumption and esophageal cancer have been published.

A meta-analysis by Italian researchers reported an increased risk of adenocarcinoma (RR 1.18, 95% CI 0.81 - 1.71) based on 6 case-control studies and 1 cohort study, and a decreased risk of squamous cell carcinoma (RR 0.87, 95% CI 0.65 - 1.17) based on 4 case-control studies. Turati F, Galeone C, La Vecchia C, Garavello W, Tavani A, "Coffee and cancers of the upper digestive and respiratory tracts: meta-analyses of observational studies," *Ann. Oncol.* (2011) 22(3):536-544.

A meta-analysis by Chinese investigators based on cohort studies reported an inverse association for coffee consumption and esophageal cancer (RR 0.55, 95% CI 0.37 - 0.74), but this meta-analysis does not indicate which studies were included in the meta-analysis, so it is impossible to assess the selection criteria or the individual study results upon which risk was based. Yu X, Bao Z, Zou J, Dong J, "Coffee consumption and risk of cancers: a meta-analysis of cohort studies," *BMC Cancer* (2011) 11:96.

Another meta-analysis by Chinese investigators, based on 10 case-control studies and 4 cohort studies, observed a non-significant deficit for esophageal cancer (OR 0.88, 95% CI 0.76 - 1.01). However, there was no inverse association, for every 2 cup per day increment in coffee intake (OR 1.00, 95% CI - 0.89 - 1.12). Several of the studies included in the analysis did not adjust for alcohol consumption or cigarette smoking (including one that contributed over 400 cases), although these are the major known causes of esophageal cancer. The investigators also failed to control for obesity, another risk factor for esophageal cancer. Zheng JS, Yang J, Fu YQ, Huang T, Huang YJ, Li D, "Effects of green tea, black tea, and coffee consumption on the risk of esophageal cancer: a systematic review and meta-analysis of observational studies," *Nutr. Cancer* (2013) 65(1):1-16.

A recent meta-analysis by Chinese investigators, based on 11 studies, reported a nonsignificant decrease in the risk of esophageal cancer comparing heavy coffee drinkers with light coffee drinkers (OR 0.93, 95% CI 0.73 - 1.12), but a nonsignificant increase in the risk of esophageal adenocarcinoma comparing heavy and light consumers. (OR 1.15, 95% CI 0.88 - 1.42). The researchers also noted a nonsignficant increased risk of esophageal cancer for coffee consumption among Euro-American populations (OR 1.05, 95% CI 0.81 - 1.29), and an inverse association in east Asian populations (OR 0.64, 95% CI 0.44 - 0.83). Zhang J, Zhou B, Hao C, "Coffee consumption and risk of esophageal cancer incidence: A meta-analysis of epidemiologic studies," *Medicine* (2018) 97(17):e0514.

The meta-analyses do not include data from an important multi-center population-based study in the United States, which demonstrated a significantly elevated risk of adenocarcinoma of the esophagus among those with a daily intake of 60 mg per dy of iosflavones (OR 1.65, 95% CI 1.02 - 2.65) for which coffee was the main source. Petrick JL, Steck SE, Bradshaw PT, Trivers KF, Abrahamson PE, Engel LS, He K, Chow WH, Mayne ST, Risch HA, Vaughan TL, Gammon MD, "Dietary intake of flavonoids and oesophageal and gastric cancer: incidence and survival in the United States of America (USA)," *Br. J. Cancer* (2015) 112(7):1291-1300.

Other epidemiological findings also suggest that coffee may be related to adenocarcinoma of the esophagus. A recent study reported a significant dose response for years of drinking coffee and Barrett's esophagus (metaplastic columnar mucosa), which confers a predisposition to esophageal adenocarcinoma. Compared to non-drinkers, those who drank coffee for more than 30 years had a greater than 4-fold excess risk of Barrett's esophagus (OR 4.18, 95% CI 1.43 - 12.3). Filiberti RA, Fontana V, De Ceglie A, Blanchi S, Grossi E, Della Casa D, Lacchin T, De Matthaeis M, Ignomirelli O, Cappiello R, Rosa A, Foti M, Laterza F, D'Onofrio V, Iaquinto G, Conio M, "Association between coffee or tea drinking and Barrett's esophagus or esophagitis: an Italian study," *Eur. J. Clin. Nutr.* (2017) 71(8):980-986.

4. Gastric Cancer

Ten meta-analyses have been published regarding coffee consumption and the risk of gastric cancer. All of these meta-analyses except one reported increased risks of gastric cancer.

The earliest meta-analysis, published by Portugese investigators in 2006, was based on 16 case-control studies and 7 cohort studies. Comparing highest and lowest exposure groups, risks were close to unity except for a significantly increased risk of gastric cancer for those studies conducted in the United States (RR 1.26, 9% CI 1.02 - 1.57). Botelho F, Lunet N, Barros H, "Coffee and gastric cancer: systematic review and meta-analysis," *Cadernos de Saude Publica* (2006) 22(5):889-900.

A meta-analysis published by Chinese investigators in 2014, based on 12 cohort studies, assessed risk comparing the highest and lowest exposure groups. These researchers reported a nonsignificantly increased risk of gastric cancer for all the cohort studies (RR 1.12, 95% CI 0.93 - 1.36) and significantly increased risks for the American cohort studies (RR 1.36, 95% CI 1.06 - 1.74) and studies with less than 10 years of followup (RR 1.24, 95% CI 1.00-1.54). Xie F, Wang D,

Huang Z, Guo Y, "Coffee consumption and risk of gastric cancer: a large updated meta-analysis of prospective studies," *Nutrients* (2014) 6(9):3734-3746.

A meta-analysis published in 2015 by Chinese researchers that was based on 8 cohort studies, found a slight, non-significant increase in risk comparing consumption versus non-consumption (RR 1.02, 95% CI 0.79 - 1.31). Fang X, Wei J, He X, An P, Wang H, Jiang L, Shao D, Liang H, Li Y, Wang F, Min J, "Landscape of Dietary Factors Associated with Risk of Gastric Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies," *Eur. J. Cancer* (2015) 51:2820-2832.

A meta-analysis published in 2015 by Chinese researchers based on 13 cohort studies, reported increased risks like those of Xie 2014 for all cohort studies (RR 1.13) and for American cohorts only (RR 1.36). Li L, Gan Y, Wu C, Qu X, Sun G, Lu Z, "Coffee consumption and the risk of gastric cancer: a meta-analysis of prospective cohort studies," *BMC Cancer* (2015) 15(1):733.

A meta-analysis by Chinese researchers of 9 cohort studies published in 2015 reported an increased risk of gastric cardia cancer (RR 1.23, 95% CI 1.04 - 1.45). Liu H, Hua Y, Zheng X, Shen Z, Luo H, Tao X, Wang Z, "Effect of coffee consumption on the risk of gastric cancer: a systematic review and meta-analysis of prospective cohort studies," *PLoS One* (2015) 10(5):e0128501.

Another meta-analysis published in 2015 by Chinese researchers, based on 8 cohort studies reported significantly increased risks of gastric cancer for consumption versus non-consumption of coffee (RR 1.24, 95% CI 1.03 - 1.49). Comparing the highest versus lowest exposure groups, this study also reported significant increased risks for the American cohort studies (RR 1.36, 95% CI 1.06 - 1.75) and for those studies with less than 15 years of followup (RR 1.29, 95% CI 1.05 - 1.59). Shen Z, Liu H, Cao H, "Coffee consumption and risk of gastric cancer: an updated meta-analysis," *Clin. Res. Hepatol. Gastroenterol.* (2015) 39:245-253.

Another meta-analysis published in 2015, also by Chinese investigators, based on 9 cohort studies, reported increased risks for all studies comparing highest and lowest exposure groups (RR 1.18, 95% CI 0.90 - 1.55), with the risk being higher for the American cohort studies (RR 1.36, 95%

CI 1.06 - 1.75). Zeng SB, Weng H, Zhou M, Duan XL, Shen XF, Zeng XT, "Long-Term Coffee Consumption and Risk of Gastric Cancer: A PRISMA-Compliant Dose–Response Meta-Analysis of Prospective Cohort Studies," *Medicine* (2015) 94(38):1-11.

A meta-analysis published in 2016 by Chinese researchers, based on 13 cohort studies, reported a significantly increased risk of gastric cardia cancer (RR 1.50, 95% CI 1.09 - 2.07) and of gastric cancer comparing highest versus lowest exposure in the American cohort studies (RR 1.36, 95% CI 1.06 - 1.74). Deng W, Yang H, Wang J, Cai J, Bai Z, Song J, Zhang Z, "Coffee consumption and the risk of incident gastric cancer—A meta-analysis of prospective cohort studies," *Nutr. Cancer* (2016) 68(1):40-47.

Another meta-analysis published in 2016 by Chinese researchers, based on 13 case-control and 9 cohort studies, reported decreased risks of gastric cancer comparing highest and lowest exposure groups in all studies (RR 0.94, 95% CI 0.80-1.10) and in case-control studies (OR 0.85, 95% CI 0.77 - 0.95). Xie Y, Huang S, He T, Su Y, "Coffee consumption and risk of gastric cancer: an updated meta-analysis," *Asia Pac. J. Clin. Nutr.* (2016) 25(3):578-588.

A recent cohort study by Scandinavian researchers supports the association between coffee consumption and gastric cancer. These researchers observed a doubling of the risk of stomach cancer in among never smokers who drank 4 or more cups of boiled coffee per day (HR 2.14, 95% CI 1.10 - 4.16), with a dose-response relationship (p-trend = 0.04). Lukic M, Nilsson LM, Skeie G, Lindahl B, Braaten T, "Coffee consumption and risk of rare cancers in Scandinavian countries," *Eur. J. Epidemiol.* (2018) 33(3):287-302. This study suggests a carcinogenic effect of diterpenes that are present in boiled, but not filtered coffee, and is consistent with the increased risks of gastric cancer reported in some observational studies and meta-analyses of coffee consumption and gastric cancer.

5. Laryngeal Cancer

Four meta-analyses have been published regarding coffee consumption and laryngeal cancer.

In 2010, the Head and Neck Cancer Epidemiology Consortium published a meta-analysis of caffeinated coffee and tea intake and head and neck cancers that was based on 5 case-control studies and 1 cohort study. They reported slightly elevated risks (ORs ranging from 1.04-1.12) for laryngeal cancer for consumption of up to 4 cups of coffee per day, but not for consumption of more than 4 cups of coffee per day. None of these results were statistically significant. Galeone C, Tavani A, Pelucchi C, Turati F, Winn DM, Levi F, Yu GP, Morgenstern H, Kelsey K, Dal Maso L, Purdue MP, McClean M, Talamini R, Hayes RB, Franceschi S, Schantz S, Zhang ZF, Ferro G, Chuang SC, Boffetta P, La Vecchia C, Hashibe M, "Coffee and tea intake and risk of head and neck cancer: pooled analysis in the international head and neck cancer epidemiology consortium,"*Cancer Epidemiol. Biomarkers Prev.* (2010) 19(7):1723-1736.

In 2011 Italian researchers published a meta-analysis of coffee consumption based on 3 case-control studies. Comparing highest and lowest consumption groups, they reported a non-significant increased risk of laryngeal cancer (RR 1.67, 95% CI 0.60 - 4.02). Turati F, Galeone C, La Vecchia C, Garavello W, Tavani A, "Coffee and cancers of the upper digestive and respiratory tracts: meta-analyses of observational studies," *Ann. Oncol.* (2011) 22(3):536-544.

In 2014 researchers from Hunan, China, published a meta-analysis of coffee consumption and the risk of laryngeal cancer based on 5 hospital-based case-control studies and 1 population-based prospective cohort study. Comparing highest to lowest consumption, they reported significant increased risks of laryngeal cancer with coffee consumption for all studies (RR 1.47, 95% CI 1.03 - 2.11), with a higher risk from the 5 case-control studies (RR 1.64, 95% CI 1.08 - 2.50) and European studies (RR 1.63, 85% CI 1.01 - 2.61), but not for Americas studies (RR1.18, 95% Ci 0.70 - 1.99). Risk was also significantly increased for ever versus never consumption (RR 1.36, 95% CI 1.13 - 1.64). The researchers also detected a dose-response relationship between coffee consumption and laryngeal cancer. Chen J, Long S, "Tea and coffee consumption and risk of laryngeal cancer: a systematic review meta-analysis," *PLoS One* (2014) 9(12):e112006.

In 2014 researchers from Shanghai published a meta-analysis of coffee consumption and laryngeal cancer based on 6 hospital-based case-control studies, 1 population-based case-control study, and 1 cohort study. Although results were not statistically significant, comparing highest to lowest consumption, the risk of laryngeal cancer was increased with data combined for all 8 studies (RR 1.22, 95% CI 0.92 - 1.62), for the seven case-control studies (RR 1.28, 95% CI 0.91 - 1.80) and for the 6 hospital-based case-control studies (RR 1.32, 95% CI 0.91 - 1.90). Ouyang Z, Wang Z, Jin J, "Association between tea and coffee consumption and risk of laryngeal cancer: a meta-analysis," *Int. J. Clin. Exp. Med.*(2014) 7(12):5192.

An association between coffee consumption and laryngeal cancer is supported by the results of case-control studies. Thus, a Yugoslavian study reported a high risk of laryngeal cancer with regular and long-term coffee consumption (RR 13.00, $p = 0.001$). Sokić SI, Adanja BJ, Marinković JP, Vlajinac HD, "Case-control study of risk factors in laryngeal cancer," *Neoplasma* (1994) 41(1):43-47. Likewise, in a study from Montenegro, on multiple logistic regression analysis, consumption of more than 5 cups of coffee per day increased the risk of laryngeal cancer 4½-fold (OR 4.52, 95% CI 1.01 - 20.12). Zvrko E, Gledović Z, Ljaljević A, "Risk Factors for Laryngeal Cancer in Montenegro," *Arh. Hig. Rada. Toksikol.* (2008) 59:11-18. More recently, a study by Greek investigators found a strong and consistent relationship between laryngeal cancer and consumption of Greek/Turkish coffee (OR 1.77, $p = 0.002$). Vassileiou A, Vlastarakos PV, Kandiloros D, Delicha E, Ferekidis E, Tzagaroulakis A, Nikolopoulos TP, "Laryngeal cancer: smoking is not the only risk factor," *B-ENT* (2012) 8:273-278. However, the only cohort study of coffee consumption and laryngeal cancer showed no association for consumption of more than 3 cups of coffee per day (HR 1.01, 95% CI 0.71 - 1.44). Ren JS, Freedman ND, Kamangar F, Dawsey SM, Hollenbeck AR, Schatzkin A, Abent CC, "Tea, coffee, carbonated soft drinks and upper gastrointestinal tract cancer risk in a large United States prospective cohort study," *Eur. J. Cancer* (2010) 46(10):1873-1881.

6. Lung Cancer

Six meta-analyses regarding consumption of coffee and lung cancer have been published.

The earliest meta-analysis, based on 8 case-control studies and 5 cohort studies, calculated increased risks comparing highest consumption with non-drinkers and lowest consumption. Risk of lung cancer was significantly increased for all 13 studies (RR 1.27, 95% CI 1.04 - 1.54), with the highest risk resulting from the 5 cohort studies (RR 1.57, 95% CI 1.15 - 2.14). Tang N, Wu Y, Ma J, Wang B, Yu R, "Coffee consumption and risk of lung cancer: a meta-analysis," *Lung Cancer* (2010) 67(1):17-22.

A meta-analysis published by Chinese investigators in 2011 based on 5 cohort studies, reported an increased risk of lung cancer when comparing coffee drinkers with non-drinkers and lowest consumption drinkers (RR 1.17, 95% CI 0.92 - 1.42). Risk was also increased among low to moderate consumers (RR 1.22, 95% CI 0.89 - 1.56), and was higher among high consumers (RR 1.46, 95% CI 0.84 - 2.07). Yu X, Bao Z, Zou J, Dong J, "Coffee consumption and risk of cancers: a meta-analysis of cohort studies," *BMC Cancer* (2011) 11:96.

A meta-analysis by Chinese researchers published in 2012 based on 9 studies, reported a significant linear relationship of coffee consumption with risk of lung cancer, with a monotonic dose-response relationship: 1 cup per day (RR 1.04, 95% CI 0.85 - 1.26), 2 cups per day (RR 1.11, 95% CI 0.92 - 1.34), 3 cups per day (RR 1.23, 95% CI 1.05 - 1.44), 4 cups per day (RR 1.36, 95% CI 1.17 - 1.59), 5 cups per day (RR 1.53, 95% CI 1.30 - 1.79), 6 cups per day (RR 1.72, 95% CI 1.39 - 2.11), 7 cups per day (RR 1.95, 95% CI 1.45 - 2.61). Wang Y, Yu X, Wu Y, Zhang D, "Coffee and tea consumption and risk of lung cancer: A dose-response analysis of observational studies," *Lung Cancer* (2012) 78:167-170.

A meta-analysis published in 2016 was based on 12 case-control studies and 5 cohort studies. Comparing coffee drinkers and nondrinkers, risks of lung cancer were increased in all 17 studies (RR 1.17, 95% CI 1.03 - 1.33), all hospital-based case-control studies (RR 1.36, 95% CI 1.10 - 1.69), all

prospective cohort studies (RR 1.59, 95% CI 1.26 - 2.00), and all studies conducted in the United States (RR 1.34, 95% CI 1.08 - 1.65). Risk was increased among smokers (RR 1.24, 95% CI 1.00 - 1.54), but not nonsmokers (RR 0.85, 95% CI 0.64 - 1.11). To exclude residual confounding from smoking, three studies with no adjustment for smoking were eliminated from the analysis. The pooled lung cancer RRs for the remaining studies were reduced, but still statistically significant: coffee drinkers vs non-drinkers (RR 1.15, 95% CI 1.01-1.32); for the highest consumption category versus the lowest consumption category of coffee drinkers (RR 1.29, 95% CI 1.08-1.54). Xie Y, Qin J, Nan G, Huang S, Wang Z, Su Y, "Coffee Consumption and the Risk of Lung Cancer: An Updated Meta-Analysis of Epidemiological Studies," *Eur. J. Clin. Nutr.* (2016) 70(2):199-206.

Another meta-analysis published in 2016, based on 13 case-control studies and 8 cohort studies, found an increased risk of lung cancer comparing drinkers with never drinkers (RR 1.09, 95% CI 1.00 - 1.19), but not among non-smokers (RR 0.92, 95% CI 0.75 - 1.10). Risk was increased for each 1 cup per day increase in consumption (RR 1.04, 95% CI 1.03 - 1.05), but not among non-smokers (RR 0.95, 95% CI - 0.83 - 1.09). Galarraga V, Boffetta P, "Coffee Drinking and Risk of Lung Cancer – A Meta-Analysis," *Cancer Epidemiol. Biomarkers Prev.* (2016) 25(6):951-957.

In the most recent meta-analysis, based on 4 high-quality cohort studies, the risk of lung cancer was more than doubled comparing consumption with non-consumption (RR 2.18, 95% CI 1.26 - 3.75), the risk being higher among men (RR 3.33, 95% CI 1.34 - 7.92) than women (RR 1.72, 95% CI 1.16 - 2.56). Risk of lung cancer was increased for the studies conducted in the United States (RR 2.33, 95% CI 1.25 - 4.32) and Europe (RR 3.06, 95% CI 0.92 - 10.13), but the increased risk was less for the Japanese studies (RR 1.20, 95% CI 0.60 - 2.40). Risk of lung cancer was increased for 1 study that did not adjust for smoking (RR 1.75, 95% CI 1.07 - 2.89), but a higher risk was noted for the 3 studies that did adjust for smoking (RR 2.45, 95% CI 1.07 - 5.59). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and Cancer Risk: A Meta-Analysis of Prospective Observational Studies," *Sci. Rep.* (2016) 6:33711.

7. Non-Hodgkin's Lymphoma

Two meta-analyses regarding consumption of coffee and non-Hodgkin's lymphoma were published in 2016, both by Chinese investigators.

One meta-analysis, based on 4 case-control and 3 cohort studies, noted a slightly increased risk comparing drinkers with non/seldom drinkers (RR 1.05, 95% CI 0.89 - 1.23), the risk being higher in the cohort studies (RR 1.29, 95% CI 0.92 - 1.80). Han T, Li J,Wang L, Xu H, "Coffee and the Risk of Lymphoma: A Meta-analysis Article," *Iran. J. Public Health* (2016) 45(9):1126-1135. Three case-control studies that reported significantly increased risks of NHL were published after the literature search was conducted by Han and were therefore not included in the meta-analysis, (Cocco P, Zucca M, Sanna S, Satta G, Angelucci E, Gabbas A, Monne M, Campagna M, Scarpa A, Ennas MG, "Interaction Between Dietary and Lifestyle risk Factors and N-Acetyltransferase Polymorphisms in B-Cell Lymphoma Etiology," *J. Environ. Anal. Toxicol.* (2015) 5(5):1000315; Cerliani MB, Pavicic W, Gili JA, Klein G, Saba S, Richard S, "Cigarette smoking, dietary habits and genetic polymorphisms in *GSTT1*, *GSTM1* and *CYP1A1* metabolic genes: A case-control study in oncohematological diseases," *World J. Clin. Oncol.* (2016) 7(5):395-405; Parodi S, Merlo FD, Stagnaro E, Working Group for the Epidemiology of Hematolymphopoietic Malignancies in Italy "Coffee consumption and risk of non-Hodgkin's lymphoma: evidence from the Italian multicentre case-control study," *Cancer Causes Control* (2017) 28(8):867-876), and a fourth was not identified (Gong Y, "Pulp and Paper Industry Emissions and Non-Hodgkin's Lymphoma Risk," *Queen's University* (2000) Kingston, Ontario, Canada [Masters' Thesis]. Therefore, the meta-analysis based on case-control studies did not take into consideration four studies that demonstrate significantly elevated risks of NHL in relation to coffee consumption. As such, it cannot be relied upon to make a determination of NHL risk in relation to coffee intake.

The other meta-analysis, based on the same three cohort studies as the Han meta-analysis, reported a higher increased risk of non-Hodgkin's lymphoma comparing highest versus lowest coffee

intake (RR 1.23, 95% CI 0.75 - 2.03). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and Cancer Risk: A Meta-Analysis of Prospective Observational Studies," *Sci. Rep.* (2016) 6:33711. Thus, the results are virtually identical to the meta-analysis by Han, et al.

8. Ovarian Cancer

Four meta-analyses of epidemiologic studies have been published regarding coffee and ovarian cancer.

In 2007 researchers from the Netherlands published results from a cohort study, and from a meta-analysis of coffee drinking and ovarian cancer risk based on data from 11 case-control studies, and 5 cohort studies. The cohort study did not show a significant dose-response. As indicated in the cohort meta-analysis, however, a comparison of low coffee intake (< 1 cup/day) with high coffee consumption (> 5 cups/day) RR 1.48, 95% CI 0.80 -2.75). For pooled cohort study results, the overall risk for ovarian cancer comparing highest and lowest coffee consumption was increased (OR 1.18, 95% CI 0.97 - 1.44). The risk of ovarian cancer also was increased based upon pooled data from the case-control studies (OR 1.15, 95% CI 0.89 - 1.47). The investigators concluded "Coffee was related to increased cancer risk when study results were pooled. A stronger, increased borderline significant association was seen in cohort studies." Steevens J, Schouten LJ, Verhage BA, Goldbohm RA, Van Den Brandt PA, "Tea and coffee drinking and ovarian cancer risk: results from the Netherlands Cohort Study and a meta-analysis," *Br. J. Cancer* (2007) 97(9):1291-1294.

In 2012 European researchers published a meta-analysis of all prospective cohort studies regarding coffee consumption and ovarian cancer until April 2011, including three studies published after the meta-analysis by Steevens, and EPIC data. They reported a nonsignificant increased risk of ovarian cancer comparing the highest and lowest categories of coffee consumption (HR 1.13, 95% CI 0.89 - 1.43). They also did a dose-response, random-effects, meta-regression analysis not

including the EPIC data, calculating a slightly increased risk of ovarian cancer for an increment of one cup of coffee per day of borderline statistical significance (HR 1.02, 95% CI 0.99 - 1.05). Braem MG, Onland-Moret NC, Schouten LJ, Tjønneland A, Hansen L, Dahm CC, Overvad K, Lukanova A, Dossus L, Floegel A, Boeing H, "Coffee and tea consumption and the risk of ovarian cancer: a prospective cohort study and updated meta-analysis," *Am. J. Clin. Nutr.* (2012) 95(5):1172-1181.

In 2016 Chinese researchers published a meta-analysis of prospective observational studies of coffee consumption and risk of cancer. The analysis of ovarian cancer was based on nine cohort studies. Comparing highest versus lowest coffee intake, the risk of ovarian cancer was slightly, but nonsignificantly increased (RR 1.04, 95% CI 0.90 - 1.20). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and Cancer Risk: A Meta-Analysis of Prospective Observational Studies," *Sci. Rep.* (2016) 6:33711.

In 2018 Italian researchers published a meta-analysis of coffee consumption and ovarian cancer based on 8 cohort studies, comprising 787,076 participants and 3,541 ovarian cancer cases. Risk of ovarian cancer was slightly, but nonsignificantly increased (RR 1.06, 95% CI 0.89 - 1.26). However, a monotonic dose-response relationships was observed for coffee consumption and ovarian cancer: 1 cup per day (HR 1.01, 95% CI 0.97 - 1.05), 2 cups per day (HR 1.02, 95% CI 0.95 - 1.10), 3 cups per day (HR 1.04, 95% CI 0.92 - 1.16), 4 cups per day (HR 1.05, 95% CI 0.90 - 1.22), 5 cups per day (HR 1.06, 95% CI 0.88 - 1.28), 6 cups per day (HR 1.07, 95% CI 0.83 - 1.35), 7 cups per day (HR 1.09, 95% CI 0.83 - 1.42). Additionally, higher risks, also exhibiting a monotonic dose-response relationship were observed for ovarian cancer in postmenopausal women: 1 cup per day (HR 1.04, 95% CI 0.98 - 1.09), 2 cups per day (HR 1.08, 95% CI 0.97 - 1.19), 3 cups per day (HR 1.12, 95% CI 0.95 - 1.30), 4 cups per day (HR 1.16, 95% CI 0.94 - 1.42), 5 cups per day (HR 1.20, 95% CI 0.93 - 1.55), 6 cups per day (HR 1.24, 95% CI 0.91 - 1.70), 7 cups per day (HR 1.29, 95% CI 0.90 - 1.85). Berretta M, Micek A, Lafranconi A, Rossetti S, Di Francia R, De Paoli P, Rossi P, Facchini G, "Coffee Consumption is Not Associated With Ovarian Cancer Risk: A Dose-Response Meta-Analysis of Prospective Cohort Studies," *Oncotarget* (2018) 9(29):20807-20815.

9. Pancreatic Cancer

Six meta-analyses regarding consumption of coffee and pancreatic cancer have been published.

Two meta-analyses, both published by Chinese investigators in 2011 and both based on 14 cohort studies, reported identical reduced risks of pancreatic cancer for drinkers versus non-drinkers (RR 0.82, 95% CI 0.69 - 0.95), low to moderate drinkers versus non-drinkers (RR 0.86, 95% CI 0.76 - 0.96), and high drinkers versus non-drinkers (RR 0.68, 95% CI 0.51 - 0.84). Dong J, Zou J, Yu XF, "Coffee Drinking and pancreatic cancer risk: a meta-analysis of cohort studies," *World J. Gastroenterol.* (2011) 17(9):1204-1210; Yu X, Bao Z, Zou J, Dong J, "Coffee consumption and risk of cancers: a meta-analysis of cohort studies," *BMC Cancer* (2011) 11:96.

A study by Italian investigators published in 2012, based on 37 case-control studies and 17 cohort studies, reported increased risks comparing highest consumption with lowest consumption, for all studies (RR 1.13, 95% CI 0.99 - 1.29), all smoking-adjusted studies (RR 1.08, 95% CI 0.94 - 1.25), all smoking-adjusted case-control studies (RR 1.10, 95% CI 0.92 - 1.31), and all smoking-adjusted cohort studies (RR 1.04 95% CI 0.80 - 1.36). Turati F, Galeone C, Edefonti V, Ferraroni M, Lagiou P, La Vecchia C, Tavani A, "A meta-analysis of coffee consumption and pancreatic cancer," *Ann. Oncol.* (2012) 23(2):311-318.

A meta-analysis published by Chinese researchers in 2016, based on 20 cohort studies that compared highest versus lowest exposure, reported a risk for all 20 cohort studies near unity (RR 0.99, 95% CI 0.81 - 1.21), which increased slightly when one heterogeneous study was excluded (RR 1.06, 95% CI 0.94 - 1.20). Nie K, Zing Z, Huang W, Wang W, Liu W, "Coffee intake and risk of pancreatic cancer: an updated meta-analysis of prospective studies," *Minerva Med.* (2016) 107(4):270-278.

Another meta-analysis published by Chinese investigators in 2016, also based on 20 cohort studies, compared highest versus lowest exposure, reporting a significantly decreased risk of

pancreatic cancer (RR 0.75, 95% CI 0.63 - 0.86). However, the risk approached unity for an incremental exposure of 1 cup of coffee per day (RR 0.99, 95% CI 0.96 - 1.03). Ran HQ, Wang JZ, Sun CQ, "Coffee Consumption and Pancreatic Cancer Risk: An Update Meta-Analysis of Cohort Studies, *Pak. J. Med. Sci.* (2016) 32(1):253-259.

Yet another meta-analysis published by Chinese investigators in 2016, based on 15 cohort studies, reported a nonsignificant risk of pancreatic cancer slightly above 1 comparing highest and lowest exposures (RR 1.02, 95% CI 0.87 - 1.18). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and Cancer Risk: A Meta-Analysis of Prospective Observational Studies," *Sci. Rep.* (2016) 6:33711.

10. Prostate Cancer

Ten meta-analyses of epidemiologic studies regarding consumption of coffee and prostate cancer have been published.

The earliest meta-analysis, published in 2010 by Korean researchers, which was based on 8 case-control studies and 4 cohort studies, reported a significantly increased risk of prostate cancer comparing highest to lowest consumption (RR 1.16, 95% CI 1.01 - 1.33). The increased risk was greater in the analysis based on the case-control studies (RR 1.21, 95% CI 1.03 - 1.43) than the analysis based on the cohort studies (RR 1.06, 95% CI 0.83 - 1.35). Park CH, Myung SK, Kim TY, Seo HG, Jeon YJ, Kim Y, "Coffee consumption and risk of prostate cancer: a meta-analysis of epidemiological studies," *BJU Int.* (2010) 106(6):762-769.

A meta-analysis published in 2011 by Chinese investigators, based on 5 cohort studies, reported a significantly reduced risk of prostate cancer comparing coffee drinkers to non-lowest drinkers (RR 0.79, 95% CI 0.61 - 0.98). However, the risk for high consumption was not statistically significant (RR 0.81, 95% CI 0.58 - 1.05). Yu X, Bao Z, Zou J, Dong J, "Coffee consumption and risk of cancers: a meta-analysis of cohort studies," *BMC Cancer* (2011) 11:96.

A meta-analysis published in 2014 by European researchers, based on 3 case-control studies and 5 cohort studies, reported risks slightly below unity for an incremental increase in exposure of 3 cups per day for low-grade nonaggressive cancer (RR 0.97, 95% CI 0.92 - 1.03), localized nonaggressive cancer (RR 0.97, 95% CI 0.94 - 0.99), and high-grade advanced cancer (RR 0.95, 95% CI 0.85 - 1.06), with lower risks for high-grade aggressive cancer (RR 0.89, 95% CI 0.78 - 1.00) and fatal cancer (RR 0.89, 95% CI 0.82 - 0.97). Discacciati A, Orsini N, Wolk A, "Coffee consumption and risk of nonaggressive, aggressive and fatal prostate cancer--a dose-response meta-analysis," *Ann. Oncol.* (2014) 25(3):584-591.

Another meta-analysis published in 2014, based on 12 case-control studies and 12 cohort studies reported a slight decrease in risk comparing highest and non-lowest consumption for all studies (RR 0.94, 95% CI 0.85 - 1.05), but a statistically significant increased risk for the hospital-based case-control studies (RR 1.29, 95% CI 1.01 - 1.65). Zhong S, Chen W, Yu X, Chen Z, Hu Q, Zhao J, "Coffee Consumption and Risk of Prostate Cancer: An Up-to-Date Meta-Analysis," *Eur. J. Clin. Nutr.* (2014) 68:330-337

Another meta-analysis published in 2014, based on 10 cohort studies, reported a significantly decreased risk of prostate cancer comparing regular coffee drinkers to seldom/never drinkers (RR 0.88, 95% CI 0.82 - 0.95). Cao S, Liu L, Yin X, Wang Y, Liu J, Lu Z, "Coffee consumption and risk of prostate cancer: a meta-analysis of prospective cohort studies," *Carcinogenesis* (2014) 35(2):256-261.

Another meta-analysis published in 2014, based on 12 case-control studies and 9 cohort studies, reported a significantly decreased risk of prostate cancer comparing highest vs. lowest consumption (RR 0.91, 95% CI 0.86 - 0.97). Lu Y, Zhai L, Zeng J, Peng Q, Wang J, Deng Y, Xie L, Mo C, Yang S, Li S, Qin X, "Coffee consumption and prostate cancer risk: an updated meta-analysis," *Cancer Causes Control* (2014) 25(5):591-604.

Yet another meta-analysis published in 2014, based on 8 cohort studies, reported a significantly decreased risk of prostate cancer for highest consumption versus none/least

consumption (RR 0.86, 95% CI 0.79 - 0.95), but the risk was not statistically significant for advanced cancer (RR 0.73, 95% CI 0.50 - 1.07). Huang TB, Guo ZF, Zhang XL, Zhang XP, Liu H, Geng J, Yao XD, Zheng JH, "Coffee consumption and urologic cancer risk: a meta-analysis of cohort studies," *Int. Urol. Nephrol.* (2014) 46(8):1481-1493.

A meta-analysis published in 2015, based on 13 cohort studies, also reported a significantly decreased risk of prostate cancer comparing highest and lowest consumption (RR 0.90 , 95% CI 0.85 - 0.95). Liu H, Hu GH, Wang XC, Huang TB, Xu L, Lai P, Guo ZF, Xu YF, "Coffee consumption and prostate cancer risk: a meta-analysis of cohort studies," *Nutr. Cancer* (2015) 67(3):392-400.

A meta-analysis by Chinese researchers, published in 2016, based on 14 cohort studies, reported a significantly decreased risk of prostate cancer comparing consumption versus non-consumption (RR 0.89, 95% CI 0.84 - 0.93), but the risk was higher for the 5 studies conducted in the United States (RR 0.93, 95% CI 0.87 - 1.00) and was increased for the one study conducted in Canada (RR 1.42, 95% CI 0.77 - 2.16). Risk of prostate cancer was significantly decreased in the 9 studies that did not adjust for smoking (RR 0.92, 95% CI 0.86 - 0.99), as well as the 5 studies that did adjust for smoking (RR 0.81, 95% CI 0.73 - 0.89). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and Cancer Risk: A Meta-Analysis of Prospective Observational Studies," *Sci. Rep.* (2016) 6:33711.

The most recent meta-analysis, published in 2017 by Chinese researchers, based on 14 case-control and 14 cohort studies, reported a slightly but nonsignificantly increased risk of prostate cancer comparing high versus non/lowest coffee consumption (RR 1.05, 95% CI 0.96 - 1.18). Prostate cancer risk was significantly increased in the case-control studies (RR 1.19, 95% CI 1.05 - 1.35) but not in the cohort studies (RR 0.97, 95% CI 0.84 - 1.12). Xia J-D, Chen J, Xue J-X, Yang J, Wang Z-J, "An Up-to-date Meta-analysis of Coffee Consumption and Risk of Prostate Cancer," *Urology J.* (2017) 14(5):4079-4088.

11. Total Cancer Mortality

Total cancer mortality is a broad category that encompasses death from all types of cancer that is often examined in epidemiological studies. Evaluating total cancer mortality is one way to assess the total impact on mortality from cancer in relation to various risk factors. Thus, assessing the association between coffee consumption and total cancer mortality is one means of examining the effect of coffee consumption on mortality from cancer in the aggregate. In its monograph, IARC identified 10 studies that evaluated coffee consumption in relation to total cancer mortality.

In an early Norwegian cohort study that was not identified in the IARC monograph regarding total cancer mortality, comparing men who consumed more than 7 cups of coffee per day with men who consumed 2 or less cups of coffee per day, after the first four years of follow-up, the risk of all cancer mortality was increased (RR 1.31, 95% confidence interval not provided, *p*-trend = 0.09). Jacobsen BK, Bjelke E, Kvåle G, Heuch I, "Coffee Drinking, Mortality, and Cancer Incidence: Results From a Norwegian Prospective Study," *J. Natl. Cancer Inst.* (1986) 76(5):823-831.

In the Iowa Women's Health Study, consumption of 6 or more cups of coffee per day was associated with nonsignificantly reduced total cancer mortality on multivariate analysis (HR 0.95, 95% CI 0.76 - 1.16). Andersen LF, Jacobs Jr DR, Carlsen MH, Blomhoff R," Consumption of Coffee is Associated with Reduced Risk of Death Attributed to Inflammatory and Cardiovascular Diseases in the Iowa Women's Health Study," *Am. J. Clin. Nutr.* (2006) 83:1039-1046.

In a small study of elderly Finnish adults, total cancer mortality was slightly but nonsignificantly increased among those consuming 5-6 cups of coffee per day (RR 1.04, 95% CI 0.56 - 1.94). Happonen P, Läärä E, Hiltunen L, Luukinen H, "Coffee consumption and mortality in a 14-Year follow-up of an elderly northern Finnish population," *Br. J. Nutr.* (2008) 99:1354-1361.

A Japanese cohort study reported a non-significant increase in total cancer mortality among men in relation to consumption of coffee. Comparing men who drank coffee occasionally to men who never drank coffee, the risk of total cancer mortality was nonsignificantly decreased (HR 0.88,

95% CI 0.67 - 1.14). Among men who consumed 1-2 cups of coffee per day, the risk of total cancer mortality was nonsignificantly increased (HR 1.09, 95% CI 0.83 - 1.44), while men who consumed more than 3 cups of coffee per day had the highest risk of total cancer mortality (HR 1.15, 95% CI 0.82 - 1.62). Sugiyama K, Kuriyama S, Akhter M, Kakizaki M, Nakaya N, Ohmori-Matsuda K, Shimazu T, Nagai M, Sugawara Y, Hozawa A, Fukao A, Tsuji I, "Coffee Consumption and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Japanese Women," *J. Nutr.* (2010) 140(5):1007-1013.

In the Japan Collaborative Cohort Study for Evaluation of Cancer Risk, total cancer mortality (excluding deaths occurring within the first 4 years) among those who drank four or more cups of coffee per day was nonsignificantly increased among men (HR 1.13, 95% CI 0.88 - 1.44) and nonsignificantly decreased among women (HR 0.90, 95% CI 0.55 - 1.49). Tamakoshi A, Lin Y, Kawado M, Yagyu K, Kikuchi S, Iso H," Effect of coffee consumption on all-cause and total cancer mortality: findings from the JACC study," *Eur. J. Epidemiol.* (2011) 26(4):285-293.

In the National Institutes of Health - AARP Diet and Health Study, nonsignificantly increased cancer mortality was observed among those who drank 6 or more cups of coffee per day in men (HR 1.08, 95% CI 0.98 - 1.10) and among women (HR 1.03, 95% CI 0.90 - 1.16). A statistically significant dose-response was found in men (p for trend = 0.02), but not in women. Freedman, ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R, "Association of Coffee Drinking with Total and Cause-Specific Mortality," *New Engl. J. Med.* (2012) 366(20):1891-1904.

In the Northern Manhattan Study, nonsignificant reductions in total cancer mortality were observed among those who drank four or more cups of coffee per day. Gardener H, Rundek T, Wright CB, Elkind MSV, Sacco RL, "Coffee and Tea Consumption Are Inversely Associated with Mortality in a Multiethnic Urban Population," *J. Nutr.* (2013) 143(8):1299-1308.

In the Swedish component of the Scandinavian Women's Lifestyle and Health Cohort, a 40% increased risk of cancer mortality was found among women older then 50 who drank more than 5 cups of coffee per day (RR 1.40, 95% CI 1.05 - 1.89). Löf M, Sandin S, Yin L, Adami H-O,

Weiderpass E, "Prospective study of coffee consumption and all-cause, cancer, and cardiovascular mortality in Swedish women," *Eur. J. Epidemiol.* (2015) 30(9):1027-1034.

In the Nurses' Health Study and Health Professionals Follow-up Study, among those who consumed more than 5 cups of coffee per day, risk of total cancer mortality was significantly increased (HR 1.16, 95% CI 1.06 - 1.27) and a dose-response was evident. Ding M, Satija A, Bhupathiraju SN, Hu Y, Sun Q, Han J, Lopez-Garcia E, Willett W, van Dam RM, Hu FB, "Association of Coffee Consumption With Total and Cause-Specific Mortality in 3 Large Prospective Cohorts," *Circulation* (2015) 132(24):2305-2315.

In the PLCO Cohort Study, among those in the highest quartile of coffee consumption, risk of total cancer mortality was increased but not quite statistically significant (RR 1.05, 95% CI 0.99 - 1.11). Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang Z-F, La Vecchia C, "Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort," *Br. J. Cancer* (2015) 113(5):809-816.

In the Japan Public Health Center-based Prospective Study, consumption of 5 or more cups of coffee per day among never smokers was nonsignificantly reduced on multivariate analysis in men (HR 0.56, 95% CI 0.18 - 1.76) and among women (HR 0.64, 95% CI 0.34 - 1.20). Saito E, Inoue M, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Sasazuki S, Noda M, Iso H, Tsugane S, "Association of coffee intake with total and cause-specific mortality in a Japanese population: the Japan Public Health Center-based Prospective Study," *Am. J. Clin. Nutr.* (2015) 101:1029-1037.

Since IARC completed its review of the literature regarding coffee consumption and cancer in 2016, four studies regarding coffee consumption and total cancer mortality have been published.

In a study of coffee consumption and death from all cancers combined and from specific cancer types among 922,896 participants in the Cancer Prevention Study II, "there was a significant positive association between coffee consumption and risk of death from all cancers. Most, though not all, of this association was eliminated by adjustment for smoking dose and duration." However, in an analysis of nonsmokers, increased mortality was observed from esophageal cancer among participants consuming six or more cups of coffee per day (HR 1.25, 95% CI 1.00 - 1.55), from lung

cancer among participants consuming 4 to 5 cups of coffee per day (HR 1.10, 95% CI 1.02 - 1.19) and six or more cups of coffee per day (HR 1.15, 95% CI 1.06 - 1.25), and from leukemia among most consumption groups: up to 1 cup of coffee per day (HR 1.13, 95% CI 1.00 - 1.28), 2 to 3 cups per day (HR 1.10, 95% CI 0.97 - 1.23), 4 to 5 cups per day (HR 1.14, 95% CI 1.00 - 1.31), and 6 or more cups per day (HR 1.17, 95% CI 1.01 - 1.37). Notably, among never smokers, excess mortality was observed among participants drinking 4 to 5 cups of coffee per day from pancreatic cancer (HR 1.13, 95% CI 1.00 - 1.28) and lung cancer (HR 1.16, 95% CI 1.01 - 1.33), and among participants drinking 6 or more cups per day from esophageal cancer (HR 1.47, 95% CI 1.00 - 2.16). Gapstur SM, Anderson RL, Campbell PT, Jacobs EJ, Hartman TJ, Hildebrand JS, Wang Y, McCullough ML, "Associations of Coffee Drinking and Cancer Mortality in the Cancer Prevention Study-II," *Cancer Epidemiol. Biomarkers Prev.* (2017) 26(10):1477-1486.

In the Three-Prefecture Cohort Study, Japanese investigators reported that in the Japnese population studied, increasing coffee consumption was associated with decreased risk of all-sites cancer incidence and mortality. Sado J, Kitamura T, Kitamura Y, Sobue T, Nishino Y, Tanaka H, Nakayama T, Tsuji I, Ito H, Suzuki T, Katanoda K, Tominaga S, "Association between coffee consumption and all-sites cancer incidence and mortality," *Cancer Sci.* (2017) 108(10):2079-2087.

In a recent publication from the Netherlands Cohort Study, in multivariable analysis, consumption of 6 or more cups of coffee per day significantly increased the risk of death from cancer almost 50% among men (HR 1.49, 95% CI 1.04 - 2.13), but not among women. Van den Brandt PA, "Coffee or Tea? A prospective cohort study on the association of coffee and tea intake with overall and cause-specific mortality in men versus women," *Eur. J. Epidemiol.* (2018) 33:183-200.

In 2018 IARC published a large study of the European Prospective Investigation into Cancer and Nutrition (EPIC) regarding coffee consumption and mortality that included 521,330 participants from 10 European countries. This study demonstrated a significant increase in total cancer mortality by quartile of coffee consumption (p-trend = 0.002). The trend appeared to be a reflection of a significantly elevated cancer risk among women (p-trend = 0.001). Compared to nondrinkers,

women who were in the highest quartile of coffee consumption had significantly increased total cancer mortality (RR 1.12, 95% CI 1.02 - 1.23). Gunter MJ, Murphy N, Cross AJ, Dossus L, Dartols L, Fagherazzi G, Kaas R, Kühn T, Boeing H, Aleksandrova K, Tjønneland A, Olsen A, Overvad K, Larsen SC, Cornejo MLR, Agudo A, Pérez, MJS, Altzibar JM , Navarro C, Ardanaz E, Khaw K-T, Butterworth A, Bradbury KE, Trichopoulou A, Lagiou P, Trichopoulos D, Palli D, Grioni S, Vineis P, Panico S, Tumino R, Bueno-de-Mesquita B, Siersema P, Leenders M, Beulens JWJ, Uiterwaal CU, Wallström P, Nilsson LM, Landberg R, Weiderpass E, Skele G, Braaten T, Brennan P, Licaj I, Muller DC, Sinha R, Wareham N, Riboli E, "Coffee Drinking and Mortality in 10 European Countries: A Multinational Cohort Study," *Ann. Intern. Med.* (2018) 168(5):380-381.

Thus, of the four studies regarding coffee consumption and total cancer mortality published since IARC completed its review in 2016, three studies showed some evidence of increased cancer mortality. The largest and most impressive of the studies, is the EPIC study in which IARC found a statistically significant increased risk of all cancer mortality with a highly significant dose-response trend. Collectively, the studies published after IARC completed its review in 2016, including IARC's own 2018 study, do not support the Working Group's conclusion that among the total cancer mortality studies there were "no exposure-response and no statistically significant overall increase or decrease in risk among the heaviest consumers."

The epidemiological studies regarding coffee consumption and total cancer mortality do not indicate an inverse association between coffee consumption and mortality from cancer. These studies also do not support OEHHA's conclusion in the Initial Statement of Reasons that consumption of coffee does not increase the risk of any cancer. Indeed, collectively, these do not show an absence of cancer risk, but rather indicate some degree of cancer mortality risk. Thus, this body of epidemiologic literature does not support OEHHA's assumption that coffee consumption causally reduces or prevents human cancer or mortality from human cancer, which assumption is one of the predicates upon which OEHHA relies to support its proposed new regulation.

C. Studies Comparing Cancer Risks of Drinking Coffee and Water

Another means of assessing the association between coffee consumption and cancer is to evaluate those studies that compare cancer risks from consumption of coffee with water intake. Some epidemiologic studies compare cancer risks of coffee consumption with water consumption. If coffee actually caused 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 association from consumption of coffee with no reduction in risk of water. However, in the few studies that have compared cancer risks of coffee consumption and water intake, this has not been observed. Rather, 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.

In a population-based case-control study, the risk of bladder cancer in the highest coffee consumption group (>40 eight-ounce servings/week) was significantly increased (OR 1.60, 95% CI 1.00 - 2.56), whereas the highest water consumption intake (> 33 eight-ounce glasses/week) was not associated with bladder cancer risk (OR 1.15, 95% CI 0.79 - 1.69). Slattery ML, West DW, Robison LM, "Fluid Intake and Bladder Cancer in Utah," *Int. J. Cancer* (1988) 42(1):17-22.

In a multi-center population-based case-control study of 1,185 histopathologically confirmed cases of kidney cancer and 1,526 controls, highest coffee consumption (≥ 42 cups/week) doubled the risk of kidney cancer in women (RR 2.11, 95% CI 1.18 - 3.77). The investigators found no association of kidney cancer with water or total beverage consumption. Wolk A, Gridley G, Niwa S, Lindblad P, McCredie M, Mellemgaard A, Mandel JS, Wahrendorf J, McLaughlin JK, Adami HO, "International Renal Cell Cancer Study. VII. Role of Diet," *Int. J. Cancer* (1996) 65:67-73.

In the Health Professionals Follow-up Study, on multivariate analysis, water was the only beverage inversely associated with risk of bladder cancer (RR 0.89, 95% CI 0.83 - 0.96, *p*-trend = 0.002). Coffee was not associated with decreased bladder cancer risk. Michaud DS, Spiegelman

D, Clinton SK, Rimm EB, Curhan GC, Willett WC, Giovannucci EL, "Fluid Intake and the Risk of Bladder Cancer in Men," *New Engl. J. Med.* (1999) 340:1390-1397.

In a population-based case-control study, risk of colon cancer was not associated with consumption of more than 4 to 6 cups of caffeinated or decaffeinated coffee per day, but was significantly decreased 19% for equivalent consumption of water (OR 0.81, 95% CI 0.68 - 0.97). Slattery ML, Caan BJ, Anderson KE, Potter JD, "Intake of Fluids and Methylxanthine-Containing Beverages: Association with Colon Cancer," *Int. J. Cancer* (1999) 81:199-204.

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 (OR 1.19, 95% CI 0.85 - 1.68), but drinking 4 to 5 glasses of water per day significantly reduced the risk of bladder cancer by about 25%. (OR 0.74, 95% CI 0.56 - 0.98). Jiang X, Castelao JE, Groshen S, Cortessis VK, Shibata DK, Conti DV, Gago-Dominguez M, "Water intake and bladder cancer risk in Los Angeles County," *Int. J. Cancer* (2008) 123:1649-1656.

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 (OR 1.33, 95% CI 1.07 - 1.66), but was not associated with consumption of more than 4½ glasses of tap water per day (OR 1.13, 95% CI 0.88 - 1.43). Hu J, Mao Y, DesMeules M, Dsizmadi I, Friedenreich C, Mery L, The Canadian Cancer Registries Epidemiology Research Group, "Total fluid and specific beverage intake and risk of renal cell carcinoma in Canada," *Cancer Epidemiol.* (2009) 33:355-362.

In a meta-analysis of 17 case-control studies and 4 cohort studies regarding total fluid intake and bladder cancer, comparing the highest and lowest level of intake, risk of bladder cancer was significantly increased for consumption of coffee (OR 1.17, 95% CI 1.03 - 1.33), but bladder cancer risk was not associated with consumption of any of the several other beverages evaluated. Bai Y, Yuan H, Li J, Tang Y, Pu C, Han P, "Relationship between bladder cancer and total fluid intake: a meta-analysis of epidemiological evidence," *World J. Surg. Oncol.* (2014) 12:223.

These studies suggest that coffee consumption does not causally reduce human cancer risk.

D. Studies Reporting Increased Risks of Cancer Since the IARC Meeting

In the approximately two years since the IARC Working Group on Coffee met in May 2016 and evaluated the published literature available at that time, several epidemiologic studies regarding coffee consumption have been published that report increased risks of various cancers.

1. Bladder Cancer

Four studies regarding consumption of coffee and bladder cancer have been published since IARC reviewed the literature in 2016. All reported increased risks of bladder cancer.

In a prospective study in India that compared bladder cancer in patients under age 40 with those over age 60, coffee consumption was a significant risk factor in young bladder cancer patients ($p = 0.033$). Singh JP, Priyadarshi V, Pal DK, "A clinicoepidemiological study of young age bladder tumors: An eastern Indian scenario," *J. Cancer Res. Ther.* (2016) 12:751-754.

In the NIH-AARP prospective cohort study, coffee drinking was positively associated with bladder cancer in models adjusted for age and sex when comparing those drinking 4 or more cups of coffee per day to nondrinkers (HR 1.91, 95% CI 1.70 - 2.14; p trend < 0.0001). After adjustment for cigarette smoking and other potential confounders, the association was attenuated, but still statistically significant (HR 1.18, 95% Ci 1.05 - 1.33, p trend = 0.0007). However, no association was found among never smokers. Loftfield E, Freedman ND, Inoue-Choi M, Graubard BI, Sinha R, "A Prospective Investigation of Coffee Drinking and Bladder Cancer Incidence in the United States," *Epidemiology* (2017) 28(5):685-693.

In an Italian hospital-based case-control study of men that investigated lifestyle exposures and genetic traits on leucocyte telomere length and bladder cancer risk, cumulative consumption of coffee was associated with a significantly increased risk of bladder cancer ($p = 0.006$). Pavanello S, Carta A, Mastrangelo G, Campisi A, Porru S, "Relationship between Telomere Length, Genetic

Traits and Environmental/Occupational Exposures in Bladder Cancer Risk by Structural Equation Modelling," *Int. J. Environ. Res. Public Health* (2018) 15:5.

In a recent study, Scandinavian researchers reported a significantly increased risk of bladder cancer among never smokers who drank four or more cups of coffee per day compared to those who drank 1 or less cups of coffee per day (HR 1.87, 95% CI 1.01 - 3.45). Lukic M, Nilsson LM, Skeie G, Lindahl B, Braaten T, "Coffee consumption and risk of rare cancers in Scandinavian countries," *Eur. J. Epidemiol.* (2018) 33(3):287-302. This is an important study because it shows an increased risk of bladder cancer among heavy coffee drinkers who never smoked cigarettes, an effect that cannot be attributed to confounding by smoking.

2. Breast Cancer

Three recent studies found increased risks of breast cancer in relation to coffee consumption.

In a relatively small hospital-based case-control study of breast cancer risk factors among Vietnamese women that was published the year after the IARC meeting, consumption of 1 or more cups of coffee per day was associated with an increased risk of breast cancer among South Vietnamese women on multivariate analysis (OR 1.5, 95% CI 1.0 - 2.6), with a greater risk among post-menopausal women South Vietnamese women (OR 2.1, 95% CI 1.0 - 4.6). Trieu PD, Mello-Thoms C, Peat JK, Do TD, Brennan PC, "Inconsistencies of Breast Cancer Risk Factors between the Northern and Southern Regions of Vietnam," *Asian Pac. J. Cancer Prev.* (2017) 18(10):2747-2754.

In a recent study of 126,182 postmenopausal women in the United Kingdom Biobank, of whom 2,636 had breast cancer, women who had received postmenopausal hormone therapy and who consumed four or more cups of coffee per day had a 22% greater risk of breast cancer than women who consumed less that 7 cups of coffee per week (HR 1.22, 95% CI 1.01 - 1.47). Yaghjyan L, Rich S, Mao L, Mai V, Egan KM, "Interactions of coffee consumption and postmenopausal hormone use in relation to breast cancer risk in UK Biobank," *Cancer Causes Control* (2018) 29:519-525.

In a study comprised of a subcohort of 3,185 women from a cohort of 39,532 female participants followed for a median period of approximately 12.2 years, 922 cases of breast cancer were obtained. While consumption of coffee was not associated with overall risk of breast cancer, the investigators observed a tendency towards an increased risk of breast cancer with increasing levels of total coffee and caffeinated coffee among premenopausal and normal weight women. Arthur R, Kirsh VA, Rohan TE, "Associations of coffee, tea and caffeine intake with risk of breast, endometrial and ovarian cancer among Canadian women," *Cancer Epidemiol.* (2018) 56:75-82.

3. Colorectal Cancer

Two epidemiological studies published since IARC completed its review have reported increased risks of colorectal cancers in association with consumption of coffee.

An investigation of 1,282 cases of colorectal cancer among postmenopausal US women in the Women's Health Initiative Observational Study revealed an increased incidence of colorectal cancer among moderate and high coffee drinkers compared to nondrinkers on multivariate analysis: (HR 1.15, 95% CI 1.02 - 1.29; HR 1.14, 95% CI 0.93 - 1.38). High risks of colorectal cancer were observed for moderate drip brew coffee intake (HR 1.20, 95% CI 1.05 - 1.36) and high nondrip brew coffee intake (HR 1.43, 95% CI 1.01 - 2.02). Groessl EJ, Allison MA, Larson JC, Ho SB, Snetslaar LG, Lane DS, Tharp KM, Stefanick ML, "Coffee Consumption and the Incidence of Colorectal Cancer in Women," *J. Cancer Epidemiol.* (2016) Article ID 6918431.

A recent study of 476,160 men and women from 10 European countries (the EPIC cohort) evaluated the association between dietary intakes of total and individual classes and subclasses of polyphenols and colorectal cancer risk. During a mean follow-up of 14 years, there were 5,991 incident colorectal cancer cases, of which 3,897 were in the colon and 2,094 were in the rectum. In multivariable-adjusted Cox regression models, a doubling in total dietary polyphenol intake was associated with an increase of colorectal cancer risk of borderline statistical significance in women

(HR 1.06, 95% CI 0.99 - 1.14), but not in men (HR 0.97, 95% CI 0.90 - 1.05). Phenolic acid intake, which is highly correlated with coffee consumption, was positively associated with rectal cancer in women (HR 1.10, 95% CI 1.02 - 1.10), but inversely associated with colon cancer in men (HR 0.91, 95% CI 0.85 - 0.97). Zamora-Ros R, Cayssials V, Jenab M, Rothwell JA, Fedirko V, Aleksndrova K, Tjønneland A, Kyrø C, Overvad K, Boutron-Urault MC, Carbonnel F, Mahamat-Saleh Y, Kaaks R, Kühn T, Boeing H, Trichopoulou A, Valanou E, Vasilopoulou E, Masala G, Pala V, Panico S, Tumino R, Ricceri F, Weiderpass E, Lukic M, Sandanger TM, Lasheras C, Agudo A, Sánchez MJ, Aminao P, Navarro C, Ardanaz E, Sonestedt E, Ohlsson B, Nilsson LM, Rutegärd M, Bueno-de-Mesquita B, Peeters PH, Khaw KT, Wareham NJ, Bradbuy K, Freisling H, Romieu I, Cross AJ, Vineis P, Scalbert A, "Dietary intake of total polyphenol and polyphonol classes and the risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort," *Eur. J. Epidemiol.* (May 15, 2018) doi: 10.1007/s10654-018-0408-6. [Epub ahead of print].

4. Lung Cancer

A few epidemiologic studies that have been published since IARC completed its review in 2016 have also reported significantly increased risks of lung cancer in relation to consumption of coffee, even after adjusting for cigarette smoking and various other factors.

In 2016, researchers from the National Cancer Institute published a study investigating coffee consumption and the incidence of lung cancer in the NIH-AARP Diet and Health Study. Typical coffee intake and smoking history were queried at baseline. During 4,155,256 person-years of follow-up, more than 9,000 incident lung cancer cases occurred. Hazard ratios were estimated using Cox proportional hazards regression and comprehensive adjustments were made for smoking. In age- and sex-adjusted models, a 4½-fold increased risk of lung cancer was associated with consumption of six or more cups of coffee per day compared with none (HR 4.56, 95% CI 4.08 - 5.10). This association was attenuated after adjustment for smoking but remained significant (HR

1.27, 95% CI 1.14 - 1.42). In multivariate-adjusted models the risk of lung cancer in the highest consumption group (6 or more cups of coffee per day) was significantly increased (HR 1.29, 95% CI 1.15 - 1.45). Statistically significant dose-response trends were observed on multivariate adjustment for all lung cancer (*p*-trend < 0.0001) and all lung cancer subtypes evaluated, including adenocarcinoma (*p*-trend = 0.0005), squamous cell carcinoma (*p*-trend = 0.0024), undifferentiated lung cancer (*p*-trend = 0.0130), and small cell carcinoma (*p*-trend = 0.0016). Guertin KA, Freedman ND, Loftfield E, Graubard BI, Caporaso NE, Sinha R, "Coffee consumption and incidence of lung cancer in the NIH-AARP Diet and Health Study," *Int. J. Epidemiol.* (2016) 45(3):929-939.

Recently, Japanese investigators published a study investigating coffee consumption and lung cancer risk among 41,727 men and 45,352 women in the Japn Public Health Center-Based Prospective Study. During 1,481,887 person-years of follow-up , a total of 1.668 lung cancer cases were identified. In a multivariate regression model, nonsignificant increases in lung cancer weer observed in both men (HR 1.16, 95% CI 0.82 - 1.63) and women (HR 1.49, 95% CI 0.79 - 2.83). However, the investigators observed a greater than 3-fold increased risk for small cell carcinoma (HR 3.52, 95% CI 1.49 - 8.28), with a significant dose-response relationship (*p*-trend < 0.001). Narita S, Saito E, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Sasazuki S, Noda M, Inoue M, Tsugane S, "Coffee Consumption and Lung Cancer Risk: The Japan Public Health Center-Based Prospective Study," *J. Epidemiol.* (2018) 28(4);207-213.

Three recent meta-analyses reported increased risks of lung cancer among coffee drinkers. In a meta-analysis of 5 cohort and 12 case-control studies, Chinese researchers reported an increased risk of lung cancer comparing drinkers with nondrinkers (OR 1.17, 95% CI 1.03 - 1.33), and a greater risk comparing highest and lowest consumption categories (OR 1.31, 5% CI 1.11 - 1.55). Risk was increased in American (OR 1.34, 95% CI 1.08 - 1.65) and Asian (OR 1.49, 95% CI 1.28 - 1.74), but not European populations. Xie Y, Qin JU, Nan G, Huang S, Wang Z, Su Y, "Coffee consumption and the risk of lung cancer: an updated meta-analysis of epidemiological studies," *Eur. J. Clin. Nutr.* (2016) 70:199-206. Researchers from New York City analyzed 8 prospective cohort

and 13 case-control studies providing data for 19,892 cases. The risk for drinking versus never drinking coffee was slightly increased (RR 1.09, 95% CI 1.00 - 1.19), but coffee was not associated with lung cancer among nonsmokers. Galarraga V, Boffetta P, "Coffee Drinking and Risk of Lung Cancer – A Meta-Analysis," *Cancer Epidemiol. Biomarkers Prev.* (2016) 25(6):951-957. In a meta-analysis of 4 cohort studies by Chinese researchers, risk of lung cancer was doubled comparing highest and lowest coffee intake (RR 2.18, 95% CI 1.26 - 3.75, $p = 0.005$). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and cancer risk: A meta-analysis of prospective observational studies," *Sci. Rep.* (2016) 6:33711.

5. Non-Hodgkin's Lymphoma

In 2017, Italian researchers analyzed data from a large Italian multicenter case-control study that included 1,310 B cell and 117 T cell cases. For all B-cell lymphomas, an increased risk was observed in the highest exposure category (consumption of more than 4 cups of coffee per day for at least 30 years (OR 1.6, 5% CI 1.2 - 2.0). In subgroup analyses, consumption of at least 4 cups of coffee per day significantly increased risks for follicular lymphoma (OR 2.0, 95% CI 1.2 - 3.4), diffuse large B cell lymphoma (OR 1.7, 95% CI 1.2 - 2.5) and Mucosa-Associated Lymphoma Tissue (OR 2.1, 95% Ci 1.2 - 3.8), but not mature B cell lymphoma (OR 1.3, 95% Ci 0.88 - 1.8). Parodi S, Merlo FD, Stagnaro E, "Coffee consumption and risk of non-Hodgkin's lymphoma: evidence from the Italian multicentre case-control study," *Cancer Causes Control* (2017) 28(8):867-876.

6. Prostate Cancer

In a meta-analysis of 14 case-control and 14 cohort studies by Chinese researchers, risk of prostate cancer risk was slightly but nonsignificantly increased comparing high versus non/lowest coffee consumption (RR 1.05, 95% CI 0.96 - 1.18). Prostate cancer risk was significantly increased

in the case-control studies (RR 1.19, 95% CI 1.05 - 1.35) but not in the cohort studies (RR 0.97, 95% CI 0.84 - 1.12). Xia J-D, Chen J, Xue J-X, Yang J, Wang Z-J, "An Up-to-date Meta-analysis of Coffee Consumption and Risk of Prostate Cancer," *Urology J.* (2017) 14(5):4079-4088.

As previously mentioned, a recent Mendelian randomization study found no association between coffee-related genetic variants and prostate cancer risk, but observed a small, significantly increased risk of nonlocalized prostate cancer compared to localized stage disease (OR 1.03, 95% CI 1.01 - 1.06). Taylor AE, et al.,"Investigating the possible causal role of coffee consumption with prostate cancer risk and progression using Mendelian randomization analysis," *Int. J. Cancer* (2017) 140(2):322-328.

VI. OEHHA'S CLAIM THAT COFFEE PREVENTS CANCER IN WOMEN

On page 6 of the Initial Statement of Reasons, OEHHA asserts, quite incredibly and rather unabashedly, that "IARC's findings . . . , when applied to American Cancer Society statistics for California, show that coffee reduces or probably reduces the risk of human cancers that account for 40 percent of cancer diagnoses in women (liver, endometrium, breast)." By this statement, OEHHA appears to suggest that increased coffee consumption will prevent 40% of cancer among women. If OEHHA's assertion were true, perhaps all women should sue their primary care physicians and gynecologists for failing to prescribe coffee as a pharmacologic agent to prevent most female cancer.

Once again, OEHHA seems oblivious to the critical distinction between association and causation. IARC did not conclude that coffee consumption probably does not cause human cancer; IARC simply reports that inverse associations have been observed. It bears repeating that according to IARC, "[a]n evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety," but rather "means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations." Further, as IARC explained on its website in 2016, "[a] Group 3 evaluation does not mean that a substances has been proven to be safe.

It means that the existing scientific data do not enable a conclusion to be made about whether it causes cancer. . . ." (Exhibit "B")

By applying "IARC's findings" to "American Cancer Society Statistics for California" and concluding "that coffee reduces or probably reduces the risk of human cancers that account for 40 percent of cancer diagnoses in women," OEHHA makes the cardinal error of assuming that reductions in statistical risks of cancer reported in observational epidemiology studies of coffee are causal and actually reduce the incidence, i.e., prevent the occurrence, of 40% of cancers in women. This leap of faith does not consider any probable confounding factors and is highly flawed.

A. Endometrial Cancer

Inverse associations regarding coffee consumption and endometrial cancer are unlikely causal for many reasons, the most important being negative confounding mainly due to cigarette smoking, but also due to use of contraceptives, intrauterine devices, aspirin, and various reproductive factors.

1. Inconsistency Among Studies

Although epidemiologic studies regarding consumption of coffee and endometrial cancer have generally reported inverse associations, the results of the studies are not entirely consistent.

In a study of coffee consumption and cause-specific mortality in three cohorts comprised of 74,890 women in the Nurses' Health Study, 93,054 women in the Nurses' Health Study II, and 40,557 men in the Health Professionals Follow-up Study, the highest risk of mortality from any type of cancer for the greatest level of consumption (more than 5 cups per day) among ***never smokers*** was observed for endometrial cancer in the multivariable analysis (RR 2.17, 95% CI 0.94 - 5.05). Ding M, Satija A, Bhupathiraju SN, Hu Y, Sun Q, Han J, Lopez-Garcia E, Willett W, van Dam RM, Hu

FB, "Association of Coffee Consumption With Total and Cause-Specific Mortality in 3 Large Prospective Cohorts," *Circulation* (2015) 132(24):2305-2315.

Some studies report little association between coffee drinking and endometrial cancer risk.

Researchers from Buffalo, New York reported a non-significant slightly inverse association between total coffee consumption and endometrial cancer (p-trend = 0.50). However, consumption of decaffeinated coffee indicated a borderline statistically significant positive trend (p-trend = 0.06). However, the study did not control for cigarette smoking – an important risk factor for endometrial cancer. Thus, confounding cannot be evaluated in the study. McCann SE, Yeh M, Rodabaugh K, Moysich KB, "Higher regular coffee and tea consumption is associated with reduced endometrial cancer risk," *Int. J. Cancer* (2009) 124:1650-1653.

Italian investigators reported an increased risk for endometrial cancer in relation to moderate coffee consumption (OR = 1.18), as well as high coffee consumption (OR = 1.22), but the trend was not statistically significant. Levi F, Franceschi S, Negri E, La Vecchia C, "Dietary Factors and the Risk of Endometrial Cancer," *Cancer* (1993) 71:3575-3581.

Norwegian researchers reported a slight increase in the risk of uterine cancer in relation to coffee consumption. Odds ratios for 3 to 4, 5 to 6, and more than 7 cups per day were 1.2, 1.3 and 0.8, respectively (p-trend not significant). However the data were only adjusted for cigarette smoking and not other risk factors related to endometrial such as obesity, dietary factors, and factors related to endogenous estrogen exposure. Stensvold I, Jacobsen BK, "Coffee and cancer: a prospective study of 43,000 Norwegian men and women," *Cancer Causes Control* (1994) 5:401-408.

An earlier study by Norwegian investigators showed no association between coffee consumption and endometrial cancer. Jacobsen BK, Bjelke E, Kvåle G, Heuch I, "Coffee Drinking, Mortality, and Cancer Incidence: Results from a Norwegian Prospective Study," *J. Natl. Cancer Inst.* (1986) 76:823-831.

Some studies did not identify significantly decreased risks of endometrial cancer for coffee consumption although risk was somewhat reduced.

A population-based case-control study in New Jersey reported a nonsignificant reduction in endometrial cancer risk at the highest level of coffee consumption (greater than 2 cups per day), with a nonsignificant trend (p-trend = 0.11). Bandera EV, Williams-King MG, Sima C, Bayuga-Miller S, Pulick , Wilcox H, Zauber AG, Olson SH, "Coffee and tea consumption and endometrial cancer risk in a population-based study in New Jersey," *Cancer Causes Control* (2010) 21(9): 1467-1473.

In a study regarding coffee consumption and endometrial cancer risk among postmenopausal women using material from the Women's Health Initiative Observational Study that included 45,696 women and 427 incident endometrial cancer cases, in the multivariable analysis risk was not significantly decreased for the highest level of consumption (4 or more cups per day) of coffee, caffeinated coffee, or decaffeinated coffee. Only among obese women who drank 2 or more cups per day of decaffeinated coffee was a significant inverse association found (HR 0.66, 95% CI 0.45 - 0.97). Giri A, Sturgeon SR, Luisi N, Bertone-Johnson E, Balasubramanian R, Reeves KW, "Caffeinated Coffee, Decaffeinated Coffee and Endomentrial Cancer Risk: A Prospective Cohort Study among US Postmenopausal Women," *Nutrients* (2011) 3:937-950.

In IARC's multinational study of the European Prospective Investigation into Cancer and Nutrition (the EPIC cohort) regarding coffee consumption and mortality that included 521,330 participants from 10 European countries, endometrial cancer mortality was not significantly decreased in any consumption category, including the highest quartile of consumption (RR 0.69, 95% CI 0.40 - 1.16), and the inverse trend was not statistically significant (p-trend = 0.28). Gunter MJ, Murphy N, Cross AJ, Dossus L, Dartols L, Fagherazzi G, Kaas R, Kühn T, Boeing H, Aleksandrova K, Tjønneland A, Olsen A, Overvad K, Larsen SC, Cornejo MLR, Agudo A, Pérez, MJS, Altzibar JM , Navarro C, Ardanaz E, Khaw K-T, Butterworth A, Bradbury KE, Trichopoulou A, Lagiou P, Trichopoulos D, Palli D, Grioni S, Vineis P, Panico S, Tumino R, Bueno-de-Mesquita B, Siersema P, Leenders M, Beulens JWJ, Uiterwaal CU, Wallström P, Nilsson LM, Landberg R, Weiderpass E, Skele G, Braaten T, Brennan P, Licaj I, Muller DC, Sinha R, Wareham N, Riboli E,

"Coffee Drinking and Mortality in 10 European Countries: A Multinational Cohort Study," *Ann. Intern. Med.* (2018) 168(5):380-381.

A case-control study of 107 women with endometrial cancer in Japan found a significant inverse trend for endometrial cancer and coffee consumption in postmenopausal women, but a slight non-significant increase in endometrial cancer by amount of coffee consumed among premenopausal women. However, the inverse association for coffee consumption and endometrial cancer identified in the multivariate analysis for postmenopausal women, did not adjust for educational status, although education was highly significantly correlated with endometrial cancer in the study. The study results may therefore have been confounded due to lack of control for educational status, but the amount of confounding cannot be determined as this necessary adjustment was not made. Koizumi T, Nakaya N, Okamura C, Sato Y, Shimazu T, Nagase S, Niikura H, Kuriyama S, Tase T, Ito , Tsubono Y, Okamura K, Yaegash N, Tsuji I, "Case-control study of coffee consumption and the risk of endometrial endometrioid adenocarcinoma," *Eur. J. Cancer Prev.* (2008) 17:358-363.

A meta-analysis of coffee consumption and endometrial cancer by Italian investigators reported a significant reduction in endometrial cancer risk based on case-control studies, but the reduction in risk based on cohort studies was not statistically significant. Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C, Tavani A, "Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies," *Am. J. Obstet. Gynecol.* (2009) 2/09:130-135.

2. Confounding

The epidemiological studies regarding coffee consumption and endometrial cancer are also confounded by numerous other factors that have been reported to significantly reduce the risk of endomentrial cancer.

a. Cigarette Smoking

All of the epidemiologic studies regarding coffee consumption and endometrial cancer are negatively confounded by cigarette smoking to some degree, most being substantially confounded.

"[S]everal prospective investigations have reported inverse associations between cigarette smoking and endometrial cancer, a finding that has been attributed to possible anti-estrogenic effects of tobacco smoke." Gunter MJ, "Re: coffee drinking and risk of endometrial cancer – a population-based cohort study," *Int. J. Cancer* (2010) 126:1770.

A meta-analysis of cigarette smoking and endometrial cancer risk, based on 10 prospective cohort studies and 24 case-control studies, reported significant inverse associations. Ever smoking was associated with a reduced risk of endometrial cancer in prospective studies (RR 0.81, 95% CI 0.74 - 0.88) and case-control studies (OR 0.72, 95% CI 0.66 - 0.79). The inverse association was significant among current and former smokers. An increase in smoking of 20 cigarettes per day was significantly associated with 16% and 27% reduced risks of endometrial cancer in prospective and case-control studies, respectively. Zhou B, Yang L, Sun Q, Cong R, Gu H, Tang N, Zhu H, Wang B, "Cigarette Smoking and the Risk of Endometrial Cancer: A Meta-Analysis," *Am. J. Med.* (2008) 121:501-508.

"The inverse relationship between cigarette smoking and endometrial carcinoma risk is well established." Felix AS, Yang HP, Gierach GL, Park Y, Brinton LA, "Cigarette smoking and endometrial carcinoma risk: the role of effect modification and tumor heterogeneity," *Cancer Causes Control* (2014) 25(4):479-489. "Endometrial cancer has been shown repeatedly to be inversely associated with cigarette smoking, with risk amongst heavy smokers up to half that of never smokers." Kuper H, Boffetta P, Adami H-O, "Tobacco use and cancer causation: association by tumour type," *J. Intern. Med.* (2002) 252:206-224.

In a study of cause-specific cancer mortality among never smokers involving three large cohorts, the risk of endometrial cancer was more than doubled among those who drank the most

coffee (more than 5 cups per day) in the multivariate analysis (RR 2.17, 95% CI 0.94 - 5.05). Ding M, Satija A, Bhupathiraju SN, Hu Y, Sun Q, Han J, Lopez-Garcia E, Willett W, van Dam RM, Hu FB, "Association of Coffee Consumption With Total and Cause-Specific Mortality in 3 Large Prospective Cohorts," *Circulation* (2015) 132(24):2305-2315. This result suggests that the inverse association between coffee consumption and endometrial cancer observed in most studies is likely due to confounding by smoking. Even though some studies that have adjusted for smoking have found significantly decreased risks of endometrial cancer related to coffee consumption, a residual effect from cigarette smoking is still a likely confounder, just as increased risks of lung cancer in coffee drinkers are likely confounded by cigarette smoking, even though some studies that adjusted for cigarette smoking demonstrate elevated risks of lung cancer in relation to coffee consumption.

b. Contraceptives

Another important negative confounder of the coffee-endometrial cancer association is the use of oral contraceptives. An early meta-analysis of endometrial cancer and use of oral contraceptives indicated a 56% reduction in risk of endometrial cancer with four years of contraceptive use and a 72% reduction in risk with 12 years of use. Schlesselman JJ, "Risk of endometrial cancer in relation to use of combined oral contraceptives. A practitioner's guide to meta-analysis," *Human Reprod.* (1997) 12(9):1851-1863.

A recent meta-analysis of 27,276 women with endometrial cancer and 115,743 women without endometrial cancer from 36 epidemiological studies found significantly decreased risks of endometrial cancer in association with the use of contraceptives. The longer that women used oral contraceptives, the greater the reduction in risk of endometrial cancer. Every 5 years of use was associated with a risk ratio of 0.76 (95% CI 0.73 - 0.78, $p < 0.0001$). This reduction in risk persisted for more than 30 years after cessation of oral contraceptive use. Collaborative Group on Epidemiological Studies on Endometrial Cancer, "Endometrial cancer and oral contraceptives: an

individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies," *Lancet* (2015) 16:1061-1070.

c. Intrauterine Devices

Another negative confounder of the association between coffee consumption and endometrial cancer is the use if intrauterine devices.

An early meta-analysis of endometrial cancer and use of intrauterine devices, based on 10 studies, reported a substantial reduction in risk of endometrial cancer with intrauterine device use (OR 0.54, 95% CI 0.47 - 0.63). Beining RM, Dennis LK, Smith EM, Doras A, "Meta-Analysis of Intrauterine Device Use and Risk of Endometrial Cancer," *Ann. Epidemiol.* (2008) 18:492-499.

A recent pooled analysis of data from the Epidemiology of Endometrial Cancer Consortium on 8,801 endometrial cancer cases and 15,357 controls showed that ever use of intrauterine devices was inversely related to endometrial cancer risk (OR 0.81, 95% CI 0.74 - 0.90). Compared with never use, reduced risk of endometrial cancer was observed for inert IUD use OR 0.69, 95% CI 0.58 - 0.82), older age (≥35 years) at first use (OR 0.53, 95% CI 0.43 - 0.67), older age (≥45 years) at last uses (OR 0.60, 95% CI 0.50 - 0.72), longer (>10 years) duration of use (OR 0.61, 95% CI 0.52 - 0.71) and recent (within 1 year of study entry) use (OR 0.39, 95% CI 0.30 - 0.49). Felix AS, Gaudet MM, La Vecchia C, Nagle CM, Shu XO, Weiderpass E, Adami HO, Beresford S, Bernstein L, Chen C, Cook LS, De Vivo I, Doherty JA, Friedenreich CM, Gapstur SM, Hill D, Horn-Ross PL, Lacey JV, Levi F, Liang X, Lu L, Magliocco A, McCann SE, Negri E, Olson SH, Palmer JR, Patel AV, Petruzella S, Prescott J, Risch HA, Rosenberg L, Sherman ME, Spurdle AB, Webb PM, Wise LA, Xiang Y-B, Xu W, Yang HP, Yu H, Zeleniuch-Jacquotte A, Brinton LA, "Intrauterine devices and endometrial cancer risk: A Pooled analysis of the Epidemiology of Endometrial Cancer Consortium, *Int. J. Cancer* (2014) 136:E410-E422.

d. Aspirin

Three meta-analyses regarding aspirin use and endometrial cancer have been published to date.

A meta-analysis regarding aspirin use and endometrial cancer, based on nine studies, yielded an overall reduced pooled risk estimate for any versus no aspirin use (OR 0.87, 95% CI 0.79 - 0.96). The pooled risk estimate for obese women (BMI $\geq$ 30 kg/m^2) was further decreased (OR 0.72, 95% CI 0.58 - 0.90). Neill AS, Nagle Cm, Protani MM, Obermair A, Spurdle AB, Webb PM, Australian National Endometrial Cancer Study Group, "Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: A case-control study, systematic review and meta-analysis," *Int. J. Cancer* (2013) 132:1146-1155.

A meta-analysis of endometrial cancer and aspirin use, based on 7 cohort studies and 6 case-control studies, showed an overall 7% reduction in endometrial cancer risk (RR 0.93, 95% CI 0.88 - 0.99). Higher dosage or frequency of aspirin use was significantly associated with reduced risk of endometrial cancer, with long-term use being protective only in obese women. Zhang D, Bai B, Xi Y, Zhao Y, "Can Aspirin Reduce the Risk of Endometrial Cancer?: A Systematic Review and Meta-analysis of Observational Studies," *Int. J. Gynecol. Cancer* (2016) 26(6):1111-1120.

A meta-analysis of non-steroidal anti-inflammatory drug use and risk of endometrial cancer, based on 6 case-control and 7 cohort studies, observed reductions in risk of endometrial cancer with regular use of aspirin (case-control: 11%, cohort: 8%). Higher risk reductions were seen with high frequency of aspirin use (case-control: 37%, cohort: 20%). The inverse association was strongest among women with a body mass index above 30 (case-control: 44%, cohort: 20%). Verdoodt F, Friis S, Dehlendorff C, Albieri V, Kjaer SK, "Non-steroidal anti-inflammatory drug use and risk of endometrial cancer: A systematic review and meta-analysis of observational studies," *Gynecol. Oncol.* (2016) 140:352-358.

e. Bisphosphonates

A meta-analysis of bisphosphonate use and risk of endometrial cancer, based on seven studies (4 cohort studies and 3 case-control studies), showed a significant reduction in the risk of endometrial cancer incidence with bisphosphonate use (RR 0.75, 95% CI 0.60 - 0.94). A statistically significant risk reduction with the use of bisphosphonate was observed for use of more than 1 to 3 years (OR 0.58, 95% CI 0.47 - 0.72) and a lower risk for use of more than 3 years (RR 0.44, 95% CI 0.28 - 0.70). Ou Y-J, Chiu H-F, Wong Y-H, Yang Y-H, "Bisphosphonate use and the risk of endometrial cancer: a meta-analysis of observational studies," *Pharmacoepidemiol. Drug Safety* (2016) 25(10):1107-1115.

f. Breastfeeding

Three meta-analyses of breastfeeding and the risk of endometrial cancer have been published, all reporting significantly reduced risks ranging from 23% to 26% of endometrial cancer in association with breastfeeding. Ma X, Zhao LG, Sun JW, Yang Y, Zheng JL, Gao J, Xiang YB, "Association between breastfeeding and risk of endometrial cancer: a meta-analysis of epidemiological studies," *Eur. J. Cancer Prev.* (2018) 27(2):144-151; Wang L, Li J, Shi Z, "Association between Breastfeeding and Endometrial Cancer Risk: Evidence from a Systematic Review and Meta-Analysis," *Nutrients* (2015) 7:5697-5711; Zhan B, Liu X, Li F, Zhang D, "Breastfeeding and the incidence of endometrial cancer: A meta-analysis," *Oncotarget* (2015) 6(35):38398-38409.

g. Reproductive Factors

In a meta-analysis of eight prospective studies involving 4,553 women with endometrial cancer, the risk of endometrial cancer was significantly reduced when comparing women with the oldest category of menarcheal age with women with the youngest category of menarcheal age (RR 0.96, 95% CI 0.94 - 0.98). Additionally, significant inverse associations were consistent within all stratified analyses. Gong T-T, Wang Y-L, Ma X-X, "Age at menarche and endometrial cancer risk: a dose-response meta-analysis of prospective studies," *Sci. Rep.* (2015) 5:14051.

In a meta-analysis of age at last birth and endometrial cancer, individual-level data from 4 cohort and 13 case-control studies in the Epidemiology of Endometrial Cancer Consortium were pooled. A total of 8,671 cases were included in the analysis. After adjustment for known risk factors, endometrial cancer risk declined with increasing age at last birth (p-trend < 0.0001). The pooled odds ratio per 5- year increase in age at last birth was significantly reduced (OR 0.87, 95 % CI 0.85 - 0.90). Setiawan VW, Pike MC, Karageorgi S, Deming SL, Anderson K, Bernstein L, Brinton LA, Cai H, Cerhan JR, Zcozen W, Chen C, Doherty J, Freudenheim JL, Goodman MT, Hankinson SE, Lacey JV, Liang X, Lissowska J, Lu L, Lurie G, Mack T, Matsuno RK, McCann S, Moysich KB, Olson Sh, Rastogi R, Rebbeck TR, Risch H, Robien K, Schairer C, Shu X-O, Spurdle AB, Strom BL, Thompson PJ, Ursin G, Webb PM, Weiss NS, Wentzensen N, Xiang Y-B, Yang HP, Yu H, Horn-Ross PL, D Vivio I, Australian National Endoemtrial Cancer Study Group, "Age at Last Birth in Relation to Risk of Endometrial Cancer: Pooled Analysis in the Epidemiology of Endometrial Cancer Consortium," *Am. J. Epidemiol. (*2012) 176(4):269-278.

Parity has also been shown to be inversely related with the risk of endometrial cancer in 2 meta-analyses. In a pooled analysis of 19,297 white and 2,011 black women by the Epidemiology of Endometrial Cancer Consortium, increasing parity was associated with decreasing risk of endometrial cancer in both white ($p < 0.001$) and black women ($p = 0.02$). Cote ML, Alhajj T, Ruterbusch JJ, Bernstein L, ,Brinton LA, Blot WJ, Chen C, Gass M, Gaussoin S, Henderson B, Lee E, Horn-Ross PL, Kolonel LN, Kaunitz A, Liang X, Nicholson WK, Park AB, Petruzella S, Rebbeck TR, Setiawan VW, Signorello LB, Simon SM, Weiss NS, Wentzensen N, Yang HP, Zeleniuch-

Jacquotte A, Olson SH, "Risk factors for endometrial cancer in black and white women: A pooled analysis from the Epidemiology of Endometrial Cancer Constortiu (E2C2)," *Cancer Causes Control* (2015) 26(2):287-296. A meta-analysis of parity and endometrial cancer, based on 10 prospective studies, 35 case-control studies and 1 pooled analysis including 69,681 patients, revealed a significant inverse association between parity and risk of endometrial cancer for parous versus nulliparous women (RR 0.69, 95% CI 0.65 - 0.74). Wu Q-J, Li YY, Tu C, Zxhu J, Qian K-Q, Feng T-B, Li C, Wu L, Ma X-X, "Parity and endometrial cancer risk: a meta-analysis of epidemiological studies," *Sci. Rep.* (2015) 5:14243.

h. Physical Activity

Physical activity has been shown to be inversely related with the risk of endometrial cancer in two meta-analyses. In a meta-analysis of 33 epidemiologic studies regarding physical activity in 19,558 endometrial cancer cases, the risk of endometrial cancer was inversely related to recreational activity (RR 0.84, 95% CI 0.78 - 0.91), to occupational activity (RR 0.81, 95% CI 0.75 - 0.87), to household activity (RR 0.79, 95% CI 0.47 - 1.02) and to walking (RR 0.82, 95% CI 0.69 - 0.97). Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, Leitzmann M, "A systematic review and meta-analysis of physical activity and endometrial cancer risk," *Eur. J. Epidemiol.* (2015) 30(5):397-412. In a meta-analysis of leisure-time physical activity and endometrial cancer risk, an increase in leisure-time physical activity by 3 metabolic equivalent of task hours per week reduced the risk of endometrial cancer (RR 0.98, 95% CI 0.95 - 1.00, $p = 0.02$), and an increased by an hour per week was associated with a 5% reduction in risk (RR 0.95, 95% CI 0.93 - 0.98, $p < 0.001$). Keum NN, Ju W, Lee DH, Ding EL, Hsieh CC, Goodman JE, Giovannucci EL, "Leisure-time physical activity and endometrial cancer risk: Dose-response meta-analysis of epidemiological studies," *Int. J. Cancer* (2014) 15:682-694.

i. Dietary Factors

A recent meta-analysis of dietary patterns and endometrial cancer risk, based on 27 epidemiologic studies, showed a decreased risk of endometrial cancer in the highest compared with the lowest categories of a healthy dietary pattern (OR 0.74, 95% CI 0.62 - 0.88, $p = 0.008$). Si CJ, Shu L, Zheng PF, Zhang XY, Yu XL, Gao W, Zhang L, "Dietary patterns and endometrial cancer: a meta-analysis," *Eurl J. Cancer Prev.* (2017) 26(4):336-345.

In a meta-analysis of 3 case-control studies of 1,411 women with histologically confirmed endometrial cancer and 3,668 hospital controls, comparing high and low adherence with the Mediterranean diet significantly reduced the risk of endometrial cancer (OR 0.43, 95% CI 0.34 - 0.56). Filomeno M, Bosetti C, Bidoli E, Levi F, Serraiino D, Montella M, La Vecchia C, Tavani A, "Mediterranean diet and risk of endometrial cancer: a pooled analysis of three Italian case-control studies," *Br. J. Cancer* (2015) 112:1816-1821.

In a meta-analysis of dietary fiber intake and endometrial cancer, the random-effects summary risk estimate for comparison of the highest with the lowest dietary fiber intake was significantly reduced (RR 0.71, 95% CI 0.59 - 0.85). Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML, "Association between dietary fiber and endometrial cancer: a dose-response meta-analysis," *Am. J. Clin. Nutr.* (2007) 86:1730-1737.

In a meta-analysis of epidemiologic studies regarding consumption of fruits and vegetables, the risk of endometrial cancer was significantly reduced comparing high and low consumption of vegetables, based on 10 studies (RR 0.71, 95% CI 0.55 - 0.91), and nonsignificantly reduced comparing high and low consumption of total fruit (RR 0.97, 95% CI 0.92 - 1.02). Bandera EV, Kushi LH, Moore Dr, Gifkins DM, McCullough ML, "Fruits and Vegetables and Endometrial Cancer Risk: A Systematic Literature Review and Meta-Analysis," *Nutr. Cancer* (2007) 58(1):6-21.

In a meta-analysis of observational studies, increased consumption of nuts was associated with a significantly reduce risk of endometrial cancer (RR 0.58, 95% CI 0.43 - 0.79). Wu L, Wang

Z, Zhu J, Murad AL, Prokop LJ, Murad MH, "Nut consumption and risk of cancer and type 2 diabetes: a systematic review and meta-analysis," *Nutr. Rev.* (2015) 73(7):409-425.

In a meta-analysis of 10 epidemiologic studies regarding soy intake and endometrial cancer, dietary soy intake was inversely associated with endometrial cancer (RR 0.81, 95% CI 0.72 - 0.91). Zhang G-Q, Chen J-L, Liu Q, Zhang Y, Zeng H, Zhao Y, "Soy Intake Is Associated With Lower Endometrial Cancer Risk: A Systematic Review and Meta-Analysis of Observational Studies," *Medicine* (2015) 94(50):e2281.

In a meta-analysis of studies regarding consumption of tea and endometrial cancer, the risk endometrial cancer was significantly decreased for ever drinkers versus non/lowest drinkers (RR 0.85, 95% CI 0.77 - 0.94). An increase in tea intake of 2 cups per day was associated with a 25% decreased risk of endometrial cancer. Tan, NP, Li H, Qiu YL, Zhou GM, Ma J, "Tea consumption and risk of endometrial cancer: a metaanalysis," *Am. J. Obstet. Gynecol.* (2009) 201(6):605.e1-8. In a more recent meta-analysis highest green tea consumption was associated with a reduced risk of endometrial cancer (RR 0.78, 95% CI 0.66 - 0.92). Zhou Q, Li H, Zhou JG, Ma Y, Wu T, Ma H, "Green tea, black tea consumption and risk of endometrial cancer: a systematic review and meta-analysis" *Arch. Gynecol. Obstet.* (2016) 293(1):143-155.

In a meta-analysis of epidemiologic studies regarding antioxidant vitamins and the risk of endometrial cancer, random-effects summary odds ratios based on case-control data were significantly reduced for beta-carotene (OR 0.88, 95% CI 0.79- 0.98) per 1,000 mcg/1,000 kcal; vitamin C (OR 0.85, 95% CI 0.73 - 0.98) per 50 mg/1,000 kcal), and vitamin E (OR 0.91, 95% CI 0.84 - 0.99) per 5 mg/1,000 kcal. Bandera EV, Gifkins DM, Moore DF, McCullough ML, Kushi LH, "Antioxidant Vitamins and the Risk of Endometrial Cancer: A Dose-Response Meta-Analysis," *Cancer Causes Control* (2009) 20(5):699-711. In another meta-analysis based on case-control data, the risk of endometrial cancer was reduced for calcium supplements, but not for Vitamin D. McCullough ML, Bandera EV, Moore DF, Kushi LH, "Vitamin D and calcium intake in relation to risk of endometrial cancer: a systematic review of the literature," *Prev. Med.* (2008) 46(4):298-302.

j. Failure to Control for Multiple Negative Confounders

The epidemiologic studies of coffee consumption and endometrial cancer have not controlled for confounding by most factors that have been shown to reduce the risk of endometrial cancer. "Some [studies] did not adjust risk estimates for important risk factors for endometrial cancer, including reproductive and menstrual variables (such as age at menopause and the use of oral contraceptives and hormone replacement therapy), obesity or overweight, and selected medical conditions (such as diabetes mellitus)." Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C, Tavani A, "Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies," *Am. J. Obstet. Gynecol.* (2009) 2/09:130-135.

"Smoking and BMI are potentially the most likely confounders of the relationship between coffee intake and endometrial cancer. Coffee intake tended to be positively related to smoking." Je Y, Giovannucci E, "Coffee Consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis," *Int. J. Cancer* (2012) 131:1700-1710.

Thus, the inverse relation between coffee consumption and endometrial cancer reported in observational studies is influenced by, and may well be the result of, the lack of control for numerous negative confounding factors related to endometrial cancer, especially cigarette smoking.

B. Liver Cancer

Although most epidemiologic studies regarding coffee consumption and liver cancer report inverse associations, these studies are potentially grossly confounded by liver disease, especially Hepatitis B and C viruses which are known causes of liver cancer. The studies are also subject to exposure misclassification and other forms of bias, especially reverse causation.

The major known cause of liver cancer is chronic liver disease, of which infectious agents, especially Hepatitis viruses, are the primary cause. Indeed, a major study by the International Agency

for Research on Cancer reported that 73.4% of liver cancers are attributable to infectious organisms. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S, "Global burden of cancers attributable to infections in 2012: a synthetic analysis," *Lancet Glob. Health* (2016) 4(9):e609-616. Among the known or probable causes of human liver cancer are infectious organisms (Hepatitis C Virus, Hepatitis B Virus, Aflatoxins, Cyanotoxins, HIV type1, and Schistosome japonicum), chronic diseases (Type 2 Diabetes, chronic liver disease and obesity), addictive products (cigarette smoking, Betel quid without tobacco, and alcohol), radiation (x-radiation and gamma radiation), hormonal products (estrogen-progestogen contraceptives and androgenic (anabolic) steroids), and industrial and other toxic chemicals (arsenic, DDT, dichloromethane, 1,2-dichloropropane, trichloroethylene, vinyl chloride). Since so many agents are known to cause liver cancer, it is critical that epidemiologic studies control or at least adjust for these known confounders of human liver cancer. Unfortunately, none of the epidemiologic studies regarding coffee consumption and liver cancer addresses all these known confounders.

1. Confounding

a. Hepatitis Virus Infections

Critically, most of the studies regarding coffee consumption and liver cancer do not control for Hepatitis virus infections.

In the Liver Cancer Pooling Project study, involving a consortium of U.S.-based cohort studies with data from 1,212,893 individuals, including 860 cases of hepatocelluar carcinoma and 260 cases of intrahepatic cholangiocarcinoma, the investigators acknowledged that "[w]hile the pooled analysis included information on the major confounders (e.g. smoking and alcohol consumption, it did not include information on other potential confounders, such as HBV and HCV status, for all individuals." Petrick JL, Freedman ND, Graubard BI, Sahasrabuddhe VV, Lai GY,

Alavanja MC, Beane-Freeman LE, Boggs DA, Buring JE, Chan AT, Chong DQ, Fuchs CS, Gapstur SM, Gaziano JM, Giovannucci EL, Hollenbeck AR, King LY, Koshiol J, Lee IM, Linet MS, Palmer JR, Poynter JN, Purdue MP, Robien K, Schairer C, Sesso HD, Sigurdson AJ, Zeleniuch-Jacquotte A, Wactawski-Wende J, Campbell PT, McGlyn KA, "Coffee Consumption and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma by Sex: The Liver Cancer Pooling Project,"*Cancer Epidemiol. Biomarkers Prev.* (2015) 24(9):1398-1406

The investigators of the US Multiethnic Cohort study acknowledged that "baseline data on BHV and HCV status were unavailable for most cohort participants; consequently we were unable to adjust for any effect of viral hepatitis on the association between coffee and HCC." Setiawan VW, Wilkens LR, Lu SC, Hernandez BY, Le Marchand L, Henderson BE, "Association of Coffee Intake with Reduced Incidence of Liver Cancer and Death from Chronic Liver Disease in the US Multiethnic Cohort," *Gastroenterology* (2015) 148(1):118-125.

The authors of a study of 27,037 Finnish male smokers followed for incident liver cancer and chronic liver disease acknowledged: "We possessed information on HBV and HCV for only a subset of our cohort." Lai GY, Weinstein Sj, Albanes D, Taylor PR, McGlynn KA, Virtamo J, Sinha R, Freedman ND, "The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers," *Br. J. Cancer* (2013) 109:1344-1351.

In a review of risk factors of hepatocellular carcinoma, Chinese researchers noted that "[a]ll of the cohort studies were from Japan where coffee consumption was less frequent and did not control for HBV/HCV infections." Gao J, Xie L, Yang W-S, Zhang W, Gao S, Wang J, Xiang Y-B, "Risk Factors of Hepatocellular Carcinoma: Current Status and Perspectives," *Asian Pac. J. Cancer Prev.* (2012) 13(3):743-752.

The authors of the Singapore Chinese Health Study, a prospective cohort study of 63,257 middle-aged and elderly Chinese men and women, acknowledged that "[p]otential limitations of this study include the lack of HBV and HCV status for all cohort participants." Johnson S, Koh WP, Wang R, Govindarajan S, Yu MC, Yuan JM, "Coffee consumption and reduced risk of

hepatocellular carcinoma: findings from the Singapore Chinese Health Study," *Cancer Causes Control* (2011) 22:503-510.

Even the authors of a case-control study of hepatocelluar carcinoma in hepatitis B carriers considered "[t]he lack of control on viral load, platelet count, alanine aminotransferase level and other possible factors for HCC" a limitation of their study. Leung WW, Ho SC, Chan HL, Wong V, Yeo W, Mok TS, "Moderate coffee consumption reduces the risk of hepatocellular carcinoma in hepatitis B chronic carriers: a case-control study *J. Epidemiol. Comm. Health* (2011) 65(6):556-558.

The investigators of the Ohsaki Cohort Study acknowledged a major shortcoming of their study: "The most substantial limitation of our study was that we had no information about history of HBV or HCV infection." Ui A, Kuriyama S, Kakizaki M, Sone T, Nakaya N, Ohmori-Matsuda K, Hozawa A, Nishino Y, Tsuji I, "Green Tea Consumption and the Risk of Liver Cancer in Japan: the Ohsaki Cohort Study," *Cancer Causes Control* (2009) 20(10):1939-1945.

The authors of a study based on the National Health and Nutrition Examination Survey likewise acknowledged: "Our study has some limitations, including the absence of data on HCV infection, which is a major cause of cirrhosis and liver cancer in the U.S." Ioannou GN, Morrow OB, Connole ML, Lee SP, "Association Between Dietary Nutrient Composition and the Incidence of Cirrhosis or Liver Cancer in the United States Population," *Hepatology* (2009) 50:175-184.

The authors of a prospective study of coffee consumption and liver cancer in 60,323 Finns followed for a median of 19.3 years acknowledged: "We had no data on history of either HBV or HCV infections at baseline." Hu G, Tuomilehto J, Pukkala E, Hakulinen T, Antikainen R, Vartiainen E, Jousilahti P, "Joint effects of coffee consumption and serum gamma-glutamyltransferase on the risk of liver cancer," *Hepatology* (2008) 48(1):129-136.

The authors of the Japanese Public Health Center-based Prospective Study also acknowledged "some obvious limitations [in this study] such as the . . . lack of determination of hepatitis virus infection status at baseline for the entire population and at follow-up for 22% of the case patients." Inoue M, Yoshimi I, Sobue T, Tsugane S, JPHC Study Group, "Influence of coffee

drinking on subsequent risk of hepatocellular carcinoma: a prospective study in Japan," *J. Natl. Cancer Inst.* (2005) 97(4):293-300.

The authors of a pooled analysis of two prospective studies regarding coffee consumption and risk of liver cancer in Japan similarly acknowledged: "We had no information about history of HBV or HCV infection." Shimazu T, Tsubono Y, Kuriyama S, Ohmori K, Koizumi Y, Nishino Y, Shibuya D, Tsuji I, "Coffee consumption and the risk of primary liver cancer: pooled analysis of two prospective studies in Japan," *Int. J. Cancer* (2005) 116(1):150-154.

Thus, an overwhelming majority of the studies of coffee consumption and liver cancer failed to adequately control for Hepatitis viruses, which therefore are major confounders of the association between coffee consumption and liver cancer.

b. Liver Disease

Many of the studies also did not control for liver disease or other chronic diseases that have been associated with liver cancer. See, Setiawan VW, Wilkens LR, Lu SC, Hernandez BY, Le Marchand L, Henderson BE, "Association of Coffee Intake with Reduced Incidence of Liver Cancer and Death from Chronic Liver Disease in the US Multiethnic Cohort," *Gastroenterology* (2015) 148(1):118-125 ("Another limitation is the lack of information on liver disease other than HCC at baseline."); Lai GY, Weinstein SJ, Albanes D, Taylor PR, McGlynn KA, Virtamo J, Sinha R, Freedman ND, "The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers," *Br. J. Cancer* (2013) 109(5):1344-1351 ("We lacked assessment of underlying liver disease"; "Associations of coffee with incident liver cancer . . . could also reflect underlying liver disease, as coffee intake has been associated with fibrosis and cirrhosis in previous studies and as caffeine is metabolised in the liver, those with underlying liver disease may drink less coffee. In other words, those with a higher risk of developing HCC would be placed into the low coffee consumption group, which would lead to an inverse association between risk of HCC and

coffee consumption."); Gellati U, Covolo L, Franceschini M, Pirali F, Tagger A, Ribero ML, Trevisi P, Martelli C, Nardi G, Donato F, Brescia HCC Study Group, "Coffee consumption reduces the risk of hepatocellular carcinoma independently of its aetiology: a case-control study," *J. Hepatol.* (2005) 42(4):528-534 ("Although controls were not affected by overt liver disease on selection, some of them had HCV or HBV infection or heavy alcohol intake and may therefore have had a chronic liver disease, although this was not the reason for admission to hospital."); Gallus S, Bertuzzi M, Tavani A, Bosetti C, Negri E, La CV, Lagiou P, Trichopoulos D, "Does coffee protect against hepatocellular carcinoma?" *Br. J. Cancer* (2002) 87(9):956-959 ("Since liver cirrhosis is strongly related to the incidence of hepatocellular carcinoma, the apparent protective effect of coffee consumption on hepatocellular carcinogenesis may be due to its inverse relation with liver cirrhosis. A diagnosis of cirrhosis was not histologically determined in all cases, although most cases of liver cancer are likely to have some degree of cirrhosis.").

2. Reverse Causation

The inverse association between coffee consumption and liver cancer may also be due to reverse causation, i.e., that the association reflects a reduction in risk because participants in prospective studies reduced their coffee consumption, either on their physician's advice or based on participants' own health concerns. See, e.g., Petrick JL, Freedman ND, Graubard BI, Sahasrabuddhe VV, Lai GY, Alavanja MC, Beane-Freeman LE, Boggs DA, Buring JE, Chan AT, Chong DQ, "Coffee Consumption and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma by Sex: The Liver Cancer Pooling Project," *Cancer Epidemiol. Biomarkers Prev.* (2015) 24(9):1398-1406("there are a number of reasons, particularly due to health concerns, that may lead individuals to alter their coffee consumption, specifically caffeinated coffee"); Jenab M, Boffetta P, "Glycemic index and glycemic load: application in observational studies and association with hepatocellular carcinoma risk. Meaningful or error prone?" *Ann. Oncol.* (2010) 21(3):437-439

("Reverse causality may also be an issue in that various symptoms may have brought about the instigation of dietary changes in HCC cases long before diagnosis and possibly within the recall reference period indicated by the questionnaires."); Inoue M, Yoshimi I, Sobue T, Tsugane S, JPHC Study Group, "Influence of coffee drinking on subsequent risk of hepatocellular carcinoma: a prospective study in Japan," *J. Natl. Cancer Inst.* (2005) 97(4):293-300 ("subjects with chronic liver disease may have reduced their coffee consumption to avoid the side effects of caffeine, and that may have led to a superficial decrease in HCC risk by coffee drinking"; "Several studies have described an inverse association between coffee drinking and liver cirrhosis. Because liver cirrhosis is strongly associated with primary liver cancer, it is possible that the observed association between coffee drinking and HCC actually represents an association with liver cirrhosis."); Kurozawa Y, Ogimoto I, Shibata A, Nose T, Yoshimura T, Suzuki H, Sakata R, Fujita Y, Ichikawa S, Iwai N, Tamakoshi A, "Coffee and risk of death from hepatocellular carcinoma in a large cohort study in Japan," *Br. J. Cancer* (2005) 93(5):607-610 ("persons might reduce coffee intake because of symptoms related to impaired caffeine clearance (Hasegawa *et al,* 1989) of poor liver function or nonspecific medical advice") . [citing Hasegawa M, Yamada S, Hirayama C, "Fasting plasma caffeine level in cirrhotic patients: relation to plasma levels of catecholamines and renin activity," *Hepatol*. (1987)10(6):973-977]. In other words, the reduction in coffee consumption for those with various types of liver disease that are related to a relatively high risk of HCC, places those at high risk of HCC in the low coffee consumption categories resulting in an inverse relation with coffee intake.

3. Spurious Association

Several researchers have observed that the inverse relationship between coffee consumption and liver cancer may be spurious.

In a meta-analysis of coffee drinking and hepatocellular carcinoma risk, Italian researchers observed: "Despite the consistency of these results, it is difficult to determine causality on the basis

of these observational studies alone. The inverse relation observed may in fact be spurious and due to the fact that subjects with a broad spectrum of digestive tract diseases, liver disorders, and cirrhosis may reduce their coffee consumption." Bravi F, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, Franceschi S, La Vecchia C, "Coffee drinking and hepatocellular carcinoma risk: a meta-analysis," *Hepatology* (2007) 46(2):430-435.

The authors of another meta-analysis regarding coffee consumption and risk of liver cancer commented on the inverse association between coffee and liver cancer: "Caffeine metabolism is impaired in persons with chronic liver disease. Hence if persons with liver disease or hepatitis virus infection who are at high risk of liver cancer consume less coffee (eg., to avoid the side effects of caffeine) compared with healthy persons, it could lead to a spurious protective association between coffee consumption and liver cancer." Larsson SC, Wolk A, "Coffee consumption and risk of liver cancer: a meta-analysis," *Gastroenterology* (2007) 132:1740-1745.

The authors of a review of the epidemiology of liver cancer concluded that the inverse relation between coffee consumption and liver cancer "may however be spurious, and due to the fact that subjects with a broad spectrum of digestive tract disorders, liver diseases or cirrhosis may reduce their coffee consumption. Indeed, caffeine metabolism is impaired in patients with cirrhosis, who could therefore reduce coffee intake in order to avoid side effects of caffeine. Thus, bias due to reduction of coffee drinking in unhealthy subjects cannot be excluded." Chuang SC, La Vecchia C, Boffetta P, "Liver cancer: descriptive epidemiology and risk factors other than HBV and HCV infection," *Cancer Lett.* (2009) 286(1):9-14.

The investigators of a Japanese case-control study of 209 incident cases of hepatocellular carcinoma commented: "HCC cases may have reduced coffee consumption because of their preexisting liver disease (e. g. impaired caffeine clearance and gastrointestinal disorders accompanying liver disease. This can lead to a spurious protective association between coffee and HCC." Tanaka K, Hara M, Sakamoto T, Higaki Y, Mizuta T, Eguchi Y, Yasutake T, Ozaki I, Yamamoto K, Onohara S, Kawazoe S, Shigematsu H, Koizumi S, "Inverse association between

coffee drinking and the risk of hepatocellular carcinoma: a case-control study in Japan," *Cancer Sci.* (2007) 98(2):214-218.

A team of investigators participating in the European Prospective Investigation into Cancer and Nutrition commented regarding their study: It has been largely speculated that the inverse association between coffee intake and liver cancer could be accounted for by reserve causation bias in epidemiological studies because of the inclusion of participants with underlying liver disease who reduce coffee consumption as a result of physician recommendations." Aleksandrova K, Bamia C, Drogan D, Lagiou P, Trichopoulou A, Jena M, Fedirko V, Romieu I, Bueno-de-Mesquita HB, Pischon T, Tsilidis K, Overvad K, Tjønneland A, Boutron-Ruault M-C, Dossus L, Racine A, Kaaks R, Kühn T, Tsironis C, Paptesta E-M, Saitakis G, Palli D, Panico S, Grioni S, Rumino R, Vineis P, Peeters PH, Weiderpass E, Lukic M, Braaten T, Quiros JR, Luján-Barroso l, Sánchez M-J, ,Chilarque M-D, Ardanaz E, Dorronsoro M, Nilsson LM, Sund M, Wallström P, Ohlsson B, Bradbury K, Khaw K-T, Wareham N, Stepien M, Duarte-Salles T, Assi N, Murphy N, Gunter MJ, Riboli E, Boeing H, Trichopoulos D, "The Association of Coffee Intake with Liver Cancer Risk is Mediated by Biomarkers of Inflammation and Hepatocellular Injury: Data from the European Prospective Investigation into Cancer and Nutrition," *Am. J. Clin. Nutr.* (2015) 102:1498-1508.

"In summary, coffee drinking pattern may be a surrogate marker of a clinical state of enhanced detoxification or clearance of hepatic carcinogens. Studies in this direction are needed before we conclude that coffee drinking will reduce risk of HCC by 40%." Patil PS, "Coffee and Hepatocellular Carcinoma: Cause or Confounding?" *Hepatology* (2007) 46(6):2046-2047.

4. Factors That Have Been Reported to Reduce Liver Cancer Risk

Epidemiological studies and meta-analyses of epidemiological studies have reported that, in addition to coffee, several other factors significantly reduce the risk of liver cancer.

a. Health Dietary Patterns

Meta-analyses have reported decreased risks of liver cancer with adherence to the Mediterranean diet. Turati F, Trichopoulos D, Polesel J, Bravi F, Rossi M, Talamini R, Franceschi S, Montella M, Trichopoulou A, La Vecchia C, Lagiou P, "Mediterranean diet and hepatocelluar carcinoma," *J. Hepatol.* (2014) 60(3):606-611; Schwingshackl L, Hoffmann G, "Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies," *Cancer Med.* (2015) 4(12):1933-1947; Schwingshackl L, Schwedhelm C, Galbete C, Hoffmann G, "Adherence to Mediterranean Diet and Risk of Cancer: An Updated Systematic Review and Meta-Analysis," *Nutrients* (2017) 9(10). pii: E1063.

Decreased risks of liver cancer have also been reported for vegetable-based dietary patterns (Zhang W, Xiang YB, Li HL, Yang G, Cai H, Ji BT, Gao YT, Zheng W, Shu XO, "Vegetable-based dietary pattern and liver cancer risk: results from the Shanghai women's and men's health studies," *Cancer Sci.* (2013) 104(10):1353-1361), and the urban prudent dietary pattern and the traditional Cantonese dietary pattern. Lan QY, Liao GC, Zhou RF, Chen PY, Wang XY, Chen MS, Chen YM, Zhu HL, "Dietary patterns and primary liver cancer in Chinese adults: a case-control study," *Oncotarget* (2018) 9(45):27872-27881.

b. Dietary Fiber

Dietary fiber has been reported to decrease the risk of liver cancer. Fedirko V, Lukanova A, Bamia C, Trichopolou A, Trepo E, Nöthlings U, Schlesinger S, Aleksandrova K, Boffetta P, Tjønneland A, Johnsen NF, Overvad K, Fagherazzi G, Racine A, Boutron-Ruault MC, Grote V, Kaaks R, Boeing H, Naska A, Adarakis G, Valanou E, Palli D, Sieri S, Tumino R, Vineis P, Panico S, Bueno-de-Mesquita HB, Siersema PD, Peeters PH, Weiderpass E, Skeie G, Engeset D, Quirós JR, Zamora-Ros R, Sánchez MJ, Amiano P, Huerta JM, Barricarte A, Johansen D, Lindkvist B, Sund

M, Werner M, Crowe F, Khaw KT, Ferrari P, Romieu I, Chuang SC, Riboli E, Jenab M, "Glycemic index, glycemic load, dietary carbohydrate, and dietary fiber intake and risk of liver and biliary tract cancers in Western Europeans," *Ann. Oncol.* (2013) 24(2):543-553; Bradbury KE, Appleby PN, Key TJ, "Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC)," *Am. J. Clin. Nutr.* (2014) 100 Suppl 1:394S-398S.

c. Vegetables

Several studies have reported decreased risks of liver cancer in association with consumption of vegetables. Sauvaget C, Nagano J, Hayashi M, Spencer E, Shimizu Y, Allen N, "Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study," *Br. J. Cancer* (2003) 88(5):689-694; Pham TM, Fujino Y, Ide R, Kubo T, Shirane K, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T, "Prospective study of vegetable consumption and liver cancer in Japan," *Int. J. Cancer* (2006) 119(10):2408-2411; Lagiou P, Rossi M, Lagiou A, Tzonou A, La Vecchia C, Trichopoulos D, "Flavonoid intake and liver cancer: a case-control study in Greece," *Cancer Causes Control* (2008) 19(8):813-818 [mostly spinach and peppers]; Zhang W, Xiang YB, Li HL, Yang G, Cai H, Ji BT, Gao YT, Zheng W, Shu XO, "Vegetable-based dietary pattern and liver cancer risk: results from the Shanghai women's and men's health studies," *Cancer Sci.* (2013) 104(10):1353-1361; Yang Y, Zhang D, Feng N, Chen G, Liu J, Chen G, Zhu Y, "Increased intake of vegetables, but not fruit, reduces risk for hepatocellular carcinoma: a meta-analysis," *Gastroenterology* (2014) 147(5):1031-1042; Luo AJ, Wang FZ, Luo D, Hu DH, Mao P, Xie WZ, He XF, Kan W, Wang Y,"Consumption of vegetables may reduce the risk of liver cancer: results from a meta-analysis of case-control and cohort studies," *Clin. Res. Hepatol. Gastroenterol.* (2015) 39(1):45-51; Bamia C, Lagiou P, Jenab M, Aleksandrova K, Fedirko V, Trichopoulos D, Overvad K, Tjønneland A, Olsen A, Clavel-Chapelon F, Boutron-Ruault MC, Kvaskoff M, Katzke VA, Kühn T, Boeing H, Nöthlings

U, Palli D, Sieri S, Panico S, Tumino R, Naccarati A, Bueno-de-Mesquita HB, Peeters PH, Weiderpass E, Skeie G, Quirós JR, Agudo A, Chirlaque MD, Sanchez MJ, Ardanaz E, Dorronsoro M, Ericson U, Nilsson LM, Wennberg M, Khaw KT, Wareham N, Key TJ, Travis RC, Ferrari P, Stepien M, Duarte-Salles T, Norat T, Murphy N, Riboli E, Trichopoulou A, "Fruit and vegetable consumption in relation to hepatocellular carcinoma in a multi-centre, European cohort study," *Br. J. Cancer* (2015) 112(7):1273-1282

d. Fish

Studies have also reported decreased risks of liver cancer in association with consumption of fish. Sawada N, Inoue M, Iwasaki M, Sasazuki S, Shimazu T, Yamaji T, Takachi R, Tanaka Y, Mizokami M, Tsugane S; Japan Public Health Center-Based Prospective Study Group, "Consumption of n-3 fatty acids and fish reduces risk of hepatocellular carcinoma," *Gastroenterology* (2012) 142(7):1468-1475; Fedirko V, Trichopolou A, Bamia C, Duarte-Salles T, Trepo E, Aleksandrova K, Nöthlings U, Lukanova A, Lagiou P, Boffetta P, Trichopoulos D, Katzke VA, Overvad K, Tjønneland A, Hansen L, Boutron-Ruault MC, Fagherazzi G, Bastide N, Panico S, Grioni S, Vineis P, Palli D, Tumino R, Bueno-de-Mesquita HB, Peeters PH, Skeie G, Engeset D, Parr CL, Jakszyn P, Sánchez MJ, Barricarte A, Amiano P, Chirlaque M, Quirós JR, Sund M, Werner M, Sonestedt E, Ericson U, Key TJ, Khaw KT, Ferrari P, Romieu I, Riboli E, Jenab M, "Consumption of fish and meats and risk of hepatocellular carcinoma: the European Prospective Investigation into Cancer and Nutrition (EPIC)," *Ann. Oncol.* (2013) 24(8):2166-21673; Yu XF, Zou J, Dong J, "Fish consumption and risk of gastrointestinal cancers: a meta-analysis of cohort studies," *World J. Gastroenterol.* (2014) 20(41):15398-15412; Huang RX, Duan YY, Hu JA, "Fish Intake and Risk of Liver Cancer: A Meta-Analysis," *PLoS One* (2015)10(1):e0096102.

e. Tea

Meta-analyses have reported decreased risks of liver cancer in association with consumption of tea, including black tea (Fon Sing M, Yang WS, Gao S, Gao J, Xiang YB, "Epidemiological studies of the association between tea drinking and primary liver cancer: a meta-analysis," *Eur. J. Cancer Prev.* (2011) 20(3):157-165) and green tea {Fon Sing M, Yang WS, Gao S, Gao J, Xiang YB, "Epidemiological studies of the association between tea drinking and primary liver cancer: a meta-analysis," *Eur. J. Cancer Prev.* (2011) 20(3):157-165; Huang YQ, Lu X, Min H, Wu QQ, Shi XT, Bian KQ, Zou XP, "Green tea and liver cancer risk: A meta-analysis of prospective cohort studies in Asian populations," *Nutrition* (2016) 32(1):3-8; Ni CX, Gong H, Liu Y, Qi Y, Jiang CL, Zhang JP, "Green Tea Consumption and the Risk of Liver Cancer: A Meta-Analysis," *Nutr. Cancer* (2017) 69(2):211-220).

f. Ginseng

One meta-analysis has also reported decreased risk of liver cancer in association with consumption of ginseng. Jin X, Che DB, Zhang ZH, Yan HM, Jia ZY, Jia XB, "Ginseng.consumption and risk of cancer: A meta-analysis," *J. Ginseng Res.* (2016) 40(3):269-277.

g. Other Dietary Factors

Decreased risks of liver cancer have also been reported in association with increased intake of betaine and choline (Zhou RF, Chen XL, Zhou ZG, Zhang YJ, Lan QY, Liao GC, Chen YM, Zhu HL, "Higher dietary intakes of choline and betaine are associated with a lower risk of primary liver cancer: a case-control study," *Sci. Rep.* (2017) 7(1):679) and starch (Fedirko V, Lukanova A, Bamia C, Trichopolou A, Trepo E, Nöthlings U, Schlesinger S, Aleksandrova K, Boffetta P, Tjønneland

A, Johnsen NF, Overvad K, Fagherazzi G, Racine A, Boutron-Ruault MC, Grote V, Kaaks R, Boeing H, Naska A, Adarakis G, Valanou E, Palli D, Sieri S, Tumino R, Vineis P, Panico S, Bueno-de-Mesquita HB, Siersema PD, Peeters PH, Weiderpass E, Skeie G, Engeset D, Quirós JR, Zamora-Ros R, Sánchez MJ, Amiano P, Huerta JM, Barricarte A, Johansen D, Lindkvist B, Sund M, Werner M, Crowe F, Khaw KT, Ferrari P, Romieu I, Chuang SC, Riboli E, Jenab M, "Glycemic index, glycemic load, dietary carbohydrate, and dietary fiber intake and risk of liver and biliary tract cancers in Western Europeans," *Ann. Oncol.* (2013) 24(2):543-553).

h. Trace Elements and Vitamins

Decreased risks of liver cancer have also been reported in association with increased intake of some trace elements and vitamins, including carotenes (Yu MW, Chiu YH, Chiang YC, Chen CH, Lee TH, Santella RM, Chern HD, Liaw YF, Chen CJ, "Plasma carotenoids, glutathione S-transferase M1 and T1 genetic polymorphisms, and risk of hepatocellular carcinoma: independent and interactive effects," *Am. J. Epidemiol.* (1999) 149(7):621-629; Polesel J, Talamini R, Montella M, Maso LD, Crovatto M, Parpinel M, Izzo F, Tommasi LG, Serraino D, La Vecchia C, Franceschi S, "Nutrients intake and the risk of hepatocellular carcinoma in Italy," *Eur. J. Cancer* (2007) 43(16):2381-2387; Lai GY, Weinstein SJ, Albanes D, Taylor PR, Virtamo J, McGlynn KA, Freedman ND, "Association of serum α-tocopherol, β-carotene, and retinol with liver cancer incidence and chronic liver disease mortality," *Br. J. Cancer* (2014) 111(11):2163-21671; Lan QY, Zhang YJ, Liao GC, Zhou RF, Zhou ZG, Chen YM, Zhu HL, "The Association between Dietary Vitamin A and Carotenes and the Risk of Primary Liver Cancer: A Case-Control Study" *Nutrients* (2016) 8(10). pii: E624)); manganese (Ma X, Yang Y, Li HL, Zheng W, Gao J, Zhang W, Yang G, Shu XO, Xiang YB, "Dietary trace element intake and liver cancer risk: Results from two population-based cohorts in China," *Int. J. Cancer.* (2017) 140(5):1050-1059); Vitamin A and retinol (Lai GY, Weinstein SJ, Albanes D, Taylor PR, Virtamo J, McGlynn KA, Freedman ND,

"Association of serum α-tocopherol, β-carotene, and retinol with liver cancer incidence and chronic liver disease mortality," *Br. J. Cancer* (2014) 111(11):2163-21671; Lan QY, Zhang YJ, Liao GC, Zhou RF, Zhou ZG, Chen YM, Zhu HL, "The Association between Dietary Vitamin A and Carotenes and the Risk of Primary Liver Cancer: A Case-Control Study" *Nutrients* (2016) 8(10). pii: E624)); selenium (Zhang Z, Bi M, Liu Q, Yang J, Xu S, "Meta-analysis of the correlation between selenium and incidence of hepatocellular carcinoma," *Oncotarget* (2016) 7(47):77110-77116; Hughes DJ, Duarte-Salles T, Hybsier S, Trichopoulou A, Stepien M, Aleksandrova K, Overvad K, Tjønneland A, Olsen A, Affret A, Fagherazzi G, Boutron-Ruault MC, Katzke V, Kaaks R, Boeing H, Bamia C, Lagiou P, Peppa E, Palli D, Krogh V, Panico S, Tumino R, Sacerdote C, Bueno-de-Mesquita HB, Peeters PH, Engeset D, Weiderpass E, Lasheras C, Agudo A, Sánchez MJ, Navarro C, Ardanaz E, Dorronsoro M, Hemmingsson O, Wareham NJ, Khaw KT, Bradbury KE, Cross AJ, Gunter M, Riboli E, Romieu I, Schomburg L, Jenab M, "Prediagnostic selenium status and hepatobiliary cancer risk in the European Prospective Investigation into Cancer and Nutrition cohort," *Am. J. Clin. Nutr.* (2016) 104(2):406-414); zinc (Stepien M, Hughes DJ, Hybsier S, Bamia C, Tjønneland A, Overvad K, Affret A, His M, Boutron-Ruault MC, Katzke V, Kühn T, Aleksandrova K, Trichopoulou A, Lagiou P, Orfanos P, Palli D, Sieri S, Tumino R, Ricceri F, Panico S, Bueno-de-Mesquita HB, Peeters PH, Weiderpass E, Lasheras C, Bonet Bonet C, Molina-Portillo E, Dorronsoro M, Huerta JM, Barricarte A, Ohlsson B, Sjöberg K, Werner M, Shungin D, Wareham N, Khaw KT, Travis RC, Freisling H, Cross AJ, Schomburg L, Jenab M, "Circulating copper and zinc levels and risk of hepatobiliary cancers in Europeans," *Br. J. Cancer* (2017) 116(5):688-696) and 25-Hydroxyvitamin E (Budhathoki S, Hidaka A, Yamaji T, Sawada N, Tanaka-Mizuno S, Kuchiba A, Charvat H, Goto A, Kojima S, Sudo N, Shimazu T, Sasazuki S, Inoue M, Tsugane S, Iwasaki M; Japan Public Health Center-based Prospective Study Group," *Br. Med. J.* (March 7, 2018) 360:k671)..

i. Medications

Decreased risks of liver cancer have been reported in association with increased consumption of certain medications, such as non-steroidal anti-inflammatory drugs (Pang Q, Jin H, Qu K, Man Z, Wang Y, Yang S, Zhou L, Liu H, "The effects of nonsteroidal anti-inflammatory drugs in the incident and recurrent risk of hepatocellular carcinoma: a meta-analysis," *Onco Targets Ther.* (2017) 10:4645-4656), including aspirin (Petrick JL, Sahasrabuddhe VV, Chan AT, Alavanja MC, Beane-Freeman LE, Buring JE, Chen J, Chong DQ, Freedman ND, Fuchs CS, Gaziano JM, Giovannucci E, Graubard BI, Hollenbeck AR, Hou L, Jacobs EJ, King LY, Koshiol J, Lee IM, Linet MS, Palmer JR, Purdue MP, Rosenberg L, Schairer C, Sesso HD, Sigurdson AJ, Wactawski-Wende J, Zeleniuch-Jacquotte A, Campbell PT, McGlynn KA, "NSAID Use and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma: The Liver Cancer Pooling Project," *Cancer Prev. Res.* (2015) 8(12):1156-1162); beta-blockers (Thiele M, Albillos A, Abazi R, Wiest R, Gluud LL, Krag A, "Non-selective beta-blockers may reduce risk of hepatocellular carcinoma: a meta-analysis of randomized trials," *Liver Int.* (2015) 35(8):2009-2016); metformin (Singh S, Singh PP, Singh AG, Murad MH, Sanchez W, "Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis," *Am. J. Gastroenterol.* (2013) 108(6):881-891; Zhou YY, Zhu GQ, Liu T, Zheng JN, Cheng Z, Zou TT, Braddock M, Fu SW, Zheng MH, "Systematic Review with Network Meta-Analysis: Antidiabetic Medication and Risk of Hepatocellular Carcinoma," *Sci. Rep.* (2016) 6:33743; Ma S, Zheng Y, Xiao Y, Zhou P, Tan H, "Meta-analysis of studies using metformin as a reducer for liver cancer risk in diabetic patients," *Medicine* (2017) 96(19):e6888); and statins (Pradelli D, Soranna D, Scotti L, Zambon A, Catapano A, Mancia G, La Vecchia C, Corrao G, "Statins and primary liver cancer: a meta-analysis of observational studies," *Eur. J. Cancer Prev.* (2013) 22(3):229-234; Shi M, Zheng H, Nie B, Gong W, Cui X, "Statin use and risk of liver cancer: an update meta-analysis," *BMJ Open* (2014) 4(9):e005399, Zhou YY, Zhu GQ, Wang Y, Zheng JN, Ruan LY, Cheng Z, Hu B, Fu SW, Zheng MH, "Systematic review with network meta-analysis:

statins and risk of hepatocellular carcinoma." *Oncotarget* (2016) 7(16):21753-21762; Zhong GC, Liu Y, Ye YY, Hao FB, Wang K, Gong JP, "Meta-analysis of studies using statins as a reducer for primary liver cancer risk," *Sci. Rep.* (2016) 6:26256; Yi C, Song Z, Wan M, Chen Y, Cheng X, "Statins intake and risk of liver cancer: A dose-response meta analysis of prospective cohort studies," *Medicine* (2017) 96(27):e7435).

j. Hormone Replacement Therapy

Meta-analyses have reported decreased risks of liver cancer in association with hormone replacementtherapy. Fernandez E, Gallus S, Bosetti C, Franceschi S, Negri E, La Vecchia C, "Hormone replacement therapy and cancer risk: a systematic analysis from a network of case-control studies," *Int. J. Cancer* (2003) 105(3):408-412; McGlynn KA, Hagberg K, Chen J, Braunlin M, Graubard BI, Suneja N, Jick S, Sahasrabuddhe VV, "Menopausal hormone therapy use and risk of primary liver cancer in the clinical practice research datalink," *Int. J. Cancer* (2016) 138(9):2146-2153; Zhong GC, Liu Y, Chen N, Hao FB, Wang K, Cheng JH, Gong JP, Ding X, "Reproductive factors, menopausal hormone therapies and primary liver cancer risk: a systematic review and dose-response meta-analysis of observational studies," *Hum. Reprod.Update* (2016) 23(1):126-138.

k. Reproductive Factors

Of reproductive factors, to date meta-analyses have only reported late age at menarche to reduce the risk of liver cancer. Zhong GC, Liu Y, Chen N, Hao FB, Wang K, Cheng JH, Gong JP, Ding X, "Reproductive factors, menopausal hormone therapies and primary liver cancer risk: a systematic review and dose-response meta-analysis of observational studies," *Hum. Reprod.Update* (2016) 23(1):126-138.

l. Confounding by Unknown Factors

The inverse association between coffee consumption and liver cancer may also be due to confounding by uncontrolled and/or unknown factors. Lai GY, Weinstein SJ, Albanes D, Taylor PR, McGlynn KA, Virtamo J, Sinha R, Freedman ND, "The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers," *Br. J. Cancer* (2013) 109(5):1344-1351 ("it is possible that our observations, despite our consideration of a number of known and potential confounders, may be due to uncontrolled confounding"); Sang LX, Chang B, Li XH, Jiang M, "Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis," *BMC Gastroenterol.* (2013) 13:34 ("Because liver cancer is a multifactorial disease, it is uncertain whether other factors may have influenced the results."); Jenab M, Boffetta P, "Glycemic index and glycemic load: application in observational studies and association with hepatocellular carcinoma risk. Meaningful or error prone?" *Ann. Oncol.*(2010) 21(3):437-439 ("In any study, whether case-control or prospective, additional bias can arise from missed or uncontrolled confounding."); Tanaka K, Hara M, Sakamoto T, Higaki Y, Mizuta T, Eguchi Y, Yasutake T, Ozaki I, Yamamoto K, Onohara S, Kawazoe S, Shigematsu H, Koizumi S, "Inverse association between coffee drinking and the risk of hepatocellular carcinoma: a case-control study in Japan," *Cancer Sci.* (2007) 98(2):214-218 ("Although potential confounding effects by known risk factors were taken into account in the data analyses, other possible confounders such as <u>dietary factors</u> (e.g. vegetable consumption) could be relevant. We did not ascertain information on other food items and thus could not address this issue.").

5. Exposure Misclassification

The inverse association between coffee consumption and liver cancer may also be due to exposure misclassification and/or other types of misclassification. Petrick JL, Freedman ND,

Graubard BI, Sahasrabuddhe VV, Lai GY, Alavanja MC, Beane-Freeman LE, Boggs DA, Buring JE, Chan AT, Chong DQ, "Coffee Consumption and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma by Sex: The Liver Cancer Pooling Project," *Cancer Epidemiol. Biomarkers Prev.* (2015) 24(9):1398-1406 ("Misclassification of long-term exposure status could result from having only a single, self-reported measurement at study baseline, which does not account for the within person variability over time;" "the null results found for the overall association between coffee drinkers, versus non-drinkers, and HCC could potentially be due to misclassification."); Setiawan VW, Wilkens LR, Lu SC, Hernandez BY, Le Marchand L, Henderson BE, "Association of Coffee Intake with Reduced Incidence of Liver Cancer and Death from Chronic Liver Disease in the US Multiethnic Cohort," *Gastroenterology* (2015) 148(1):118-125 ("The limitations include coffee intake assessment by self-report at baseline which may not reflect long-term patterns of consumption." Among the participants who responded to the follow up questionnaire . . . , the intraclass correlation coefficient between the baseline and the follow up questionnaires was 0.60. This imperfect correlation reflects potential exposure misclassification due to measurement error, which might have attenuated the observed associations."); Sang LX, Chang B, Li XH, Jiang M, "Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis," *BMC Gastroenterol.* (2013) 13:34 ("Each study presented coffee consumption in different units (cups/week, cups/day, days/week, drinks/day, times/week). Therefore, differential misclassification could bias the results."); Jenab M, Boffetta P, "Glycemic index and glycemic load: application in observational studies and association with hepatocellular carcinoma risk. Meaningful or error prone?" *Ann. Oncol.*(2010) 21(3):437-439 ("Significant imprecision is a fact of life in dietary assessment, particularly when carried out retrospectively where the magnitude of errors may be different between cases and controls. Although nondifferential classification errors in terms of carbo-hydrate intake estimation may cause a bias of the risk estimate toward the null, differential reporting errors may result in either an overestimation or an underestimation of disease risk depending on the error structure of the dataset. In the case of HCC, where cases are diagnosed in

late stages and are likely very sick, the potential of differential error is difficult to ignore."); Inoue M, Kurahashi N, Iwasaki M, Shimazu T, Tanaka Y, Mizokami M, Tsugane S, "Effect of coffee and green tea consumption on the risk of liver cancer: cohort analysis by hepatitis virus infection status," *Cancer Epidemiol. Biomarkers Prev.* (2009) 18(6):1746-1753 ("[S]everal limitations can be identified. First, the correlation coefficients were moderate for coffee . . . . Inaccurate measurement of coffee . . . consumption necessarily results in random misclassification, which in turn attenuate the true association. Second, misclassification might also have resulted form our evaluation of coffee . . . consumption by a single, self-reported measurement at baseline."); Hu G, Tuomilehto J, Pukkala E, Hakulinen T, Antikainen R, Vartiainen E, Jousilahti P, "Joint effects of coffee consumption and serum gamma-glutamyltransferase on the risk of liver cancer," *Hepatology* (2008) 48(1):129-136 ("A limitation of our study was that we used self-[reported data on coffee intake only at baseline."). In other words, if coffee consumption changed between the initial interview and diagnosis with HCC, it was not accounted for in the study. Tanaka K, Hara M, Sakamoto T, Higaki Y, Mizuta T, Eguchi Y, Yasutake T, Ozaki I, Yamamoto K, Onohara S, Kawazoe S, Shigematsu H, Koizumi S, "Inverse association between coffee drinking and the risk of hepatocellular carcinoma: a case-control study in Japan," *Cancer Sci.* (2007) 98(2):214-218 ("the major limitation of the present study was a possible decrease of coffee use among HCC cases due to their advanced liver disease."); Wakai K, Kurozawa Y, Shibata A, Fujita Y, Kotani K, Ogimoto I, Naito M, Nishio K, Suzuki H, Yoshimura T, Tamakoshi A; JACC Study Group, "Liver cancer risk, coffee, and hepatitis C virus infection: a nested case-control study in Japan," *Br. J. Cancer* (2007) 97(3):426-428 ("Some patients with hepatitis or liver cirrhosis, however, may have decreased coffee consumption on their physician's advice or due to impaired caffeine metabolism in the liver."); Montella M, Polesel J, La Vecchia C, Maso LD, Crispo A, Crovatto M, Casarin P, Izzo F, Tommasi LG, Talamini R, Franceschi S, "Coffee and tea consumption and risk of hepatocellular carcinoma in Italy," *Int. J. Cancer* (2007) 120(7):1555-1559 ("Physicians' recommendation about restriction of coffee drinking in patients with liver diseases could have influenced the results"); Inoue M, Yoshimi I, Sobue T,

Tsugane S, JPHC Study Group, "Influence of coffee drinking on subsequent risk of hepatocellular carcinoma: a prospective study in Japan," *J. Natl. Cancer Inst.* (2005) 97(4):293-300 ("there are some obvious limitations [in this study] such as the assessment of coffee intake solely on the basis of the self-report at a single time point"; "changes in coffee intake that arose from symptoms related to a subsequent diagnosis of HCC after the start of the study may have resulted in some misclassification."); Shimazu T, Tsubono Y, Kuriyama S, Ohmori K, Koizumi Y, Nishino Y, Shibuya D, Tsuji I, "Coffee consumption and the risk of primary liver cancer: pooled analysis of two prospective studies in Japan," *Int. J. Cancer* (2005) 116(1):150-154 ("we were unable to distinguish between never and former coffee drinkers, as this information was not collected at the baseline"; "primary liver cancer cases identified on the basis of death certifications alone without confirmation by medical records might have a possibility of misclassifying secondary metastasis to the liver as primary liver cancer.")

C. Breast Cancer

1. Inconsistency of Studies

a. Case-Control Studies

Some case-control studies have reported increased risks of breast cancer in association with consumption of coffee.

In a case-control study nested within a cohort of French-Canadian women, significantly increased risks of breast cancer with coffee consumption were observed in the multivariate analysis that adjusted for age, education, physical activity, smoking, alcohol consumption and total energy. Breast cancer risk was increased among women drinking between 2 and 8 cups of coffee per day (OR 1.79, 95% CI 1.17 - 2.57) and more than 8 cups of coffee per day (OR 1.40, 95% CI 1.09 - 2.24).

Bissonauth V, Shatenstein B, Fafard E, Maugard C, Robidoux A, Narod S, Ghadirian P, "Risk of Breast Cancer Among French-Canadian Women, Noncarriers of More Frequent *BRCA1/2* Mutations and Consumption of Total Energy, Coffee, and Alcohol," *Breast J.* (2009) 15(Suppl. 1):63-71.

In a case-control study of 3,234 women in eastern New York State, the risk of breast cancer was significantly increased on multiple logistic regression analysis for consumption of decaffeinated coffee (OR 1.20, 95% CI 1.03 - 1.39), but not caffeinated coffee (OR 0.98, 95% CI 0.76-1.26). McLaughlin CC, Mahoney MC, Nasca PC, Metzger BB, Baptiste MS, Field NA, "Breast cancer and methylxanthine consumption," *Cancer Causes Control* (1992) 3:175-178.

In a relatively small hospital-based case-control study of breast cancer risk factors among Vietnamese women that was published the year after the IARC meeting, consumption of 1 or more cups of coffee per day was associated with an increased risk of breast cancer among South Vietnamese women on multivariate analysis (OR 1.5, 95% CI 1.0 - 2.6), with a greater risk among post-menopausal women South Vietnamese women (OR 2.1, 95% CI 1.0 - 4.6). Trieu PD, Mello-Thoms C, Peat JK, Do TD, Brennan PC, "Inconsistencies of Breast Cancer Risk Factors between the Northern and Southern Regions of Vietnam," *Asian Pac. J. Cancer Prev.* (2017) 18(10):2747-2754.

In a recent study of 126,182 postmenopausal women in the United Kingdom Biobank, of whom 2,636 had breast cancer, women who had received postmenopausal hormone therapy and who consumed four or more cups of coffee per day had a 22% greater risk of breast cancer than women who consumed less that 7 cups of coffee per week (HR 1.22, 95% CI 1.01 - 1.47). Yaghjyan L, Rich S, Mao L, Mai V, Egan KM, "Interactions of coffee consumption and postmenopausal hormone use in relation to breast cancer risk in UK Biobank," *Cancer Causes Control* (2018) 29:519-525.

b. Cohort Studies

Some cohort studies have reported increased risks of breast cancer in association with consumption of coffee.

In a prospective cohort study of 38,432 women age 45 years or older who were followed for 10 years, significantly increased risks of breast cancer were observed among those women with benign breast disease who drank 4 or more cups of coffee per day (RR 1.35, 95% CI 1.01 - 1.80), among those women in the highest quintile of total caffeine consumption with ER-/PR- breast cancer (RR 1.68, 95% CI 1.01 - 2.81, *p*-trend = 0.02), and among women with tumors larger than 2 centimeters (RR 1.79, 95% CI 1.18 - 2.72, *p*-trend = 0.02). Ishitani K, Lin J, Manson JE, Buring JE, Zhang SM, "Caffeine Consumption and the Risk of Breast Cancer in a Large Prospective Cohort of Women," *Arch. Intern. Med.* (2008) 168(18):2022-2031.

In a cohort study of 64,603 Swedish women, including 3,034 cases of breast cancer, risk of breast cancer among women less than 49 years of age who drank 4 or more cups of filtered coffee per day was significantly increased on multivariate analysis (HR 1.76, 95% CI 1.04 - 3.00, *p*-trend = 0.037), but was significantly reduced for those older than 55 years (HR 0.64, 95% CI 0.44 - 0.94, p-trend = 0.024). For those who drank boiled coffee, the risk was reduced, but not significantly. Nilsson LM, Johansson I, Lenner P, Lindahl B, Van Guelpen B, "Consumption of filtered and boiled coffee and the risk of incidence cancer: a prospective cohort study," *Cancer Causes Control* (2010) 21:1533-1544.

In a population-based prospective cohort study of 27,323 participants in the Netherlands, coffee intake increased the risk of breast cancer by more than twofold as compared to non-consumers (HR 2.25, 95% CI 1.30 - 3.90), but the increased risk was attenuated on multivariate adjustment (HR 1.17, 95% CI 0.65 - 2.12). Bhoo Pathy N, Peeters P, van Gils C, Beulens JWJ, van der Graaf Y, Bueno-de-Mesquita B, Bulgiba A, Uiterwaal CSPM, "Coffee and tea intake and risk of breast cancer," *Breast Cancer Res. Treat.* (2010) 121:461-467.

In a study of 96 women treated for breast cancer, consumption of coffee was associated with increased mortality. Survival was 79.2% among women who drank one cup of coffee per day, 72.7% among women who drank two cups per day, and 42.9% among women who drank 3 or more cups per day. The effect of coffee consumption on survival was highly significant ($p = 0.006$, log

rank test). Lehrer S, Green S, Rosenzweig KE, "Coffee Consumption Associated with Increased Mortality of Women with Brest Cancer," *J. Caffeine Res.* (2013) 3(1):38-40.

In a prospective cohort of 35,303 Singapore Chinese women followed for a mean period of 11 years, 629 women developed breast cancer. Coffee intake of 2 or more cups per day increased the risk of breast cancer (HR 1.23, 95% CI 0.98 - 1.54) and the risk was further increased among women with advanced breast cancer (HR 1.90, 95% CI 1.30 - 2.77, *p*-trend < 0.01). In stratified analyses, the adverse effect of coffee intake on the development of advanced breast cancer was present only among larger women (BMI > median, 23 kg/m2) (HR 2.35, 95% CI 1.51 - 3.66) comparing daily intake versus none (*p*-for interaction = 0.02). The authors concluded that a higher BMI may influence the adverse effect of coffee on advanced breast cancer development. Zhu L, Butler LM, Wang R, Koh W-P, Yu MC, Yuan J-M, "Coffee consumption increases risk of advanced breast cancer among Singapore Chinese women," *AACR Annual Meeting* (2013) Abstract No. 135.

In a prospective study of 14,593 Norwegian women, for those consuming 5 or more cups of coffee per day, a positive association between coffee consumption and breast cancer was observed among obese women (IRR 2.1, 95% CI 0.8 - 5.2) and a negative association between coffee consumption and breast cancer among lean women (IRR 0.5, 95% CI 0.3 - 0.9). The authors concluded coffee consumption could have both effects depending upon BMI of the women. Vatten LJ, Solvoll K, Løken EB, "Coffee consumption and the risk of breast cancer. A prospective study of 14,593 Norwegian women," *Br. J. Cancer* (1990) 62:267-270.

c. Meta-Analyses

Five meta-analyses regarding coffee consumption and breast cancer have been published to date, all by Chinese investigators.

In 2009 Chinese researchers from Shanghai published a meta-analysis of coffee consumption and breast cancer based on 9 cohort studies and 9 case-control studies. The combined RR showed

a borderline significant decrease in breast cancer for the highest coffee consumption versus the lowest (RR 0.95, 95% CI 0.90 - 1.00). For an increment of 2 cups/day, the breast cancer risk was borderline significantly reduced with the data for Europe, the USA and Asia combined with the exclusion of 3 studies (RR 0.98, 95% CI 0.96 - 1.00), but results were not statistically significant with data for all 3 countries analyzed separately, e.g., USA (RR 0.99, 95% CI 0.95 - 1.02). Tang N, Zhou B, Wang B, Yu R, "Coffee consumption and risk of breast cancer: a metaanalysis," *Am. J. Obstet. Gynecol.* (2009) 200:290.e1-290.e9.

In 2011, researchers from Shanghai published a meta-analysis of prospective cohort studies regarding coffee consumption and risk of cancers. Based on 11 cohort studies, the risk of breast cancer was slightly decreased (RR 0.94, 95% CI 0.91 - 0.99). Yu X, Bao Z, Zou J, Dong J, "Coffee consumption and risk of cancers: a meta-analysis of cohort studies," *BMC Cancer* (2011) 11:96.

In 2013 Chinese researchers from Xuzhou published a meta-analysis of epidemiologic studies regarding coffee consumption and breast cancer. A total of 26 studies (16 cohort and 10 case-control studies) on coffee intake with 49497 breast cancer cases were included in the analysis. The pooled RR showed a borderline significant influence of highest coffee consumption (RR 0.96, 95% CI 0.93 -1.00). Low-to moderate coffee consumption showed no association with risk of breast cancer (RR 0.99, 95% CI 0.95 - 1.04); for an increment of 2 cups/day of coffee consumption the risk of breast cancer was (RR 0.98, 95% CI 0.97-1.00). In stratified analysis, a significant inverse association was observed in ER-negative subgroup. However, no significant association was noted in the others. The investigators concluded that increased coffee intake is not associated with a significantly reduced risk of breast cancer, but noted that an inverse association was observed in the ER-negative subgroup analysis. Li XJ, Ren ZJ, Qin JW, Zhao JH, Tang JH, Ji MH, Wu JZ, "Coffee Consumption and Risk of Breast Cancer: An Up-To-Date Meta-Analysis," *PLoS One* (2013) 81:e52681.

In 2013 Chinese researchers from Qingdao published a meta-analysis of 37 published studies regarding coffee consumption and breast cancer. This study included 966,263 participants and 59,018 breast cancer cases were included in the meta-analysis. No significant association was found

between breast cancer risk and coffee (RR 0.97, $p = 0.09$), decaffeinated coffee (RR 0.98, $p = 0.55$) and caffeine (RR 0.99, $p = .73$), respectively. However, an inverse association of coffee/caffeine with breast cancer risk was found for postmenopausal women (RR 0.94, $p = 0.02$), and a strong and significant association of coffee with breast cancer risk was found for BRCA1 mutation carriers (RR 0.69, $p < 0.01$). A linear dose-response relationship was found for breast cancer risk with coffee consumption; the risk of breast cancer decreased by 2% ($p = 0.05$) for every 2 cups/day increment in coffee intake. The researchers concluded that the findings from their study suggested that coffee/caffeine might be weakly associated with breast cancer risk for postmenopausal women. Jiang W, Wu Y, Jiang X, "Coffee and caffeine intake and breast cancer risk: An updated dose-response meta-analysis of 37 published studies," *Gynecol. Oncol.* (2013) 129(3):620-629.

In 2016, researchers from Beijing and Tianjin published a meta-analysis of prospective cohort studies regarding coffee consumption and cancer risk. Seventeen cohort studies were included in the analysis of breast cancer. Comparing the highest versus lowest intake of coffee consumption, no association with risk of breast cancer risk was observed. (RR 0.99, 95% CI 0.94 - 1.04). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and cancer risk: A meta-analysis of prospective observational studies," *Sci. Rep.* (2016) 6:33711.

2. Confounding

Several other factors have been reported to significantly reduce the risk of breast cancer, thereby confounding the association between coffee consumption and breast cancer.

a. Cigarette Smoking

The inverse association of coffee consumption and breast cancer among postmenopausal women (and the absence of an association between coffee consumption and breast cancer generally) is likely due, at least in part, to confounding by cigarette smoking.

"A review of 14 case-control studies and five cohort studies found that the RR for breast cancer among heavy smokers compared with never smokers generally ranged from 0.9 to 1.2." (Kuper 2002, citing Palmer JR, Rosenberg L, "Cigarette smoking and the risk of breast cancer," *Epidemiol. Rev.* (1993) 15(1):145-156.

"Although an association has rarely been found by epidemiological studies, a role of cigarette smoking in the aetiology of breast cancer is biologically plausible. Smoking has anti-oestrogenic effects and menopause occurs at an earlier age in smokers, supporting a protective effect on breast cancer risk." Kuper H, Boffetta P, Adami HO, "Tobacco use and cancer causation: association by tumour type," *J. Intern. Med.* (2002) 252:206-224.

The investigators of an early case-control study of breast cancer and coffee consumption commented: "The recent paper by Vessey et al. reporting a statistically significant protective effect of smoking in BC patients is intriguing because smoking is known to be positively correlated with coffee consumption. Furthermore, in a review of the literature on smoking and estrogen-related disease, Baron found smoking to be a protective factor in several studies, even when weight and age at menopause were included as covariates. Inasmuch as our questionnaire did not include any data on smoking, we were unable to examine this possible confounding effect." (Lubin F, Ron E, Wax Y, Modan B, "Coffee and methylxanthines and breast cancer: a case-control study," *J. Natl Cancer Inst.* (1985) 74(3):569-573.

In a cohort study of Swedish breast cancer patients, Swedish researchers commented that "coffee intake and smoking have been shown to be associated" and observed that "in the present study, current smoking was significantly associated with increasing coffee consumption."

Simonsson M, Söderlind V, Henningson M, Hjertberg M, Rose C, Ingvar C, Jernström H, "Coffee prevents early events in tamoxifen-treated breast cancer patients and modulates hormone receptor status," *Cancer Causes Control* (2013) 45(5):929-950.

The inverse association of coffee/caffeine with breast cancer risk in postmenopausal women observed in Jiang meta-analysis may be due to confounding by the anti-estrogenic effect of cigarette smoking. Jiang W, Wu Y, Jiang X, "Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies," *Gynecol. Oncol.* (2013) 129(3):620-629.

b. Factors Other Than Smoking

The authors of one prospective cohort study commented on the effect of confounding by multiple confounders: "Even though most of the previous prospective studies adjusted for multiple confounders mainly age, risk factors of breast cancer, smoking (except in 1 study), and total energy intake, many did not adjust for other important nutritional variables such as fiber intake (except two studies), saturated fat intake, alcohol intake (except 4 studies), or mutually adjusted coffee for tea intake since these beverages are inversely correlated (except two studies). Even if these variables are solely not capable of changing the hazard ratios for developing breast cancer drastically, they may in combination confound the association between coffee . . . intake and risk of breast cancer." Bhoo Pathy N, Peeters P, van Gils C, Beulens JWJ, van der Graaf Y, Bueno-de-Mesquita B, Bulgiba A, Uiterwaal CSPM, "Coffee and tea intake and risk of breast cancer," *Breast Cancer Res. Treat.* (2010) 121:461-467.

The authors of another cohort study acknowledged the problem that many factors that affect breast cancer risk are unknown: "A limitation of this study is the lack of information on factors that are known to affect the risk of breast cancer." Vatten LJ, Solvoll K, Løken EB, "Coffee consumption and the risk of breast cancer. A prospective study of 14,593 Norwegian women," *Br.*

J. Cancer (1990) 62(2):267-270. The authors stated that they had no information on variables like age at menarche and age at first full term pregnancy.

Women who undergo menopause later in life have an increased risk of breast cancer compared to women who go through menopause earlier. Collaborative Group on Hormonal Factors in Breast Cancer, "Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies," *Lancet Oncol.* (2012) 31(11):1141-1151. Some studies regarding coffee consumption and breast cancer have acknowledged confounding by menopausal status. Bhoo Pathy N, Peeters PH, Uiterwaal CS, Bueno-de-Mesquita HB, Bulgiba Am, Bech BH, Overvad K, Tjønneland A, Olsen A, Clavel-Chapelon F, Fagherazzi G, "Coffee and tea consumption and risk of pre- and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study," *Breast Cancer Res.* (2015) 17(1):15 ("We do, however, acknowledge that data on menopausal status at diagnosis was not available, and we had to use age at breast cancer diagnosis as a proxy."); Oh JK, Sandin S, Ström P, Löf M, Adami HO, Weiderpass E, "Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden," *Int. J. Cancer* (2015) 137(8):1979-1989 ("Misclassification of menopausal status due to imputation for women without information on age at menopause may also have occurred in our study.").

At least one study has commented on potential confounding by energy intake. Nkondjock A, Ghadirian P, Kotsopoulos J, Lubinski J, Lynch H, Kim-Sing C, Horsman D, Rosen B, Isaacs C, Weber B, Foulkes W, "Coffee consumption and breast cancer risk among BRCA1 and BRCA2 mutation carriers," *Int. J. Cancer* (2006) 118(1):103-107 ("We cannot completely rule out the potential residual confounding effects of unmeasured dietary factors, such as total energy intake [because] this information was not collected at baseline."). A more recent study demonstrates a positive association between energy intake and breast cancer in post menopausal women. Sue, LY, et al. (2009) "Energy intake and risk of postmenopausal breast cancer: An expanded analysis in the

prostate, lung, colorectal, and ovarian cancer screening trial (PLCO) cohort," *Cancer Epidemiol. Biomarkers Prev.* (2009) 18:2842-2850.

Brewing methods affect the chemical composition of coffee beverages and are therefore another potential source of confounding. Nilsson LM, Johansson I, Lenner P, Lindahl B, Van Guelpen B, "Consumption of filtered and boiled coffee and the risk of incident cancer: a prospective cohort study," *Cancer Causes Control* (2010) 21(10):1533-1544. Brewing method has been recognized as a source of confounding in a few studies of coffee consumption and breast cancer. Bhoo-Pathy N, Peeters PH, Uiterwaal CS, Bueno-de-Mesquita HB, Bulgiba AM, Bech BH, Overvad K, Tjønneland A, Olsen A, Clavel-Chapelon F, Fagherazzi G, " Coffee and tea consumption and risk of pre-and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study," *Breast Cancer Res.* (2015) 17(1):15("We did not have information on the type of . . . brewing methods, which may vary across the countries . . . ." It has recently been highlighted that coffee brewing methods may[] be relevant with respect to breast cancer risk. A cohort study in Sweden showed that a decreased risk of breast cancer was observed in women drinking boiled coffee but no association was observed with filtered coffee consumption."); Gierach GL, Freedman ND, Andaya A, Hollenbeck AR, Park Y, Schatzkin A, Brinton LA, "Coffee intake and breast cancer risk in the NIH-AARP diet and health study cohort," *Int. J. Cancer* (2012) 131(2):452-460 ("[W]e did not collect information on the coffee brewing method.")\

c. Factors Reported to Reduce Breast Cancer Risk

Epidemiology studies regarding coffee consumption and breast cancer have neither controlled nor adjusted for several factors that have been shown to reduce the risk of breast cancer in epidemiologic studies or meta-analyses:

(1) Dietary Factors

Case-control studies and meta-analyses have reported reduced risks of breast cancer in association with several dietary factors.

(a) Calcium

Studies have reported decreased risks of breast cancer in association with calcium intkae. Hidayat K, Chen GC, Zhang R, Du X, Zou SY, Shi BM, Qin LQ, "Calcium intake and breast cancer risk: meta-analysis of prospective cohort studies," *Br. J. Nutr.* (2016) 116(1):158-166; Wulaningsih W, Sagoo HK, Hamza M, Melvin J, Holmberg L, Garmo H, Malmström H, Lambe M, Hammar N, Walldius G, Jungner I, Van Hemelrijck M, "Serum Calcium and the Risk of Breast Cancer: Findings from the Swedish AMORIS Study and a Meta-Analysis of Prospective Studies," *Int. J. Mol. Sci.* (2016) 17(9). pii: E1487).

(b) Carotenoids

Carotenoid intake has also been reported to reduce the risk of breast cancer. Nagel G, Linseisen J, Van Gils CH, Peeters PH, Boutron-Ruault MC, Clavel-Chapelon F, Romieu I, Tjønneland A, Olsen A, Roswall N, Witt PM, "Dietary Beta-carotene, vitamin C and E intake and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC)," *Breast Cancer Res. Treat*. (2010) 119(3):753-765; Eliassen AH, Hendrickson SJ, Brinton LA, Buring JE, Campos H, Dai Q, Dorgan JF, Franke AA, Gao YT, Goodman MT, Hallmans G, "Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies," *J. Natl. Cancer Inst.* (2012) 104(24):1905-1916.

(c) Dietary Fiber

Dietary fiber has also been reported to reduce the risk of breast cancer. Aune D, Chan DS, Greenwood DC, Vieira AR, Rosenblatt DN, Vieira R, Norat T, "Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies," *Ann. Oncol.* (2012) 23(6):1394-1402).

(d) Fatty Acids and Fish

Several studies have reported that atty acids and fish reduce the risk of breast cancer. Saadatian-Elahi M, Norat T, Goudable J, Riboli E, "Biomarkers of dietary fatty acid intake and the risk of breast cancer: A meta-analysis," *Int. J. Cancer* (2004) 111(4):584-591; Kim J, Lim SY, Shin A, Sung MK, Ro J, Kang HS, Lee KS, Kim SW, Lee ES, "Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study," *BMC Cancer* (2009) 9(1):216; Zheng JS, Hu SJ, Zhao YM, Yang J, Li D, "Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies," *Br. Med. J.* (2013) 346:f3706; fish (Kim J, Lim SY, Shin A, Sung MK, Ro J, Kang HS, Lee KS, Kim SW, Lee ES, "Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study," *BMC Cancer* (2009) 9(1):216; Zheng JS, Hu XJ, Zhao YM, Yang J, Li D, "Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies" *Br. Med. J.* (2013) 346:f3706; Haraldsdottir A, Steingrimsdottir L, Valdimarsdottir UA, Aspelund T, Tryggvadottir L, Harris TB, Launer LJ, Mucci LA, Giovannucci EL, Adami HO, Gudnason V, "Early Life Residence, Fish Consumption, and Risk of Breast Cancer," *Cancer Epidemiol. Biomarkers Prev.* (2017) 26(3):346-354.

(e) Flavan-3-ols

Flavanols have been reported to reduce the risk of breast cancer. Lei L, Yang Y, He H, Chen E, Du L, Dong J, Yang J, "Flavan-3-ols consumption and cancer risk: A meta-analysis of epidemiologic studies," *Oncotarget*. (2016) 7(45):73573-73592.

(f) Folate

Likewise, folate has been reported to reduce the risk of breast cancer. Li B, Lu Y, Wang L, Zhang CX, "Folate intake and breast cancer prognosis: a meta-analysis of prospective observational studies," *Eur. J. Cancer Prev.* (2015) 24(2):113-121)

(g) Fruit

Several studies have reported decreased risks of breast cancer associated with increased fruit consumptiont. Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, Lubin F, Marubini E, Modan B, Rohan T, Toniolo P, "Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies," *J. Natl. Cancer Inst.* (1990) 82(7):561-569; Jung S, Spiegelman D, Baglietto L, Bernstein L, Boggs DA, Van Den Brandt PA, Buring JE, Cerhan JR, Gaudet MM, Giles GG, Goodman G, "Fruit and vegetable intake and risk of breast cancer by hormone receptor status," *J. Natl Cancer Inst*. (2013) 105(3):219-236; Song JK, Bae JM, "Citrus fruit intake and breast cancer risk: a quantitative systematic review," *J. Breast Cancer* (2013) 16(1):72-76.

(h) Mediterranean Diet

The Mediterranean Diet has been reported to decrease risk of breast cancer. Schwingshackl L, Hoffmann G, "Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies," *Cancer Med.* (2015) 4(12):1933-1947).

(i) Soy

Soy intake has also been associated with decreased risk of breast cancer. Key TJ, Sharp GB, Appleby PN, Beral V, Goodman MT, Soda M, Mabuchi K, "Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan," *Br. J. Cancer* (1999) 81(7):1248-1256; Trock BJ, Hilakivi-Clarke L, Clarke R, "Meta-analysis of soy intake and breast cancer risk," *J. Natl. Cancer Inst.* (2006) 98(7):459-471; Dong JY, Qin LQ, "Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies," *Breast Cancer Res. Treat.* (2011) 125(2):315-323.

(j) Tea

Some meta-analyses regarding tea consumption and breast cancer have reported significantly decreased risks of breast cancer. Gao Y, Huang YB, Liu XO, Chen C, Dai HJ, Song FJ, Wang J, Chen KX, Wang YG, "Tea consumption, alcohol drinking and physical activity associations with breast cancer risk among Chinese females: a systematic review and meta-analysis," *Asian Pac. J. Cancer Prev.* (2013) 14(12):7543-7550. The association is stronger for green tea than black tea. The most recent meta-analysis, based on 14 studies (9 case-control studies, 4 cohort studies, and 1 clinical trial), indicated a 19% reduction in breast cancer risk comparing the highest and lowest levels of green tea consumption (OR 0.81, 95% CI 0.66 - 0.98). Najaf Najafi M, Salehi M,

Ghazanfarpour M, Hoseini ZS, Khadem-Rezaiyan M, "The association between green tea consumption and breast cancer risk: A systematic review and meta-analysis," *Phytother Res.* (June 7, 2018) doi: 10.1002/ptr.6124. [Epub ahead of print] A meta-analysis by researchers from Harvard reported a 19% reduction in risk of breast cancer recurrence for consumption of more than three cups of green tea per day (RR 0.73, 95% CI 0.56 - 0.96). Ogunleye AA, Xue F, Michels KB, "Green tea consumption and breast cancer risk or recurrence: a meta-analysis," *Breast Cancer Res. Treat.* (2010) 119(2):477-484.

(k) Vegetables

Studies have also reported decreased risks of breast cancer in association with increased consumption of vegetables. Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, Lubin F, Marubini E, Modan B, Rohan T, Toniolo P, "Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies, " *J. Natl. Cancer Inst.* (1990) 82(7):561-569; Jung S, Spiegelman D, Baglietto L, Bernstein L, Boggs DA, Van Den Brandt PA, Buring JE, Cerhan JR, Gaudet MM, Giles GG, Goodman G, "Fruit and vegetable intake and risk of breast cancer by hormone receptor status," *J. Natl. Cancer Inst.* (2013) 105(3):219-236)

(l) Vitamins

Several studies have reported decreased risks of breast cancer in association with consumption of vitamins, including Vitamin B (Wu S, Kang S, Zhang D, "Association of vitamin B6, vitamin B12 and methionine with risk of breast cancer: a dose-response meta-analysis," *Br. J. Cancer* (2013) 109(7):1926-1944); Vitamin C (Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, Lubin F, Marubini E, Modan B, Rohan T, Toniolo P, "Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies, " *J. Natl. Cancer Inst.* (1990)

82(7):561-569; Nagel G, Linseisen J, Van Gils CH, Peeters PH, Boutron-Ruault MC, Clavel-Chapelon F, Romieu I, Tjønneland A, Olsen A, Roswall N, Witt PM, "Dietary Beta-carotene, vitamin C and E intake and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC)," *Breast Cancer Res. Treat*. (2010) 119(3):753-765;), Vitamin D (Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H, "Meta-analysis: serum vitamin D and breast cancer risk," *Eur. J. Cancer* (2010) 46(12):2196-2205; Bauer SR, Hankinson SE, Bertone-Johnson ER, Ding EL, "Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies," *Medicine* (2013) 92(3):123-131; Wang J, He Q, Shao YG, Ji M, Bao W, "Associations between vitamin D receptor polymorphisms and breast cancer risk," *Tumour Biol.* (2013) 34(6):3823-3830; Jamshidinaeini Y, Akbari ME, Abdollahi M, Ajami M, Davoodi SH, "Vitamin D status and risk of breast cancer in Iranian women: a case–control study," *J. Am. Coll. Nutr*. (2016) 35(7):639-646; Sofi NY, Jain M, Kapil U, Seenu V, Kamal VK, Pandey RM, "Nutritional risk factors and status of serum 25(OH)D levels in patients with breast cancer: A case control study in India," *J. Steroid. Biochem. Mol. Biol.* (2018) 175:55-59).

(2) Physical Activity

Increased physical activity has also been associated with reduced breast cancer risk. Mathew A, Gajalakshmi V, Rajan B, Kanimozhi VC, Brennan P, Binukumar BP, Boffetta P, "Physical activity levels among urban and rural women in south India and the risk of breast cancer: a case–control study," *Eur. J. Cancer Prev*. (2009) 18(5):368-376; Wu Y, Zhang D, Kang S, "Physical activity and risk of breast cancer: a meta-analysis of prospective studies," *Breast Cancer Res. Treat.* (2013) 137;869-882.

(3) Breastfeeding

Breastfeeding has also been associated with decreased risk of breast cancer in a number of studies. Gajalakshmi V, Mathew A, Brennan P, Rajan B, Kanimozhi VC, Mathews A, Mathew BS, Boffetta P, "Breastfeeding and breast cancer risk in India: A multicenter case-control study," *Int. J. Cancer* (2009) 125(3):662-665); Islami F, Liu Y, Jemal A, Zhou J, Weiderpass E, Colditz G, Boffetta P, Weiss M, "Breastfeeding and breast cancer risk by receptor status—a systematic review and meta-analysis," *Ann. Oncol*. (2015) 26(12):2398-2407. See, especially, Kim J., et al. (2009) "Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study," *BMC Cancer* 9:216-226. doi:10.1186/1471-2407-9-216.

3. Exposure Misclassification

Several epidemiologic studies regarding coffee consumption and breast cancer have acknowledged problems with exposure misclassification. Oh JK, Sandin S, Ström P, Löf M, Adami HO, Weiderpass E, "Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden," *Int. J. Cancer* (2015) 137(8):1979-1989 ("The women in our cohort were aged 30-49 years at enrollment in 1991-1992, thus their responses in the questionnaire reflect mainly coffee consumption . . . at premenopausal ages. Moreover, coffee consumption [was] only assessed at enrollment. This may attenuate our associations if women changed their coffee . . . habits during follow-up.");Bhoo-Pathy N, Peeters PH, Uiterwaal CS, Bueno-de-Mesquita HB, Bulgiba AM, Bech BH, Overvad K, Tjønneland A, Olsen A, Clavel-Chapelon F, Fagherazzi G, "Coffee and tea consumption and risk of pre-and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study," *Breast Cancer Res.* (2015) 17(1):15 ("[C]offee . . . intakes were measured only at baseline."); Harris HR, Bergkvist L, Wolk A, "Coffee and black tea consumption and breast cancer mortality in a cohort of Swedish women," *Br. J. Cancer*

(2012) 107(5):874 ("A limitation of our study was for the majority of our participants we only had a pre-diagnosis assessment of diet and thus had limited power to examine diet post diagnosis during the follow-up period."); Bhoo Pathy N, Peeters P, van Gils C, Beulens JWJ, van der Graaf Y, Bueno-de-Mesquita B, ,Bulgiba A, Uiterwaal CSPM, "Coffee and tea intake and risk of breast cancer," *Breast Cancer Res. Treat.* (2010) 121:461-467 ("Since the measurement of coffee . . . intake was done at baseline only, we are uncertain about the effects of participants subsequently changing their pattern of . . . consumption."); Ishitani K, Lin J, Manson JE, Buring JE, Zhang SM, "Caffeine consumption and the risk of breast cancer in a large prospective cohort of women," *Arch. Ingtern. Med.* (2008) 168(18):2022-2031 ("Because we used the information on consumption of caffeine and caffeinated beverages . . . at baseline only, which did not account for changes in caffeine consumption across time, measurement error due to random within-person variation is inevitable. Such misclassification in prospective studies tends to weaken any true associations."); Kotsopoulos J, Ghadirian P, El-Sohemy A, Lynch HT, Snyder C, Daly M, Domchek S, Randall S, Karlan B, Zhang P, Zhang S, "The CYP1A2 genotype modifies the association between coffee consumption and breast cancer risk among BRCA1 mutation carriers," *Cancer Epidemiol. Biomarkers Prev.* (2007) 16(5):912-916 ("We grouped women based on the presence or absence of a history of coffee consumption, and did not distinguish between those women who regularly consumed coffee versus those who were occasional drinkers. Nor did we take into account the amount and duration of intake.")

Some studies have acknowledged that exposure misclassification is inevitable from use of food frequency questionnaires and from self-reporting of consumption. Larsson SC, Bergkvist K, Wolk A, "Coffee and black tea consumption and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort," *Cancer Causes Control* (2009) 20(10):2039-2044 ("A limitation is that coffee . . . consumption was assessed with a FFQ, which will inevitably lead to some measurement error and attenuated relative risk estimates."); Simonsson M, Söderlind V, Henningson M, Hjertberg M, Rose C, Ingvar C, Jernström H, "Coffee prevents early events in

tamoxifen-treated breast cancer patients and modulates hormone receptor status," *Cancer Causes Control* (2013) 24(5):929-940 ("The coffee variable and other potential risk factors were self-reported and may thus constitute an error in measurement."); Oh JK, Sandin S, Ström P, Löf M, Adami HO, Weiderpass E, "Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden," *Int. J. Cancer* (2015) 137(8):1979-1989 ("Misclassification of coffee . . . consumption due to measurement error associated with the FFQ certainly occurred in our study.").

D. Conclusion Regarding Coffee Protecting Against Cancer in Women

The foregoing discussion shows that OEHHA's conclusion that consumption of coffee is protective against cancer in women is unfounded and is based on observational studies that are heavily confounded, that neither control nor adjust for multiple confounders that have been reported to reduce the risk of cancer in women, and that cannot appropriately serve as the basis for causal interpretation.

VII. OEHHA'S CLAIM THAT COFFEE PREVENTS COLORECTAL CANCER RISK

In its overall evaluation, IARC concluded that "[i]nverse associations with drinking coffee have been observed with cancers of the liver and uterine endometrium," but not colorectal cancer. IARC Monograph at p. 425. Indeed, "the Working Group judged the evidence to be inadequate for [colorectal cancer and many other cancers] for reasons including inconsistency of findings across studies, inadequate control for potential confounding, potential for measurement error, selection bias or recall bias, or insufficient number of studies." Loomis D, Guyton KZ, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Mattock H, Straif K, "Carcinogenicity of drinking coffee, mate, and very hot beverages," *Lancet Oncology* (2016) 17:877-878. In its Initial

Statement of Reasons, OEHHA nevertheless asserts that "coffee consumption has consistently been found to be protective for colorectal cancer risk" based on "epidemiological studies published since IARC completed its literature search in 2016." Initial Statement of Reasons at p. 7.

Preliminarily, it is scientifically improper for OEHHA to cherry pick one type of cancer that it believes supports its conclusion that coffee consumption is protective against human cancer and conduct a literature review of studies post-dating IARC's literature review of that one cancer. Indeed, if OEHHA considers the literature regarding coffee and cancer published after IARC completed its literature search in 2016 (as CERT believes it should), OEHHA should consider all of the relevant studies published after the completion of IARC's literature search, especially the studies regarding maternal consumption of coffee and childhood leukemia, which strengthens the positive association for both types of childhood leukemia from maternal consumption of coffee.

Additionally, it is scientifically improper for OEHHA to consider only those studies published during the two-year period since IARC completed its literature search to conclude that coffee consumption is "protective for colorectal cancer risk." To properly render such a scientific conclusion, it is necessary to consider the entire body of scientific literature regarding consumption of coffee and colorectal cancer - not just those studies published during a two-year period. It is precisely such an analysis that Dr. Peter Infante did in preparing his July 2017 report regarding the epidemiological studies relating to the consumption of coffee and human cancers. In that report, Dr. Infante appropriately considers all of the epidemiological studies regarding consumption of coffee and colorectal cancer that had been published by the summer of 2017 and concludes that those studies show "mixed" results, rather than any allegedly cancer-protective effect.

A. Epidemiological Studies Regarding Colorectal Cancer

1. Case-Control Studies

Some case-control studies report increased risks of colorectal cancer in association with coffee consumption.

In a case-control study of colorectal cancer and diet in Singapore, a significantly elevated risk was noted in association with low consumption of coffee (OR 1.59, 95% CI 1.05 - 2.38), but not for high coffee consumption (OR 0.72, 95% CI 0.46 - 1.12). Lee HP, Gourley L, Duffy SW, Estève J, Lee J, Day NE, "Colorectal cancer and diet in an Asian population: a case-control study among Singapore Chinese," *Int. J. Cancer* (1989) 43(6):1007-1016.

In a case-control study of 49 patients with cancers of the large intestine in Denmark, risk was non-significantly increased on logistic regression analysis for consumption of 4 to 7 cups of coffee per day (OR 1.8, 95% CI 0.8 - 3.9), but less so for consumption of more than 8 cups of coffee per day (OR 1.1, 95% CI 0.3 - 3.6) as compared to those who consumed 0-3 cups/day. However, the category of > 8 cups/day included only 6 cases as compared to 30 cases in the 4-7 cup category. Thus, the risk estimate for large intestine cancer in the highest coffee consumption category is more unstable. Olsen J, Kronborg O, "Coffee, tobacco and alcohol as risk factors for cancer and adenoma of the large intestine," *Int. J. Epidemiol.* (1993) 22:398-402.

In a case-control study of 171 colorectal cancer cases and 309 population controls, controlling for age and caloric intake, increased risks of colorectal cancer were observed for consumption of 2 cups of coffee per day (OR 2.4, 95% CI 1.4 - 4.2, $p < 0.01$), 3 cups of coffee per day (OR 1.4, 95% CI 0.8 - 2.5) and 4 cups of coffee per day (OR 1.9, 95% CI 1.1 - 3.4). Boutron-Ruault MC, Senesse P, Faivre J, Chatelain N, Belghiti C, Méance S, "Foods as risk factors for colorectal cancer: a case-control study in Burgundy (France)," *Eur. J. Cancer Prev.* (1999) 8(3):229-235.

In a case-control study in rural China, the risk of colorectal cancer among current drinkers was increased among men (RR 3.80, 95% CI 0.97 - 14.96), but not among women (RR 0.50, 95% 0.14 - 1.81). Zhang B, Li X, Nakama H, Zhang X, Wei N, Zhang X, Zhang L, "A case-control study on risk of changing food consumption for colorectal cancer," *Cancer Invest.* (2002) 20(4):458-463

In a hospital-based case-control study in Taiwan, the risk of colorectal cancer was significantly increased on multiple logistic regression analysis comparing men who drank coffee to nondrinkers. Risks were more than doubled for both colon cancer (OR 2.24, 95% CI 1.19 - 4.21) and for rectal cancer (OR 2.72, 95% CI 1.57 - 4.72). Yeh CC, Hsieh LL, Tang R, Chang-Chieh CR, Sung FC, "Risk factors for colorectal cancer in Taiwan: a hospital-based case-control study," *J. Formos. Med. Assoc.* (2003) 102(5):305-312.

In a case-control study of 250 cases of colorectal cancer, Greek researchers reported a significantly increased greater than 3-fold risk of colorectal cancer in association with coffee consumption in the conditional logistic regression analysis (OR 3.27, 95% CI 1.09 - 9.80). Kontou N, Psaltopoulou T, Soupos N, Polychronopoulos E, Linos A, Xinopoulos D, Panagiotakos DB, "The role of number of meals, coffee intake, salt and type of cookware on colorectal cancer development in the context of the Mediterranean diet," *Public Health Nutr.* (2013) 16(5):928-935.

In a case-control study of 854 cases of colorectal cancer in Western Australia, in the multivariate analysis, risk of colorectal cancer was increased for hot coffee consumption of less than 1 cup per day (OR 1.22, 95% CI 0.85 - 1.75), 1 cup per day (OR 1.36, 95% CI 0.95 - 1.96) and 2 or more cups per day (OR 1.24, 95% CI 0.84 - 1.84); for iced coffee consumption of less than 1 cup per week (OR 1.64, 95% CI 1.20 - 2.24) and 1 or more cups per week (OR 1.19, 95% CI 0.80 - 1.76), p-trend 0.035; and for decaffeinated coffee consumption of less than 1 cup per week (OR 1.28, 95% CI 0.72 - 2.27) and 1 or more cups per week (OR 1.14, 95% CI 0.79 - 1.65). Green CJ, de Dauwe P, Boyle T, Tabatabaei SM, Fritschi L, Heyworth JS, "Tea, Coffee, and milk consumption and colorectal cancer risk," *J. Epidemiol.* (2014) 24(2):146-153.

2. Cohort Studies

Several cohort studies regarding consumption of coffee and colorectal cancer also report increased risks.

In a cohort study of 25,493 white California Seventh-Day Adventists followed for 21 years, the risk of fatal colorectal cancer was increased by 50% for consumption of 1 cup of coffee per day (RR 1.5, 95% CI 0.9 - 2.3) and for 2 or more cups of coffee per day (RR 1.5, 95% CI 1.0 - 2.2), with a significant dose-response trend ($p = 0.02$). Colon cancer during the last 11 years of followup was particularly elevated (male RR = 3.5); female RR = 1.9). Phillips RL, Snowdon DA, "Dietary relationships with fatal colorectal cancer among Seventh-Day Adventists," *J. Natl. Cancer Inst.* (1985) 74(2):307-317.

In a cohort study of 11,888 residents of a retirement community, the risk of colorectal cancer was increased for consumption of 2 to 3 cups of coffee per day among men (RR 1.32, 95% CI 0.7 - 2.5) and women (RR 1.51, 95% CI 0.8 - 2.7), as well as for consumption of 4 or more cups of coffee per day among men (RR 1.54, 95% CI 0.6 - 3.7) and women (RR 1.17, 95% CI 0.4 - 3.1). Wu AH, Paganini-Hill A, Ross RK, Henderson BE, "Alcohol, Physical activity and other risk factors for colorectal cancer: a prospective study," *Br. J. Cancer* (1987) 55:687-694

In a study regarding coffee consumption and colorectal cancer risk in the Swedish Mammography Cohort and the Cohort of Swedish Men, the risk of colorectal cancer was nonsignificantly increased on multivariate analysis in the pooled cohort for coffee consumption of 1 cup per day (RR 1.26, 95% CI 0.99 - 1.60), 2 to 3 cups per day (RR 1.19, 95% CI 0.96 - 1.47), and 4 or more cups per day (RR 1.14, 95% CI 0.90 - 1.44). Larsson SC, Bergkvist L, Giovannucci E, Wolk A, "Coffee consumption and incidence of colorectal cancer in two prospective cohort studies of swedish women and men," *Am. J. Epidemiol.* (2006) 163(7):638-644.

In a prospective cohort study of coffee consumption and colorectal cancer risk, a nonsignificantly increased risk of colorectal cancer was observed in the fully adjusted model for

consumption of 3 or more cups of coffee per day among Japanese men (RR 1.10, 95% CI 0.82 - 1.47), but not among Japanese women (RR 0.68, 95% CI 0.40 - 1.15). Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S; JPHC Study Group, "Coffee consumption and risk of colorectal cancer in a population-based prospective cohort of Japanese men and women," *Int. J. Cancer* (2007) 121(6):1312-1318.

In a study of 60,041 adult Finnish men and women followed up for a mean period of 18 years, the risk of colorectal cancer was about 25% increased between consumption of 2-9 cups/day; >10 cups/day an elevated risk was not apparent, RR 1.03, 95% CI - 0.58 - 1.83. Among never smokers, however, the risk was doubled for those who drank 3 to 4 cups of coffee per day (HR 2.07, 95% CI 1.04 - 4.11) and 5 to 6 cups of coffee per day (HR 2.05, 95% CI 1.03 - 4.06), but the increase was slightly attenuated among never smokers who drank 7 to 9 cups of coffee per day (HR 1.92 (95% CI 0.91 - 4.01) and more than 10 cups of coffee per day (HR 1.55, 95% CI 0.63 - 3.82). Bidel S, Hu G, Jousilahti P, Antikainen R, Pukkala E, Hakulinen T, Tuomilehto J, "Coffee consumption and risk of colorectal cancer," *Eur. J. Clin. Nutr.* (2010) 64(9):917-923.

In a prospective cohort study of 64,603 Swedish residents of the county of Västerbotten turning 40, 50 and 60 years of age, the risk of colorectal cancer was increased in the multivariate analysis among those drinking 1 to 3 cups of coffee per day (RR 1.56, 95% CI 0.96 - 2.54), as well as those drinking 4 or more cups of coffee per day (RR 1.43, 95% CI 0.86 - 2.38). Nilsson LM, Johansson I, Lenner P, Lindahl B, Van Guelpen B, "Consumption of filtered and boiled coffee and the risk of incident cancer: a prospective cohort study," *Cancer Causes Control* (2010) 21(10):1533-1544.

In a prospective evaluation of colorectal cancer risk in the Singapore Chinese Health Study, among never-smoker coffee drinkers the risk of advanced colorectal cancer was nonsignificantly increased after adjustment for age at baseline, gender, dialect group, year of recruitment, level of education, body mass index, alcohol consumption, physical activity, history of diabetes, family history of colorectal cancer, and green tea intake. Peterson S, Yuan JM, Koh WP, Sun CL, Wang

R, Turesky RJ, Yu MC, "Coffee intake and risk of colorectal cancer among Chinese in Singapore: the Singapore Chinese Health Study," *Nutr. Cancer* (2010) 62(1):21-29. Since the study reported the data for colon and rectal cancer separately, the data will be summarized below for these cancers.

Using data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, the National Cancer Institute conducted a prospective study to examine the relationship of coffee and tea intake with colorectal cancer risk in 57,398 men and women aged 55-74. During a median follow-up of 11.4 years, 681 colorectal cancer cases were identified. On multivariate analysis, the researchers found that the risk of colorectal cancer was nonsignificantly increased for coffee consumption of 2 to 3 cups per day (RR 1.03, 95% CI 0.77 - 1.37) and 4 or more cups per day (RR 1.08, 95% CI 0.79 - 1.48). They concluded that "the findings of this study do not provide evidence to suggest that drinking coffee . . . is beneficial in protecting against colorectal cancer." Dominianni C, Huang WY, Berndt S, Hayes RB, Ahn J, "Prospective study of the relationship between coffee and tea with colorectal cancer risk: the PLCO Cancer Screening Trial," *Br. J. Cancer* (2013) 109:1352-1359

In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, the risk of colorectal cancer from coffee consumption was investigated in 477,071 participants, of whom 4,234 developed colorectal cancer after a median follow-up of 11.6 years. Comparing high versus non/low coffee consumption, the risk of colorectal cancer was slightly increased (HR 1.06, 95% CI 0.95 - 1.18), the risk being a bit higher for consumption of caffeinated coffee (HR 1.10, 95% CI 0.97 - 1.26). Dik VK, Bueno-de-Mesquita HB, Van Oijen MG, Siersema PD, Uiterwaal CS, Van Gils CH, Van Duijnhoven FJ, Cauchi S, Yengo L, Froguel P, Overvad K, Bech BH, Tjønneland A, Olsen A, Boutron-Ruault MC, Racine A, Fagherazzi G, Kühn T, Campa D, Boeing H, Aleksandrova K, Trichopoulou A, Peppa E, Oikonomou E, Palli D, Grioni S, Vineis P, Tumino R, Panico S, Peeters PH, Weiderpass E, Engeset D, Braaten T, Dorronsoro M, Chirlaque MD, Sánchez MJ, Barricarte A, Zamora-Ros R, Argüelles M, Jirström K, Wallström P, Nilsson LM, Ljuslinder I, Travis RC, Khaw KT, Wareham N, Freisling H, Licaj I, Jenab M, Gunter MJ, Murphy N, Romaguera-Bosch D, Riboli

E, "Coffee and tea consumption, genotype based CYP1A2 and NAT2 activity, and colorectal cancer risk –results from the EPIC cohort study," *Int. J. Cancer* (2014) 135(2):401-412.

Using data from the Japan Collaborative Cohort Study, Japanese researchers, following 58,221 people from 1988 to the end of 2009, identified 687 cases of colon cancer and 314 cases of rectal cancer. Using the Cox proportional-hazard regression model to estimate hazard ratio, compared to those who consumed less than 1 cup of coffee per day, men who drank 2 to 3 cups of coffee per day had an increased risk of colorectal cancer (HR 1.21, 95% CI 0.95 - 1.54), as did men who drank more than 4 cups of coffee per day (HR 1.57, 95% CI 0.97 - 2.55). The trend was statistically significant (p-trend = 0.03). Women in the highest coffee consumption category (> 4 cups/day) also had the highest risk of colorectal cancer (HR 1.42, 95% CI - 0.57 - 3.50), but the trend was not statistically significant. Yamada H, Kawado M, Aoyama N, Hashimoto S, Suzuki K, Wakai K, Suzuki S, Watanabe Y, Tamakoshi A; JACC Study Group, "Coffee consumption and risk of colorectal cancer: the Japan Collaborative Cohort Study," *J. Epidemiol.* (2014) 24(5):370-378.

An investigation of 1,282 cases of colorectal cancer among postmenopausal US women in the Women's Health Initiative Observational Study revealed an increased incidence of colorectal cancer among moderate and high coffee drinkers compared to nondrinkers on multivariate analysis: (HR 1.15, 95% CI 1.02 - 1.29; HR 1.14, 95% CI 0.93 - 1.38). High risks of colorectal cancer were observed for moderate drip brew coffee intake (HR 1.20, 95% CI 1.05 - 1.36) and high nondrip brew coffee intake (HR 1.43, 95% CI 1.01 - 2.02). The investigators concluded that their "results suggesting increased incidence of colorectal cancer associated with higher coffee consumption contradict recent meta-analyses but agree with a number of other studies showing that coffee increases risk or has no effect." Groessl EJ, Allison MA, Larson JC, Ho SB, Snetslaar LG, Lane DS, Tharp KM, Stefanick ML, "Coffee Consumption and the Incidence of Colorectal Cancer in Women," *J. Cancer Epidemiol.* (2016) 2016:6918431.

The most recent evaluation of data from the EPIC cohort based on 521,330 participants observed a significant positive trend in the risk of colorectal cancer in relation to coffee consumption

(p-trend = 0.01), which was mostly related to women (p-trend = 0.006). Gunter MJ, Murphy N, Cross AJ, Dossus L, Dartois L, Fagherazzi G, Kaaks R, Kühn T, Boeing H, Aleksandrova K, Tjønneland A, Olsen A, Overvad K, Larsen SC, Redondo Cornejo ML, Agudo A, Sánchez Pérez MJ, Altzibar JM, Navarro C, Ardanaz E, Khaw KT, Butterworth A, Bradbury KE, Trichopoulou A, Lagiou P, Trichopoulos D, Palli D, Grioni S, Vineis P, Panico S, Tumino R, Bueno-de-Mesquita B, Siersema P, Leenders M, Beulens JWJ, Uiterwaal CU, Wallström P, Nilsson LM, Landberg R, Weiderpass E, Skeie G, Braaten T, Brennan P, Licaj I, Muller DC, Sinha R, Wareham N, Riboli E, "Coffee Drinking and Mortality in 10 European Countries: A Multinational Cohort Study," *Ann. Intern. Med.* (2017) 167(4):236-247.

3. Meta-Analyses

About a dozen meta-analyses or pooled analyses have been published regarding coffee consumption and the risk of colorectal cancer.

The first meta-analysis of coffee consumption and risk of colorectal cancer was published in 1998 and included 12 case-control studies and 5 cohort studies. Using a semi-quantitative approach, the author assessed the risk of colorectal cancer comparing high versus low consumption. The combined results from the 12 case-control studies showed an inverse association for high versus low consumption (RR 0.72, 95% CI 0.61 - 0.84). However, the five cohort studies did not support an association (RR 0.97, 95% CI 0.73 - 1.29). Giovanucci E, "Meta-analysis of coffee consumption and risk of colorectal cancer," *Am. J. Epidemiol.* (1998) 147(11):1043-1052.

In a meta-analysis of prospective cohort studies, researchers from Harvard reported a non-significantly decreased risk of colorectal cancer from consumption of coffee (RR 0.91, 95% CI 0.81 - 1.02). Je Y, Liu W, Giovannucci E, "Coffee Consumption and risk of colorectal cancer: a systematic review and meta-analysis of prospective cohort studies," *Int. J. Cancer* (2009) 124(7):1662-1668.

In a meta-analysis of case-control studies of coffee consumption and colorectal cancer, Italian investigators reported a decreased risk of colorectal cancer comparing coffee drinkers to non/occasional drinkers (OR 0.83, 95% CI 0.73 - 0.95), with a lower risk for the highest coffee drinkers (OR 0.70, 95% CI 0.60 - 0.81). Galeone C, Turati F, La Vecchia C, Tavani A, "Coffee consumption and risk of colorectal cancer: a meta-analysis of case-control studies," *Cancer Causes Control* (2010) 21(11):1949-1959.

In a meta-analysis of prospective cohort studies, coffee consumption was inversely related with colorectal cancer (RR 0.89, 95% CI 0.80 - 0.97). Yu X, Bao Z, Zou J, Dong J, "Coffee consumption and risk of cancers: a meta-analysis of cohort studies," *BMC Cancer* (2011) 11:96.

In a meta-analysis of 21 case-control studies and 16 cohort studies of coffee consumption and colorectal cancer risk, comparing the highest versus lowest levels of coffee consumption, the risk of colorectal cancer was significantly reduced on meta-analysis of the case-control studies (OR 0.85, 95% CI 0.75 - 0.97) but not the cohort studies (RR 0.94, 95% CI 0.88 - 1.01). Li G, Ma D, Zhang Y, Zheng W, Wang P, "Coffee consumption and risk of colorectal cancer: a meta-analysis of observational studies," *Publ. Health Nutr.* (2013) 14:1-12.

In a meta-analysis of observational studies of coffee consumption and colorectal cancer, the risk of colorectal cancer was significantly decreased in both case-control and cohort studies for high coffee consumption. Tian C, Wang W, Hong Z, Zhang X, "Coffee consumption and risk of colorectal cancer: a dose-response analysis of observational studies," *Cancer Causes Control* (2013) 24(6):1265-1268.

In a meta-analysis of cohort studies by Chinese researchers, the risk of colorectal cancer from consumption of coffee was slightly decreased (OR 0.98, 95% CI 0.90 - 1.06). Gan Y, Wu J, Zhang S, Li L, Cao S, Mkandawire N, Ji K, Herath C, Gao C, Xu H, Zhou Y, Song X, Chen S, Chen Y, Yang T, Li J, Qiao Y, Hu S, Yin X, Lu Z, "Association of coffee consumption with risk of colorectal cancer: a meta-analysis of prospective cohort studies," *Oncotarget* (2017) 8(12):18699-18711.

In a meta-analysis of 21 cohort studies, risk of colorectal cancer from consumption of coffee was nonsignificantly reduced (RR 0.96, 95% CI 0.91 - 1.02). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and cancer risk: a meta-analysis of prospective observational studies," *Sci. Rep.* (2016) 6:33711.

In a meta-analysis of 5 cohort and 9 case-control studies regarding consumption of coffee and risk of colorectal cancer in the Japanese population, investigators from the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan concluded that high consumption of coffee was not appreciably associated with colorectal cancer risk in cohort studies (RR 0.95, 95% CI 0.77 - 1.17), but was associated with reduced risk in case control studies (RR 0.78, 95% CI 0.65 - 0.95). The investigators concluded that "[t]he evidence is insufficient to support that coffee drinking increases or decreases the risk of colorectal cancer among the Japanese population." Akter S, Kashino I, Mizoue T, Matsuo K, Ito H, Wakai K, Nagata C, Nakayama T, Sadakane A, Tanaka K, Tamakoshi A, Sugawara Y, Sawada N, Inoue M, Tsugane S, Sasazuki S; ; for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan, "Coffee drinking and colorectal cancer risk: an evaluation based on a systematic review and meta-analysis among the Japanese population," *Jpn. J. Clin. Oncol.* (2016) 46(8):781-787.

A pooled analysis using data from two case-control studies in Japan (HERPACC-1 AND -2), identified 2,696 cases of colorectal cancer. Overall compared to non-drinkers, an inverse trend ($p = 0.009$) was identified for consumers of < 1 to ≥ 3 cups/day. The authors concluded "given the limited evidence for an association between coffee consumption and a substantial impact on colorectal cancer prevention and the inherent limitations of our study, verification of these findings awaits further studies, especially prospective cohort studies." Nakagawa-Senda H, Ito H, Hosono S, Oze I, Tanaka H, Matsuo K, "Coffee consumption and the risk of colorectal cancer by anatomical subsite in Japan: Results from the HERPACC studies," *Int. J Cancer* (2017) 141(2):298-308.

A recent meta-analysis of 111 cohort studies evaluating associations between foods and beverages and colorectal cancer reported inverse associations for consumption of whole grains, dairy

products, vegetables, and fish, but observed no association for coffee. Vieira AR, Abar L, Chan DSM, Vingeliene S, Polemiti E, Stevens C, Greenwood D, Norat T, "Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project," *Ann. Oncol.* (2017) 28(8):1788-1802.

A recent pooled analysis of 476,160 adults from 10 European countries evaluated the association between dietary polyphenol intake and colorectal cancer risk. During a mean follow-up of 14 years, there were 5,991 incident colorectal cancer cases, of which 3897 were in the colon and 2094 were in the rectum. In multivariable-adjusted Cox regression models, a doubling in total dietary polyphenol intake was associated with an increase of colorectal cancer risk in women (HR 1.06, 95% CI 0.99 - 1.14), but not in men (HR 0.97, 95% CI 0.90 - 1.05). Phenolic acid intake, which is highly correlated with coffee consumption, was positively associated with rectal cancer in women (HR 1.10, 95% CI 1.02 - 1.10), but inversely associated with colon cancer in men (HR 0.91, 95% CI 0.85 - 0.97). Zamora-Ros R, Cayssials V, Jenab M, Rothwell JA, Fedirko V, Aleksndrova K, Tjønneland A, Kyrø C, Overvad K, Boutron-Urault MC, Carbonnel F, Mahamat-Saleh Y, Kaaks R, Kühn T, Boeing H, Trichopoulou A, Valanou E, Vasilopoulou E, Masala G, Pala V, Panico S, Tumino R, Ricceri F, Weiderpass E, Lukic M, Sandanger TM, Lasheras C, Agudo A, Sánchez MJ, Aminao P, Navarro C, Ardanaz E, Sonestedt E, Ohlsson B, Nilsson LM, Rutegärd M, Bueno-de-Mesquita B, Peeters PH, Khaw KT, Wareham NJ, Bradbuy K, Freisling H, Romieu I, Cross AJ, Vineis P, Scalbert A, "Dietary intake of total polyphenol and polyphonol classes and the risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort," *Eur. J. Epidemiol.* (2018) doi: 10.1007/s10654-018-0408-6. [Epub ahead of print].

Recently, Japanese investigators published a two-stage random-effects dose-response meta-analysis of the association between different levels of coffee consumption and colorectal cancer among the Japanese population. The study was performed by modeling coffee consumption using restricted cubic splines to be able to examine a potential nonlinear relationship. Data from 14 cohort studies showed that the pooled relative risks for colorectal cancers were less than 1.0 for

consumption of 3 or less cups of coffee per day, but increased monotonically but not significantly for consumption of 4 or more cups of coffee per day: 4 cups per day (RR 1.04, 95% CI 0.89 - 1.22), 5 cups per day (RR 1.13, 95 CI 0.87 - 1.46), 6 cups per day (RR 1.22, 95% CI 0.84 - 1.78). Horisaki K, Takahashi K, Ito H, Matsui S, "A Dose-Response Meta-analysis of Coffee Consumption and Colorectal Cancer Risk in the Japanese Population: Application of a Cubic-Spline Model," *J. Epidemiol.* 2018 Jun 2. doi: 10.2188/jea.JE20170201. [Epub ahead of print]

B. Epidemiological Studies Regarding Colon Cancer

1. Case-Control Studies

In an early case-control study of 256 white men with colon cancer and 330 white men with rectal cancer, "a significant but small excess was noted for frequent drinking of coffee for cancer of the colon but not rectum." Graham S, Dayal H, Swanson M, Mittelman A, Wilkinson G. "Diet in the epidemiology of cancer of the colon and rectum," *J. Natl. Cancer Inst.* (1978) 61(3):709-714.

In a case-control study of 88 Yugoslavian patients with histologically confirmed colon cancer, compared to hospital controls, the risk of colon cancer was increased 2.5 times among patients who drank coffee (OR 2.50, 95% CI 1.0 - 6.23, $p < 0.05$) and was increased three-fold among those patients who drank coffee for 20 or more years (OR 3.00, 95% CI 1.33 - 6.77, $p < 0.01$). Vlajinac H, Jarebinski M, Adanja B, "Relationship of some biosocial factors to colon cancer in Belgrade (Yugoslavia), "*Neoplasma* (1987)34(4):503-507.

In a population-based case-control study of risk factors for colon cancer among 112 male cases and 119 female cases of histologically confirmed, first primary colon cancers in Utah white males and females age 40 to 79 years, the risk of colon cancer was increased among men consuming 1to 480 grams/day of coffee (OR 1.7, 95% CI 0.9 - 3.0) and more than 480 grams/day of coffee (approximately 2-3 cups per day) (OR 2.2, 95% CI 1.2 - 4.0), with a dose-response trend ($p = 0.006$).

Slattery ML, West DW. Robison LM, French TK, Ford MH, Schuman KL, Sorenson AW, "Tobacco, alcohol, coffee, and caffeine as risk factors for colon cancer in a low-risk population," *Epidemiology* (1990) 1(2):141-145.

In a case-control study of 238 men and 186 women diagnosed with colon cancer in the Seattle area, the risk of colon cancer adjusted for age and total energy was increased among men drinking up to one cup of coffee per day (OR 1.39, 95% CI 0.78 - 2.45) and drinking more than one cup of coffee per day (OR 1.21, 95% CI 0.70-2.08). Shannon J, White E, Shattuck AL, Potter JD, "Relationship of food groups and water intake to colon cancer risk," *Cancer Epidemiol. Biomarkers Prev.* (1996) 5(7):495-502.

In 2000, American researchers published a study in which they sought to determine whether cruciferous vegetables and coffee, two dietary inducers of glutathione-S transferases, interact with *GSTM-1* genotype to alter the risk of colon cancer. Data were available on 1,579 incident cases of adenocarcinoma of the colon and 1,898 population-based controls. Among nonsmokers with the *GSTM-1* genotype, after adjustment for age, sex, BMI, long-term vigorous physical activity, and total energy intake, the risk of colon cancer was significantly increased for consumption of 6 or more cups of coffee per day (OR 1.78, 95% CI 1.02 - 3.08), but was not significantly increased for 4 or more servings per week of cruciferous vegetables (OR 1.19, 95% CI 0.71 - 1.98) and brocoli (OR 1.48, 95% CI 0.85 - 2.58). Slattery ML, Kampman E, Samowitz W, Caan BJ, Potter JD, "Interplay between dietary inducers of GST and the GSTM-1 genotype in colon cancer," *Int. J. Cancer* (2000) 87(5):728-733.

In a case-control study of 352 Taiwanese patients with histologically confirmed colon cancer, risk of colon cancer was significantly increased among men in the multiple logistic regression analysis (OR 2.24, 95% CI 1.19 - 4.21). Yeh CC, Hsieh LL, Tang R, Chang-Chieh CR, Sung FC, "Risk factors for colorectal cancer in Taiwan: a hospital-based case-control study," *J. Formos. Med. Assoc.* (2003) 102(5):305-312.

2. Cohort Studies

In a cohort study of 23,912 white Seventh Day Adventists, the risk of fatal colon cancer was increased among those drinking 1 cup of coffee per day (RR 1.2, 95% CI 0.7 - 2.2) and 2 or more cups of coffee per day (RR 1.7, 95% CI 1.1 - 2.5), with a dose-response trend ($p = 0.02$). Snowdon DA, Phillips RL, "Coffee consumption and risk of fatal cancers," *Am. J. Public Health* (1984) 74(8):820-823.

In a cohort study of 25,493 Seventh Day Adventists, the risk of colon cancer was increased for consumption of 2 or more cups of coffee per day among men (RR 2.0, 95% CI 1.1 - 3.6) and women (RR 1.5, 95% CI 0.8 - 2.6), with a dose-response trend in men ($p = 0.04$). Phillips RL, Snowdon DA, "Dietary relationships with fatal colorectal cancer among Seventh-Day Adventists," *J. Natl. Cancer Inst.* (1985) 74(2):307-317.

In a Norwegian cohort study of 21,735 men and 21,238 women aged 35-54 years, the risk of colon cancer was increased 40% among men who drank 3-4 cups of coffee per day and 50% among men who drank 5-6 cups of coffee per day, but only 20% among those who drank 7 or more cups of coffee per day, in the analysis with age, cigarettes smoked per day and county of residence as covariates. Stensvold I, Jacobsen BK, "Coffee and cancer: a prospective study of 43,000 Norwegian men and women," *Cancer Causes Control* (1994) 5:401-408. In a cohort study of 61,463 Swedish women aged 40-74, the risk of colon cancer was slightly increased in the multivariate analysis among those women who drank 4 or more cups of coffee per day (RR 1.06, 95% 0.65 - 1.72), with the risk being higher for cancer of the proximal colon (RR 1.17, 95% CI 0.56 - 2.43). Terry P, Bergkvist L, Holmberg L, Wolk A, "Coffee consumption and risk of colorectal cancer in a population based prospective cohort of Swedish women," *Gut* (2001) 49(1):87-90.

In a prospective evaluation of colorectal cancer risk in the Singapore Chinese Health Study, among never-smokers the risk of advanced colon cancer was increased among coffee drinkers after adjustment for age at baseline, gender, dialect group, year of recruitment, level of education, body

mass index, alcohol consumption, physical activity, history of diabetes, family history of colorectal cancer, and green tea intake: 1 cup of coffee per day (HR 1.34, 95% CI CI 0.96 - 1.86), 2+ cups of coffee per day (HR 1.17, 95% CI 0.81 - 1.70). Peterson S, Yuan JM, Koh WP, Sun CL, Wang R, Turesky RJ, Yu MC, "Coffee intake and risk of colorectal cancer among Chinese in Singapore: the Singapore Chinese Health Study," *Nutr. Cancer* (2010) 62(1):21-29. Since the study reported the data for colon and rectal cancer separately, the data will be summarized below for these cancers.

Using data from the Japan Collaborative Cohort Study, Japanese researchers, following 58,221 people from 1988 to the end of 2009, identified 687 cases of colon cancer and 314 cases of rectal cancer. Using the Cox proportional-hazard regression model to estimate hazard ratio, compared to those who consumed less than 1 cup of coffee per day, men who drank 2 to 3 cups of coffee per day had an increased risk of colon cancer (HR 1.26, 95% CI 0.93 - 1.70), as did men who drank more than 4 cups of coffee per day (HR 1.79, 95% CI 1.01 - 3.18), p-trend = 0.03. Women did not show a significant trend for colon cancer risk with an increase in coffee consumption though the high coffee consumption category indicated a HR 2.02, 95% CI 0.81-5.03. When stratified by smoking status, the risk of colon cancer increased monotonically among male never smokers who drank 1 cup of coffee per day (HR 1.18), 2 to 3 cups of coffee per day (HR 1.85), and 4 or more cups of coffee per day (HR 5.58, $p = 0.02$), with a significant dose-response trend ($p = 0.01$). When stratified by smoking status, the risk of colon cancer also increased monotonically among female never smokers who drank 1 cup of coffee per day (HR 1.03), 2 to 3 cups of coffee per day (HR 1.46), and 4 or more cups of coffee per day (HR 1.69) although the trend was not statistically significant. Among current smokers, the trend for increasing risk of colon cancer with increased coffee consumption was monotonic for both men and women with the trend being statistically significant for women, but not for men. Yamada H, Kawado M, Aoyama N, Hashimoto S, Suzuki K, Wakai K, Suzuki S, Watanabe Y, Tamakoshi A; JACC Study Group, "Coffee consumption and risk of colorectal cancer: the Japan Collaborative Cohort Study," *J. Epidemiol.* (2014) 24(5):370-378.

In the Women's Health Initiative Observational Study, 83,778 women were followed for almost 13 years, and 1,282 cases of colorectal cancer were diagnosed. In the multivariate adjusted analysis, compared to nondrinkers, women who drank up to 4 cups of coffee per day had an increased risk of colon cancer (HR 1.11, 95% CI 0.98 - 1.27), as did women who drank more than 4 cups of coffee per day (HR 1.17, 95% CI 0.94 - 1.44), p-trend = 0.07. Groessl EJ, Allison MA, Larson JC, Ho SB, Snetslaar LG, Lane DS, Tharp KM, Stefanick ML, "Coffee Consumption and the Incidence of Colorectal Cancer in Women," *J. Cancer Epidemiol.* (2016) 2016:6918431.

3. Meta-Analyses

In a pooled analysis of 2,180 cases of histologically confirmed colon cancer from two hospital-based case-control studies in six Italian centers, consumption of more than 2 cups of coffee per day significantly increased the risk of colon cancer, the risk increasing with years of education: 7 to9 years of education (OR 1.40, 95% CI 1.13 - 1.74), 10 to 15 years of education (OR 1.68, 95% CI 1.34 - 2.12), 16 or more years of eduction (OR 2.01, 95% CI 1.41 - 2.88). Within each tertile of years of education, a dose response relationship was observed for consumption of coffee and the risk of colon cancer. Tavani A, Fioretti F, Franceschi S, Gallus S, Negri E, Montella M, Conti E, La Vecchia C, "Education, socioeconomic status and risk of cancer of the colon and rectum," *Int. J. Epidemiol.* (1999) 28(3):380-385.

In a pooled analysis of primary data from 13 cohort studies, compared with nonconsumers, the pooled multivariable relative risks for colon cancer were increased for coffee consumption greater than 1400 grams/day (about six 8-ounce cups) (RR 1.07, 95% CI 0.89 - 1.30), with the risk being higher in men (RR 1.24, 95% CI 0.87 - 1.77). Zhang X, Albanes D, Beeson WL, van den Brandt PA, Buring JE, Flood A, Freudenheim JL, Giovannucci EL, Goldbohm RA, Jaceldo-Siegl K, Jacobs EJ, Krogh V, Larsson SC, Marshall JR, McCullough ML, Miller AB, Robien K, Rohan TE, Schatzkin A, Sieri S, Spiegelman D, Virtamo J, Wolk A, Willett WC, Zhang SM, Smith-Warner

SA, "Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies," *J. Natl. Cancer Inst.* (2010) 102(11):771-783.

A recent meta-analysis using data from two case-control studies in Japan (HERPACC-1 and -2), compared non-drinkers to those who drank < 1, 1-2 and ≥ 3 cups/day. For colon cancer in general, the dose-response was flat (low dose to high dose ORs ranging between 0.85 and 0.84, p-trend = 0.14). For the subsite of "distal" colon cancer, those who drank > 3 cups/day (OR 0.77; 95% CI 0.55 - 1.07). Although the results were not statistically significant, the p-trend for an inverse relation was borderline statistically significant, p = 0.05. The authors concluded that inherent limitations of the study warranted verification using prospective cohort studies. Nakagawa-Senda H, Ito H, Hosono S, Oze I, Tanaka H, Matsuo K, "Coffee consumption and the risk of colorectal cancer by anatomical subsite in Japan: Results from the HERPACC studies," *Int. J Cancer* (2017) 141(2):298-308.

B. Epidemiological Studies Regarding Rectal Cancer

1. Case-Control Studies

In a hospital-based case-control study of 538 cases of rectal cancer in major cities in the Northeast United States, the risk of rectal cancer was increased for consumption of 5 or more cups of coffee of per day within the past year (OR 1.8, 95% CI 1.0 - 3.2) and less so within the past 3 years (OR 1.2, 95% CI 0.7 - 1.9). Rosenberg L, Werler MM, Palmer JR, Kaufman DW, Warshauer ME, Stolley PD, Shapiro S. "The risks of cancers of the colon and rectum in relation to coffee consumption," *Am. J. Epidemiol.* (1989) 130(5):895-903.

In a case-control study of 375 patients with histologically confirmed rectal cancer, risk of rectal cancer was increased among male coffee drinkers on multiple logistic regression analysis (OR 2.72, 95% CI 1.57 - 4.72). Yeh CC, Hsieh LL, Tang R, Chang-Chieh CR, Sung FC, "Risk factors

for colorectal cancer in Taiwan: a hospital-based case-control study," *J. Formos. Med. Assoc.* (2003) 102(5):305-312.

In a case-control study of colorectal cancer in Western Australia, after adjustment for age group, sex, energy intake from food, alcohol intake, smoking status, use of multivitamins, diabetes, physical activity during the age period 19-34 years, body mass index at age 40 years, socioeconomic status, and country of birth, consumption of 1 or more cups of iced coffee per week was associated with an increased risk of rectal cancer (OR 1.52, 95% CI 0.91 - 2.54, *p*-trend = 0.004). Green CJ, de Dauwe P, Boyle T, Tabatabaei SM, Fritschi L, Heyworth JS, "Tea, coffee, and milk consumption and colorectal cancer risk," *J. Epidemiol.* (2014) 24(2):146-153.

2. Cohort Studies

In a cohort study of 61,463 Swedish women aged 40-74, the risk of rectal cancer was nonsignificantly increased slightly on multivariate analysis among women who drank 4 or more cups of coffee per day (RR 1.06, 95% CI 0.54 - 2.10). Terry P, Bergkvist L, Holmberg L, Wolk A, "Coffee consumption and risk of colorectal cancer in a population based prospective cohort of Swedish women," *Gut* (2001) 49(1):87-90.

In a study of data from two cohort studies - the Nurses' Health Study (women) and the Health Professionals' Follow-up Study (men) – the risk of rectal cancer was increased for participants who drank 4 to 5 cups of coffee per day (HR 1.55, 95% CI 0.97 - 2.45), with the risk being higher in women (HR 1.80, 95% CI 0.94 - 3.44) than men (HR 1.33, 95% CI 0.69 - 2.56). Michels KB, Willett WC, Fuchs CS, Giovannucci E, "Coffee, tea, and caffeine consumption and incidence of colon and rectal cancer.," *J. Natl. Cancer Inst.* (2005) 97(4):282-292.

In the Netherlands Cohort Study, involving 120, 852 participants followed for 13.3 years, the risk of rectal cancer in men increased monotonically on multivariate analysis for consumption of between 2 and 4 cups of coffee per day (HR 1.32, 95% CI 0.87 - 1.99), between 4 and 6 cups of

coffee per day (HR 1.50, 95% CI).97 - 2.31), and more than 6 cups of coffee per day (HR 1.60, 95% CI 0.96 - 2.66), p-trend 0.05. In women the risk of rectal cancer was highest for the greatest consumption of coffee (> 6 cups/day, HR 1.41, 95% CI 0.75 - 2.63) although the trend was not statistically significant. Simons CC, Leurs LJ, Weijenberg MP, Schouten LJ, Goldbohm RA, van den Brandt PA, "Fluid intake and colorectal cancer risk in the netherlands cohort study," *Nutr. Cancer* (2010) 62(3):307-321.

In a prospective evaluation of colorectal cancer risk in the Singapore Chinese Health Study, among never-smokers the risk of advanced rectal cancer was increased among coffee drinkers after adjustment for age at baseline, gender, dialect group, year of recruitment, level of education, body mass index, alcohol consumption, physical activity, history of diabetes, family history of colorectal cancer, and green tea intake: 1 cup of coffee per day (HR 1.14, 95% CI CI 0.72 - 1.82), 2+ cups of coffee per day (HR 1.32, 95% CI 0.81 - 2.14). Peterson S, Yuan JM, Koh WP, Sun CL, Wang R, Turesky RJ, Yu MC, "Coffee intake and risk of colorectal cancer among Chinese in Singapore: the Singapore Chinese Health Study," *Nutr. Cancer* (2010) 62(1):21-29. Since the study reported the data for colon and rectal cancer separately, the data will be summarized below for these cancers.

In the European Investigation into Cancer and Nutrition (EPIC) cohort study, involving 477,071 participants, risk of rectal cancer was significantly increased for high (625 ml) consumption of coffee per day (HR 1.20, 95% CI 1.00 - 1.44), with the increased risk being concentrated in women (HR 1.31, 95% CI 1.02 - 1.68). Dik VK, Bueno-de-Mesquita HB, Van Oijen MG, Siersema PD, Uiterwaal CS, Van Gils CH, Van Duijnhoven FJ, Cauchi S, Yengo L, Froguel P, Overvad K, Bech BH, Tjønneland A, Olsen A, Boutron-Ruault MC, Racine A, Fagherazzi G, Kühn T, Campa D, Boeing H, Aleksandrova K, Trichopoulou A, Peppa E, Oikonomou E, Palli D, Grioni S, Vineis P, Tumino R, Panico S, Peeters PH, Weiderpass E, Engeset D, Braaten T, Dorronsoro M, Chirlaque MD, Sánchez MJ, Barricarte A, Zamora-Ros R, Argüelles M, Jirström K, Wallström P, Nilsson LM, Ljuslinder I, Travis RC, Khaw KT, Wareham N, Freisling H, Licaj I, Jenab M, Gunter MJ, Murphy N, Romaguera-Bosch D, Riboli E, "Coffee and tea consumption, genotype based CYP1A2 and

NAT2 activity, and colorectal cancer risk – results from the EPIC cohort study," *Int. J. Cancer* (2014) 135(2):401-412.

In a recent study evaluating the association between dietary intake of polyphenols and colorectal cancer risk in the European Prospective investigation into Cancer and Nutrition (EPIC) cohort, phenolic acid intake, which was highly correlated with coffee consumption, was positively associated with rectal cancer in women (HR 1.10, 95% CI 1.02 - 1.19). Zamora-Ros R, Cayssials V, Jenab M, Rothwell JA, Fedirko V, Aleksandrova K, Tjønneland A, Kyrø C, Overvad K, Boutron-Ruault MC, Carbonnel F, Mahamat-Saleh Y, Kaaks R, Kühn T, Boeing H, Trichopoulou A, Valanou E, Vasilopoulou E, Masala G, Pala V, Panico S, Tumino R, Ricceri F, Weiderpass E, Lukic M, Sandanger TM, Lasheras C, Agudo A, Sánchez MJ, Amiano P, Navarro C, Ardanaz E, Sonestedt E, Ohlsson B, Nilsson LM, Rutegård M, Bueno-de-Mesquita B, Peeters PH, Khaw KT, Wareham NJ, Bradbury K, Freisling H, Romieu I, Cross AJ, Vineis P, Scalbert A, "Dietary intake of total polyphenol and polyphenol classes and the risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort," *Eur. J. Epidemiol.* (May 15, 2018) doi: 10.1007/s10654-018-0408-6. [Epub ahead of print].

D. Confounding

The inverse relationship between coffee consumption and colorectal cancer that has been reported in some studies may be due to confounding by factors that have been shown in meta-analyses to significantly reduce the risk of colorectal cancer and by other as yet unknown factors.

1. Dietary Factors

The association between coffee consumption and colorectal cancer may be confounded by several dietary factors that have been reported to reduce the risk of colorectal cancer in meta-

analyses, including the Mediterranean diet (Schwingshackl L, Schwedhelm C, Galbete C, Hoffmann G, "Adherence to Mediterranean Diet and Risk of Cancer: An Updated Systematic Review and Meta-Analysis," *Nutrients* (2017) 9(10). pii: E1063); cruciferous vegetables (Wu QJ, Yang Y, Vogtmann E, Wang J, Han LH, Li HL, Xiang YB, "Cruciferous vegetables intake and the risk of colorectal cancer: a meta-analysis of observational studies," *Ann. Oncol.* (2013) 24(4):1079-1087; Tse G, Eslick GD, "Cruciferous vegetables and risk of colorectal neoplasms: a systematic review and meta-analysis," *Nutr. Cancer* (2014) 66(1):128-139); dietary fibre (Aune D, Chan DS, Lau R, Vieira R, Greenwood DC, Kampman E, Norat T, "Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies," *Br. Med. J.* (2011) 343:d6617; Ben Q, Sun Y, Chai R, Qian A, Xu B, Yuan Y, "Dietary fiber intake reduces risk for colorectal adenoma: a meta-analysis," *Gastroenterology* (2014) 146(3):689-699); dairy products (Huncharek M, Muscat J, Kupelnick. "Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies," *Nutr. Cancer* (2009) 61(1):47-69; Ralston RA, Truby H, Palermo CE, Walker KZ, "Colorectal cancer and nonfermented milk, solid cheese, and fermented milk consumption: a systematic review and meta-analysis of prospective studies," *Crit. Rev. Food Sci. Nutr.* (2014) 54(9):1167-1179; Aune D, Lau R, Chan DS, Vieira R, Greenwood DC, Kampman E, Norat T, "Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies," *Ann. Oncol.* (2012) 23(1):37-45); fish (Wu S, Feng B, Li K, Zhu X, Liang S, Liu X, Han S, Wang B, Wu K, Miao D, Liang J, Fan D, "Fish consumption and colorectal cancer risk in humans: a systematic review and meta-analysis," *Am. J. Med.* (2012) 125(6):551-559); garlic (Hu JY, Hu YW, Zhou JJ, Zhang MW, Li D, Zheng S, "Consumption of garlic and risk of colorectal cancer: an updated meta-analysis of prospective studies," *World J. Gastroenterol.* (2014) 20(41):15413-15422; Chiavarini M, Minelli L, Fabiani R, "Garlic consumption and colorectal cancer risk in man: a systematic review and meta-analysis," *Public Health Nutr.* (2016) 19(2):308-317); nuts (Wu L, Wang Z, Zhu J, Murad AL, Prokop LJ, Murad MH, "Nut consumption and risk of cancer and type 2 diabetes: a systematic review and meta-

analysis," *Nutr. Rev.* (2015) 73(7):409-425; omega-3 polyunsaturated fatty acids (Li D, "Omega-3 polyunsaturated fatty acids and non-communicable diseases: meta-analysis based systematic review," *Asia Pac. J. Clin Nutr.* (2015) 24(1):10-15); soy and isoflavones (Tse G, Eslick GD, "Soy and isoflavone consumption and risk of gastrointestinal cancer: a systematic review and meta-analysis," *Eur. J. Nutr.* (2016) 55(1):63-73; Yu Y, Jing X, Li H, Zhao X, Wang D, "Soy isoflavone consumption and colorectal cancer risk: a systematic review and meta-analysis," *Sci. Rep.* (2016) 6:25939).

2. Physical Activity

The association between coffee consumption and colorectal cancer may also be confounded by physical activity, which has been reported to reduce the risk of colorectal cancer in several meta-analyses. Johnson CM, Wei C, Ensor JE, Smolenski DJ, Amos CI, Levin B, Berry DA, "Meta-analyses of colorectal cancer risk factors," *Cancer Causes Control* (2013) 24(6):1207-1222; Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA, "Association between physical activity and mortality in colorectal cancer: a meta-analysis of prospective cohort studies," *Int. J. Cancer* (2013) 133(8):1905-1913; Robsahm TE, Aagnes B, Hjartåker A, Langseth H, Bray FI, Larsen IK, "Body mass index, physical activity, and colorectal cancer by anatomical subsites: a systematic review and meta-analysis of cohort studies," *Eur. J. Cancer Prev.* (2013) 22(6):492-505; Liu L, Shi Y, Li T, Qin Q, Yin J, Pang S, Nie S, Wei S, "Leisure time physical activity and cancer risk: evaluation of the WHO's recommendation based on 126 high-quality epidemiological studies," *Br. J. Sports Med.* (2016) 50(6):372-378; Mahmood S, MacInnis RJ, English DR, Karahalios A, Lynch BM, "Domain-specific physical activity and sedentary behaviour in relation to colon and rectal cancer risk: a systematic review and meta-analysis," *Int. J. Epidemiol.* (2017) 46(6):1797-1813; Shaw E, Farris MS, Stone CR, Derksen JWG, Johnson R, Hilsden RJ, Friedenreich CM, Brenner DR, "Effects of physical

activity on colorectal cancer risk among family history and body mass index subgroups: a systematic review and meta-analysis," *BMC Cancer* (2018) 18(1):71.

3. Vitamins

The association between coffee consumption and colorectal cancer may also be confounded by consumption of various vitamins, which have been reported to reduce the risk of colorectal cancer in several meta-analyses: Vitamin B2 (Liu Y, Yu Q, Zhu Z, Zhang J, Chen M, Tang P, Li K, "Vitamin and multiple-vitamin supplement intake and incidence of colorectal cancer: a meta-analysis of cohort studies," *Med Oncol.* (2015) 32(1):434; Liu Y, Yu QY, Zhu ZL, Tang PY, Li K, "Vitamin B2 intake and the risk of colorectal cancer: a meta-analysis of observational studies," *Asian Pac. J. Cancer Prev.* (2015) 16(3):909-913); Vitamin B6 (Larsson SC, Orsini N, Wolk A, "Vitamin B6 and risk of colorectal cancer: a meta-analysis of prospective studies," *J. Am. Med. Assn.* (2010) 303(11):1077-10783; Liu Y, Yu Q, Zhu Z, Zhang J, Chen M, Tang P, Li K, "Vitamin and multiple-vitamin supplement intake and incidence of colorectal cancer: a meta-analysis of cohort studies," *Med Oncol.* (2015) 32(1):434; Jia K, Wang R, Tian J, "Vitamin B_6 Intake and the Risk of Colorectal Cancer: A Meta-Analysis of Prospective Cohort Studies," *Nutr. Cancer* (2017) 69(5):723-731); Vitamin B9 - folate (Kennedy DA, Stern SJ, Moretti M, Matok I, Sarkar M, Nickel C, Koren G, "Folate intake and the risk of colorectal cancer: a systematic review and meta-analysis," *Cancer Epidemiol.* (2011) 35(1):2-10; Liu Y, Yu Q, Zhu Z, Zhang J, Chen M, Tang P, Li K, "Vitamin and multiple-vitamin supplement intake and incidence of colorectal cancer: a meta-analysis of cohort studies," *Med Oncol.* (2015) 32(1):434); Vitamin B12 (Sun NH, Huang XZ, Wang SB, Li Y, Wang LY, Wang HC, Zhang CW, Zhang C, Liu HP, Wang ZN, "A dose-response meta-analysis reveals an association between vitamin B12 and colorectal cancer risk," *Public Health Nutr.* (2016) 19(8):1446-1456) Vitamin C (Xu X, Yu E, Liu L, Zhang W, Wei X, Gao X, Song N, Fu C, "Dietary intake of vitamins A, C, and E and the risk of colorectal adenoma: a meta-analysis of observational

studies," *Eur. J. Cancer Prev.* (2013) 22(6):529-539; Vitamin D (Touvier M, Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, Riboli E, Hercberg S, Norat T, "Meta-analyses of vitamin D intake, 25-hydroxyvitamin D status, vitamin D receptor polymorphisms, and colorectal cancer risk," *Cancer Epidemiol. Biomarkers Prev.* (2011) 20(5):1003-1016; Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H, "Meta-analysis: Serum vitamin D and colorectal adenoma risk," *Prev. Med.* (2011) 53(1-2):10-16; Ma Y, Zhang P, Wang F, Yang J, Liu Z, Qin H, "Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies," *J. Clin. Oncol.* (2011) 29(28):3775-3782; Liu Y, Yu Q, Zhu Z, Zhang J, Chen M, Tang P, Li K, "Vitamin and multiple-vitamin supplement intake and incidence of colorectal cancer: a meta-analysis of cohort studies," *Med Oncol.* (2015) 32(1):434; Choi YJ, Kim YH, Cho CH, Kim SH, Lee JE, "Circulating levels of vitamin D and colorectal adenoma: A case-control study and a meta-analysis," *World J. Gastroenterol.* (2015) 21(29):8868-8877; Garland CF, Gorham ED, "Dose-response of serum 25-hydroxyvitamin D in association with risk of colorectal cancer: A meta-analysis," *J. Steroid Biochem. Mol. Biol.* (2017) 168:1-8; Ekmekcioglu C, Haluza D, Kundi M, "25-Hydroxyvitamin D Status and Risk for Colorectal Cancer and Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Epidemiological Studies," *Int. J. Environ. Res. Public Health* (2017) 14(2). pii: E127); Vitamin E (Dong Y, Liu Y, Shu Y, Chen X, Hu J, Zheng R, Ma D, Yang C, Guan X, "Link between risk of colorectal cancer and serum vitamin E levels: A meta-analysis of case-control studies," *Medicine* (2017) 96(27):e7470); calcium (Huncharek M, Muscat J, Kupelnick. "Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies," *Nutr. Cancer* (2009) 61(1):47-69; Keum N, Aune D, Greenwood DC, Ju W, Giovannucci EL. "Calcium intake and colorectal cancer risk: dose-response meta-analysis of prospective observational studies," *Int. J. Cancer* (2014) 135(8):1940-1948; Heine-Bröring RC, Winkels RM, Renkema JM, Kragt L, van Orten-Luiten AC, Tigchelaar EF, Chan DS, Norat T, Kampman E, "Dietary supplement use and colorectal cancer risk: a systematic review and meta-analyses of prospective cohort studies," *Int. J. Cancer* (2015) 136(10):2388-2401; Keum N,

Lee DH, Greenwood DC, Zhang X, Giovannucci EL, "Calcium intake and colorectal adenoma risk: dose-response meta-analysis of prospective observational studies," *Int. J. Cancer* (2015) 136(7):1680-1687; Bonovas S, Fiorino G, Lytras T, Malesci A, Danese S, "Calcium supplementation for the prevention of colorectal adenomas: A systematic review and meta-analysis of randomized controlled trials," *World J Gastroenterol.* (2016) 22(18):4594-4603); magnesium (Wark PA, Lau R, Norat T, Kampman E, "Magnesium intake and colorectal tumor risk: a case-control study and meta-analysis," *Am. J. Clin. Nutr.* (2012) 96(3):622-631; Chen GC, Pang Z, Liu QF, "Magnesium intake and risk of colorectal cancer: a meta-analysis of prospective studies," *Eur. J. Clin. Nutr.* (2012) 66(11):1182-1186; Ko HJ, Youn CH, Kim HM, Cho YJ, Lee GH, Lee WK, "Dietary magnesium intake and risk of cancer: a meta-analysis of epidemiologic studies," *Nutr. Cancer* (2014) 66(6):915-923); and zinc (Qiao L, Feng Y, "Intakes of heme iron and zinc and colorectal cancer incidence: a meta-analysis of prospective studies," *Cancer Causes Control* (2013) 24(6):1175-1183; Li P, Xu J, Shi Y, Ye Y, Chen K, Yang J, Wu Y, "Association between zinc intake and risk of digestive tract cancers: a systematic review and meta-analysis," *Clin Nutr.* (2014) Jun;33(3):415-420.

4. Pharmaceuticals

The association between coffee consumption and colorectal cancer may also be confounded by use of certain pharmaceuticals that have been reported to reduce the risk of colorectal cancer in meta-analyses: Aspirin (Algra AM, Rothwell PM, "Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials," *Lancet Oncol.* (2012) 13(5):518-527; Ye X, Fu J, Yang Y, Chen S, "Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies," *PLoS One* (2013) 8(2):e57578); Bisphosphonates (Oh YH, Yoon C, Park SM, "Bisphosphonate use and gastrointestinal tract cancer risk: meta-analysis of observational studies,"

World J. Gastroenterol. (2012) 18(40):5779-5788; Singh S, Singh AG, Murad MH, Limburg PJ, "Bisphosphonates are associated with reduced risk of colorectal cancer: a systematic review and meta-analysis," *Clin. Gastroenterol. Hepatol.* (2013) 11(3):232-239; Thosani N, Thosani SN, Kumar S, Nugent Z, Jimenez C, Singh H, Guha S, "Reduced risk of colorectal cancer with use of oral bisphosphonates: a systematic review and meta-analysis," *J. Clin. Oncol.* (2013) 31(5):623-630; Ma J, Gao S, Ni X, Chen F, Liu X, Xie H, Yin H, Lu C, "Exposure to bisphosphonates and risk of colorectal cancer," *Br. J. Clin. Pharmacol.* (2013) 76(3):320-328; Bonovas S, Nikolopoulos G, Bagos P, "Bisphosphonate use and risk of colorectal cancer: a systematic review and meta-analysis," *Br. J. Clin. Pharmacol.* (2013) 76(3):329-337; Yang G, Hu H, Zeng R, Huang J, "Oral bisphosphonates and the risk of colorectal cancer: a meta-analysis," *J. Clin. Gastroenterol.* (2013) 47(9):741-748); and Statins (Lytras T, Nikolopoulos G, Bonovas S, "Statins and the risk of colorectal cancer: an updated systematic review and meta-analysis of 40 studies," *World J. Gastroenterol.* (2014) 20(7):1858-1870; Jung YS, Park CH, Eun CS, Park DI, Han DS, "Statin use and the risk of colorectal adenoma: A meta-analysis," *J. Gastroenterol Hepatol.* (2016) 31(11):1823-1830.

5. Reproductive Factors

The association between coffee consumption and colorectal cancer may also be confounded by reproductive factors, including menopausal hormone therapy (Green J, Czanner G, Reeves G, Watson J, Wise L, Roddam A, Beral V, "Menopausal hormone therapy and risk of gastrointestinal cancer: nested case-control study within a prospective cohort, and meta-analysis," *Int. J. Cancer* (2012) 130(10):2387-2396) and oral contraceptive use (Fernandez E, La Vecchia C, Balducci A, Chatenoud L, Franceschi S, Negri E, "Oral contraceptives and colorectal cancer risk: a meta-analysis," *Br. J. Cancer* (2001) 84(5):722-727; Bosetti C, Bravi F, Negri E, La Vecchia C, "Oral contraceptives and colorectal cancer risk: a systematic review and meta-analysis," *Hum. Reprod*

Update (2009) 15(5):489-498; Luan NN, Wu L, Gong TT, Wang YL, Lin B, Wu QJ, "Nonlinear reduction in risk for colorectal cancer by oral contraceptive use: a meta-analysis of epidemiological studies," *Cancer Causes Control* (2015) 26(1):65-78.

6. Conclusion Regarding Confounding

With so many factors that have been shown to significantly reduce the risk of colorectal cancer in so many meta-analyses of epidemiologic studies, inverse associations between coffee consumption and colorectal cancer that have been reported in some epidemiological studies is therefore substantially confounded. IARC did not address the potential impact of the confounding factors noted above in its evaluation of colorectal cancer risk. The overall human cancer data on coffee consumption and risk of colorectal cancer show that the IARC criteria for no carcinogenic hazard have clearly not been met.

As previously mentioned, in its Initial Statement of Reasons OEHHA asserts that "[i]n epidemiological studies published since IARC completed its literature search in 2016, coffee consumption has consistently been found to be protective for colorectal cancer risk." ISOR at p. 7. This assertion is incorrect for two reasons. First, the inverse associations reported in some studies have not been proven to be "protective," but are merely associational and likely due to confounding. Second, the inverse association is not consistent, because one cohort study reported significantly increased risks of colorectal cancer for coffee consumption (Groessl 2016), another reported a highly significant positive trend for coffee consumption (Gunter 2017), three meta-analyses of cohort studies observed no association (Akter 2016, Vieira 2017, Horisake 2018), and one pooled analysis showed a significant increased risk for phenolic acid intake in women (Zamora-Ross 2018) .

VIII. IARC'S EVALUATION OF CANCER RISKS ASSOCIATED WITH COFFEE

In its evaluation of the cancer epidemiological data on coffee, IARC concluded : "There is *inadequate evidence* in humans for the carcinogenicity of drinking coffee. There is *evidence suggesting lack of carcinogenicity* of drinking coffee in humans for cancers of the pancreas, liver, female breast, uterine endometrium, and prostate. Inverse associations with drinking coffee have been observed with cancers of the liver and uterine endometrium." This means that for all other sites there is *inadequate evidence of carcinogenicity*, i.e., "the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available." As noted above in Sections V, VI and VII, numerous positive responses have been observed at many sites, however, because of other findings of no or non-significant effects at many of these sites and/or confounding or bias, cancer risks at those sites have not been resolved.

For some types of cancers, there is compelling evidence of increased risk associated with coffee consumption. For example, several studies show increased risk of childhood leukemia associated with maternal coffee consumption. As noted by IARC, "all [meta-analyses] reported elevated risks with higher levels of maternal coffee intake." Several signatories of this document who have served on numerous expert Working Groups of the IARC Monographs program find that based on their past experiences as participants in IARC evaluations of carcinogenic risks to humans, the evidence for childhood leukemia reaches at least the level of *limited evidence of carcinogenicity*, i.e., "a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the IARC Monograph Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence." In any case, the epidemiological data certainly do not support the claim by OEHHA that coffee "has not been found to increase the risk of any cancers."

The IARC category of *not classifiable as to it carcinogenicity to humans* (Group 3) "is used most commonly for agents for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals." This is the overall classification IARC made for cancer risk associated with consumption of coffee. The Working Group did not conclude that coffee is *probably not carcinogenic to humans* (Group 4), because there were numerous studies which showed evidence of carcinogenicity in humans or the data were inadequate for evaluation.

The IARC Working Group concluded that for five cancer types there is *evidence suggesting lack of carcinogenicity* for coffee in humans. This classification requires that "there are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up." In discussing criteria for causality, IARC notes "latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity." IARC also notes that "the possibility of a very small risk at the levels of exposure studied can never be excluded." With these criteria in mind, Section V of this document noted inconsistencies in the results among studies and explained how measurement errors and failure to adequately control confounding factors could lead to exposure misclassifications and influence any apparent relationships (such as producing inverse associations) between coffee consumption and risk of endometrial cancer, liver cancer, and breast cancer. Thus, a major review of 1,277 published human studies on health effects associated with coffee consumption cautioned about interpreting the studies because "results and generalizations are complicated by a number of factors, including differences in age, gender, health status, type of coffee preparation, serving size, and source of coffee." Pourshahidi, LK, Navarini L, Petracco M, Strain JJ, "A Comprehensive Overview of the Risks and Benefits of Coffee Consumption," (2016) *Comp. Rev. Food Sci. Food Safety* 15:671-684.

Critically, the authors of this comprehensive review concluded that "causality cannot be established for either [benefit or risk] with the research currently available as these are largely based on observational data," and "heterogeneity between study populations and designs, and also lack of control for many other confounding factors, add limitations to the existing literature." *Id.*

Of the five cancer sites for which IARC reported *evidence suggesting lack of carcinogenicity* of coffee, IARC found inverse associations for only two cancer sites: liver cancer and endometrial cancer. For the other three cancer sites – cancer of the breast cancer, pancreas and prostate – IARC did not observe inverse associations. Since the IARC Working Group concluded that there was *evidence suggesting lack of carcinogenicity* of coffee for these five cancer sites, the epidemiologic data for these sites merits discussion in relation to IARC's criteria for this categorization..

A. Liver Cancer

As discussed in Section VI.B., the major limitations of the studies regarding coffee consumption and liver cancer are confounding by liver disease (especially hepatitis viruses) and reverse causation. People who have liver disease often can't drink coffee because of its acidity and their inability to metabolize caffeine and other constituents of coffee due to their underlying liver disease. So they either reduce their consumption on their own or because their doctors tell them to reduce coffee intake. Thus, the inverse association between coffee consumption and liver cancer is likely due to confounding by liver disease and reverse causation, the decreased risk of liver cancer being reflective of decreased (rather than increased) coffee consumption. Indeed, as discussed at length in Section VI.B.4, the authors of most of the studies regarding coffee and liver cancer acknowledge that the inverse associations may well be "spurious" due to reverse causation.

In its summary regarding cohort studies that evaluated the association between coffee consumption and liver cancer, IARC wrote: "A total of 14 cohort studies and 11 case-control studies conducted in Asia, Europe and North America examined the association between coffee

consumption and the risk of cancer of the liver. All cohort studies adjusted for smoking and alcohol intake and, where possible, for hepatitis virus infection status and diabetes. All cohort studies observed inverse associations, which were statistically significant in most studies." Separate analyses by sex and by hepatitis C virus and/or hepatitis B virus infection status yielded similar results."

While this summary acknowledges that the cohort studies only adjusted for hepatitis virus infection status and diabetes "where possible," it is somewhat misleading because most of the studies could not and did not adjust for hepatitis virus infection status – a major limitation of the studies. Additionally, IARC does not indicate that the studies adjusted for any confounders of liver cancer other than smoking and alcohol consumption, although many other factors have been associated with increased risks of liver cancer, including aflatoxins, androgenic (anabolic) steroids, betel quid, chronic liver disease, cyanotoxins, DDT, dichloromethane, 1,2- dichloropropane, estrogen-progestogen contraceptives, gamma radiation, HIV type 1, inorganic arsenic, obesity, contaminated (road, ditch and river) water, schistosome japonicum, trichloroethylene, vinyl chloride, x-radiation, and a few factors have been associated with decreased risks: green tea, tea, uncontaminated water. [See Appendix to the Report of Dr. Infante for the Phase 2 Trial].

"The Working Group concluded that a consistent, statistically significant, inverse association between coffee drinking and risk of liver cancer has been observed in multiple studies." (Monograph at p. 417). IARC concluded that there was *evidence suggesting lack of carcinogenicity* of drinking coffee for . . . cancers of the liver" and that "[i]nverse associations with drinking coffee have been observed with cancers of the liver . . . ." (Monograph at p. 425).

As previously mentioned, according to IARC, to find *evidence suggesting lack of carcinogenicity,* "bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up." However, nowhere in its discussion regarding coffee and liver cancer does IARC indicate whether the Working Group was able to rule out bias and confounding with reasonable confidence. Indeed, whereas the original studies acknowledge major

limitations including their inability to control or adjust for hepatitis viruses and other confounding factors, the monograph doesn't mention any of these shortcomings of the studies. Moreover, even though many authors of the studies acknowledge that their results may be "spurious" due to reverse causation, the monograph does not indicate whether the Working Group even considered this issue. Critically, the studies neither control nor adjust for multiple factors that have been reported to significantly decrease the risk of liver cancer in observational epidemiologic studies and meta-analyses, including the Mediterranean diet and other healthy dietary patterns, dietary fiber, vegetables, fish, tea, ginseng, various other dietary factors, trace elements and vitamins, medications, hormone replacement therapy and reproductive factors.

Thus, OEHHA needs to resolve the impact of bias and confounding on reported liver cancer risk before accepting observations of inverse associations as being causally related to the consumption of coffee.

B. Endometrial Cancer

As discussed in Section VI.A., the major limitations of the studies regarding coffee consumption and endometrial cancer are negative confounding by cigarette smoking, which substantially reduces the risk of endometrial cancer, most likely due to its anti-estrogenic effect. Additionally, as discussed in Section VI.A.2-9, case-control studies and meta-analyses have identified many factors that significantly reduce the risk of endometrial cancer, including cigarette smoking, use of contraceptives, use of intrauterine devices, use of aspirin, use of bisphosphonates, breastfeeding, reproductive factors, physical activity, and multiple dietary factors. Since so many factors have been shown to reduce the risk of endometrial cancer, epidemiologic studies regarding coffee consumption and endometrial cancer would have to carefully control or adjust for all of these negative confounders to determine whether the inverse associations reported in epidemiologic studies regarding coffee consumption and endometrial cancer are due to coffee or the other multiple

negative confounders. However, none of the studies controlled or adjusted for all of the factors that have been reported to decrease the risk of endometrial cancer. Accordingly, the epidemiologic studies regarding coffee consumption and endometrial cancer are not only negatively confounded by smoking, but by multiple other negative confounders. According to IARC's criteria, it would therefore be inappropriate to attribute the inverse associations to consumption of coffee.

In its summary regarding endometrial cancer, IARC wrote: "Evidence of the association between drinking coffee and risk of endometrial cancer was available from 20 informative studies (12 cohort and 8 case-control studies) where body mass index and smoking were taken into account." Evidence from four of the largest cohort studies (the Swedish Mammography Cohort, the National Institutes of Health– American Association of Retired Persons (NIH-AARP Diet and Health Study, the Nurses' Health Study (NHS) and NHS II, and European Prospective Investigation into Cancer and Nutrition (EPIC)) with over 600 cases showed an inverse association with coffee drinking. The Million Women Study, including another 4000 cases, found a null association. Evidence from case-control studies is consistent with that of cohort studies, suggesting an inverse or a null association. A meta-analysis published in 2012 found a 30% lower risk of endometrial cancer among coffee drinkers, consistent with the majority of cohort and case-control studies." (IARC Monograph at p. 417). In its overall evaluation, IARC concluded that "there is *evidence suggesting lack of carcinogenicity* of drinking coffee in humans for cancers of the . . . uterine endometrium," with "[i]nverse associations ... observed with cancers of the ... uterine endometrium." (IARC Monograph at p. 425).

According to IARC, to find *evidence suggesting lack of carcinogenicity,* "bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up." However, nowhere in its discussion regarding coffee and endometrial cancer does IARC indicate whether the Working Group was able to rule out bias and confounding with reasonable confidence or whether the length of follow-up in the studies was adequate for endometrial cancer to develop. The major negative confounder of the coffee-endometrial cancer studies is, of course, cigarette smoking, which has consistently been reported to substantially reduce

endometrial cancer risk. Moreover, the studies neither control nor adjust for multiple other factors that have been reported to significantly decrease the risk of endometrial cancer in observational studies and meta-analyses, including use of contraceptives, including intrauterine devices, aspiring, bisphosphonates, breastfeeding reproductive factors, physical activity, and multiple dietary factors, including health dietary patterns, the Mediterranean diet, dietary fiber, fruits and vegetables, nuts, soy, and vitamins, including vitamin A, beta-carotene, vitamin C, vitamin D, vitamin E, and calcium. Regrettably, nowhere in its Monograph did IARC address the many confounding factors which have been reported to reduce the risk of endometrial cancer, so it doubtful that IARC considered them and it is unclear whether IARC was able to and did actually rule them out with reasonable confidence in reaching its overall conclusion regarding coffee consumption and endometrial cancer.

While IARC notes that "inverses associations with drinking coffee have been observed with cancers of the liver and uterine endometrium," OEHHA attempts to justify its proposal in its Initial Statement of Reasons by promoting these observations as actual causal associations. OEHHA clearly does this by asserting that coffee consumption "reduces the risk of human cancers that account for 40 percent of cancer diagnoses in women (liver, endometrium, and breast)." Before making this leap of faith (i.e., accepting observations of inverse associations as causally related to consumption of coffee), OEHHA needs to resolve the impact of the numerous known negative confounding factors on reported liver and uterine cancer risks.

C. Breast Cancer

As discussed in Section VI.C.1, the epidemiologic studies regarding coffee consumption and breast cancer are inconsistent. As discussed in Section VI.C.2., the studies are also confounded by cigarette smoking, which may decrease the risk of breast cancer due to its anti-estrogenic effects. Additionally, as discussed in Section VI.C.4, several other factors have been shown to significantly reduce the risk of breast cancer, including physical activity, breastfeeding, and multiple dietary

factors, including calcium, carotenoids, dietary fiber, fatty acids and fish, flavan-3-ols, folate, fruit, the Mediterranean diet, soy, vegetables, tea (especially green tea), and vitamins.

In its summary regarding coffee consumption and breast cancer, IARC wrote: "Evidence of the association between coffee consumption and risk of cancer of the breast was available from 23 cohort and 22 case-control studies. Most of the reviewed studies showed no association, and several reported statistically significant inverse associations between coffee intake and breast cancer overall or among subgroups of premenopausal or postmenopausal women. The most recent meta-analysis of about one million women and more than 50 000 breast cancer cases reported a modestly decreased risk for the highest compared with lowest levels of coffee consumption,with an indication of an inverse dose-response relationship. Studies published after this meta-analysis reported null or inverse associations overall and among postmenopausal women. An inverse association was also observed in the recent large cohort study (2016). Inverse associations were reported in a small number [of] studies among women with *BRCA1* mutations. One population-based case-control study among non-carriers of *BRCA 1/2* mutations reported a positive association." (IARC Monograph at p. 417). IARC concluded that "[t]here is *evidence* suggesting lack of carcinogenicity of drinking coffee in humans for cancers of the . . . female breast . . . ." (IARC Monograph at p. 425).

According to IARC, to find *evidence suggesting lack of carcinogenicity,* "bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up." However, nowhere in its discussion regarding coffee and breast cancer does IARC indicate whether the Working Group was able to rule out bias and confounding with reasonable confidence. Indeed, the Monograph doesn't even mention that meta-analyses have reported significantly decreased risks of breast cancer for multiple dietary factors, including calcium, carotenoids, dietary fiber, fatty acids and fish, flavan-3-ols, folate, fruit, the Mediterranean diet, soy, vegetables, tea (especially green tea), and vitamins, as well as physical activity and breastfeeding. It is therefore doubtful that IARC considered these negative confounders of the association between coffee consumption and breast cancer, and it is unclear whether IARC was able to and did actually

rule them out with reasonable confidence in reaching its conclusion regarding coffee consumption and breast cancer.

D. Pancreatic Cancer

In summarizing the studies regarding coffee consumption and pancreatic cancer, IARC wrote: "Evidence of the association between coffee drinking and cancer of the pancreas was available from 20 cohort studies and 22 case-control studies that controlled for smoking, of which 14 were population-based and 8 hospital-based. The review of epidemiological studies was restricted to those that adjusted for smoking. Cohort studies and population-based case-control studies, adjusting for multiple confounders, showed no overall association with total coffee drinking or with decaffeinated coffee drinking. The most important set of studies on which this conclusion is based is a pooled analysis of cohort studies with comparable methodology which found no association, including in non-smokers. A high-quality meta-analysis also showed no association with coffee intake in cohort studies or in case-control studies that adjusted for smoking. Several large cohort studies published after this meta-analysis similarly found null associations. Overall, based on many large studies, there is no evidence of an association between coffee drinking and risk of pancreatic cancer." (IARC Monograph at pp. 416-417). IARC concluded that "[t]here is *evidence* suggesting lack of carcinogenicity of drinking coffee in humans for cancers of the pancreas . . . ." (IARC Monograph at p. 425).

IARC does not discuss whether the null association it observed for consumption of coffee and pancreatic cancer may be influenced by confounding due to factors that have been reported to reduce the risk of pancreatic cancer. In fact, many factors have been reported in meta-analyses to significantly reduce the risk of pancreatic cancer.

1. Physical Activity

Meta-analyses have reported that increased physical activity is associated with decreased risk of pancreatic cancer. O'Rorke MA, Cantwell MM, Cardwell CR, Mulholland HG, Murray LJ, "Can physical activity modulate pancreatic cancer risk? a systematic review and meta-analysis," *Int. J. Cancer* (2010) 126(12):2957-2968; Behrens G, Jochem C, Schmid D, Keimling M, Ricci C, Leitzmann MF, "Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis," *Eur. J. Epidemiol.* (2015) 30(4):279-298; Farris MS, Mosli MH, McFadden AA, Friedenreich CM, Brenner DR,"The Association between Leisure Time Physical Activity and Pancreatic Cancer Risk in Adults: A Systematic Review and Meta-analysis," *Cancer Epidemiol. Biomarkers Prev.* (2015) 24(10):1462-1473.

2 Medications

Meta-analyses of studies regarding medication use have consistently reported that use of aspirin and metformin significantly reduce the risk of pancreatic cancer.

a. Aspirin

Meta-analyses have consistently reported decreased risks of pancreatic cancer with aspirin use. Cui XJ, He Q, Zhang JM, Fan HJ, Wen ZF, Qin YR, "High-dose aspirin consumption contributes to decreased risk for pancreatic cancer in a systematic review and meta-analysis," *Pancreas.* (2014) 43(1):135-140; Zhang YP, Wan YD, Sun YL, Li J, Zhu RT, "Aspirin might reduce the incidence of pancreatic cancer: A meta-analysis of observational studies," *Sci. Rep.* (2015) 5:15460; Qiao Y, Yang T, Gan Y, Li W, Wang C, Gong Y, Lu Z, "Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies," *BMC Cancer* (2018) 18(1):288.

b. Metformin

Several meta-analyses have reported that use of metformin decreases the risk of pancreatic cancer. Zhang P, Li H, Tan X, Chen L, Wang S, "Association of metformin use with cancer incidence and mortality: a meta-analysis," *Cancer Epidemiol.* (2013) 37(3):207-218; Singh S, Singh PP, Singh AG, Murad MH, McWilliams RR, Chari ST, "Anti-diabetic medications and risk of pancreatic cancer in patients with diabetes mellitus: a systematic review and meta-analysis," *Am. J. Gastroenterol.* (2013) 108(4):510-519; Mohammed A, Janakiram NB, Brewer M, Ritchie RL, Marya A, Lightfoot S, Steele VE, Rao CV, "Antidiabetic Drug Metformin Prevents Progression of Pancreatic Cancer by Targeting in Part Cancer Stem Cells and mTOR Signaling," *Transl. Oncol.* (2013) 6(6):649-659; Bosetti C, Rosato V, Li D, Silverman D, Petersen GM, Bracci PM, Neale RE, Muscat J, Anderson K, Gallinger S, Olson SH, Miller AB, Bas Bueno-de-Mesquita H, Scelo G, Janout V, Holcatova I, Lagiou P, Serraino D, Lucenteforte E, Fabianova E, Ghadirian P, Baghurst PA, Zatonski W, Foretova L, Fontham E, Bamlet WR, Holly EA, Negri E, Hassan M, Prizment A, Cotterchio M, Cleary S, Kurtz RC, Maisonneuve P, Trichopoulos D, Polesel J, Duell EJ, Boffetta P, La Vecchia C, "Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium," *Ann. Oncol.* (2014) 25(10):2065-2072; Wang Z, Lai ST, Xie L, Zhao JD, Ma NY, Zhu J, Ren ZG, Jiang GL, "Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis," *Diabetes Res. Clin. Pract.* (2014) 106(1):19-26.

3. Dietary Factors

Meta-analyses have reported that the Mediterranean diet and certain foods significantly reduce the risk of pancreatic cancer.

a. Mediterranean Diet

Meta-analyses have reported that the Mediterranean diet reduces pancreatic cancer risk. Schwingshackl L, Hoffmann G, "Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies," *Int. J. Cancer* (2014) 135(8):1884-1897; Schwingshackl L, Hoffmann G. "Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies," *Cancer Med.* (2015) 4(12):1933-1947; Lu PY, Shu L, Shen SS, Chen XJ, Zhang XY, "Dietary Patterns and Pancreatic Cancer Risk: A Meta-Analysis," *Nutrients* (January 5, 2017) 9(1). pii: E38.

b. Fruits and Vegetables

Several meta-analyses have reported significantly reduced risks of pancreatic cancer in association with consumption of fruits and vegetables. Bae JM, Lee EJ, Guyatt G, "Citrus fruit intake and pancreatic cancer risk: a quantitative systematic review," *Pancreas* (2009) 38(2):168-174; Koushik A, Spiegelman D, Albanes D, Anderson KE, Bernstein L, van den Brandt PA, Bergkvist L, English DR, Freudenheim JL, Fuchs CS, Genkinger JM, Giles GG, Goldbohm RA, Horn-Ross PL, Männistö S, McCullough ML, Millen AE, Miller AB, Robien K, Rohan TE, Schatzkin A, Shikany JM, Stolzenberg-Solomon RZ, Willett WC, Wolk A, Ziegler RG, Smith-Warner SA, "Intake of fruits and vegetables and risk of pancreatic cancer in a pooled analysis of 14 cohort studies," *Am. J. Epidemiol.* (2012) 76(5):373-386; Li LY, Luo Y, Lu MD, Xu XW, Lin HD, Zheng ZQ, "Cruciferous vegetable consumption and the risk of pancreatic cancer: a meta-analysis," *World J. Surg. Oncol.* (2015) 13:44; Wu QJ, Wu L, Zheng LQ, Xu X, Ji C, Gong TT, "Consumption of fruit and vegetables reduces risk of pancreatic cancer: evidence from epidemiological studies," *Eur. J. Cancer Prev.* (2016) 25(3):196-205.

c. Dietary Fiber

Meta-analyses have also reported significantly reduced risks of pancreatic cancer in association with increased dietary fiber intake. Wang CH, Qiao C, Wang RC, Zhou WP, "Dietary fiber intake and pancreatic cancer risk: a meta-analysis of epidemiologic studies," *Sci. Rep.* (2015) 5:10834; Mao QQ, Lin YW, Chen H, Qin J, Zheng XY, Xu X, Xie LP, "Dietary fiber intake is inversely associated with risk of pancreatic cancer: a meta-analysis," *Asia Pac. J. Clin Nutr.* (2017) 26(1):89-96.

d. Whole Grains

Meta-analyses have also reported reduced risks of pancreatic cancer in association with increased intake of whole grain foods. Jacobs DR Jr, Marquart L, Slavin J, Kushi LH, "Whole-grain intake and cancer: an expanded review and meta-analysis," *Nutr. Cancer.* (1998) 30(2):85-96; Lei Q, Zheng H, Bi J, Wang X, Jiang T, Gao X, Tian F, Xu M, Wu C, Zhang L, Li N, Li J, "Whole Grain Intake Reduces Pancreatic Cancer Risk: A Meta-Analysis of Observational Studies," *Medicine* (March 9, 2016) 95(9):e2747.

e. Other Dietary Factors

Meta-analyses have also reported decreased risk of pancreatic cancer with consumption of nuts (Wu L, Wang Z, Zhu J, Murad AL, Prokop LJ, Murad MH, "Nut consumption and risk of cancer and type 2 diabetes: a systematic review and meta-analysis," *Nutr. Rev.* (2015) 73(7):409-425), unsaturated fatty acid intake (Yao X, Tian Z, "Saturated, Monounsaturated and Polyunsaturated Fatty Acids Intake and Risk of Pancreatic Cancer: Evidence from Observational Studies," *PLoS One.* (2015) 10(6):e0130870), green tea (Chen K, Zhang Q, Peng M, Shen Y, Wan P, Xie G,

"Relationship between tea consumption and pancreatic cancer risk: a meta-analysis based on prospective cohort studies and case-control studies," *Eur. J. Cancer Prev.* (2014) 23(5):353-360) and plasma adiponectin. Bao Y, Giovannucci EL, Kraft P, Stampfer MJ, Ogino S, Ma J, Buring JE, Sesso HD, Lee IM, Gaziano JM, Rifai N, Pollak MN, Cochrane BB, Kaklamani V, Lin JH, Manson JE, Fuchs CS, Wolpin BM, "A prospective study of plasma adiponectin and pancreatic cancer risk in five US cohorts," .*J. Natl. Cancer Inst.* (2013) 105(2):95-103.

f. Vitamins

Meta-analyses of observational studies have reported decreased risks of pancreatic cancer in association with consumption of vitamins. Kong P, Cai Q, Geng Q, Wang J, Lan Y, Zhan Y, Xu D, "Vitamin intake reduce the risk of gastric cancer: meta-analysis and systematic review of randomized and observational studies," *PLoS One.* (2014) 9(12):e116060; Liu Y, Wang X, Sun X, Lu S, Liu S, ."Vitamin intake and pancreatic cancer risk reduction: A meta-analysis of observational studies," *Medicine* (March 2018) 97(13):e0114.

(1) Vitamin A

Meta-analyses have reported decreased risk of pancreatic cancer in association with use of Vitamin A. Zhang T, Chen H, Qin S, Wang M, Wang X, Zhang X, Liu F, Zhang S, "The association between dietary vitamin A intake and pancreatic cancer risk: a meta-analysis of 11 studies, "*Biosci. Rep.* (November 22, 2016) 36(6). pii: e00414; Huang X, Gao Y, Zhi X, Ta N, Jiang H, Zheng J, "Association between vitamin A, retinol and carotenoid intake and pancreatic cancer risk: Evidence from epidemiologic studies, *Sci. Rep.* (December 12, 2016) 6:38936.

(2) Folate

Several meta-analyses have reported decreased risks of pancreatic cancer in association with increased folate intake. Larsson SC, Giovannucci E, Wolk A, "Folate intake, MTHFR polymorphisms, and risk of esophageal, gastric, and pancreatic cancer: a meta-analysis," *Gastroenterology* (2006) 131(4):1271-1283.; Bao Y, Michaud DS, Spiegelman D, Albanes D, Anderson KE, Bernstein L, van den Brandt PA, English DR, Freudenheim JL, Fuchs CS, Giles GG, Giovannucci E, Goldbohm RA, Håkansson N, Horn-Ross PL, Jacobs EJ, Kitahara CM, Marshall JR, Miller AB, Robien K, Rohan TE, Schatzkin A, Stevens VL, Stolzenberg-Solomon RZ, Virtamo J, Wolk A, Ziegler RG, Smith-Warner SA, "Folate intake and risk of pancreatic cancer: pooled analysis of prospective cohort studies," *J. Natl. Cancer Inst.* (2011) 103(24):1840-1850; Lin HL, An QZ, Wang QZ, Liu CX, "Folate intake and pancreatic cancer risk: an overall and dose-response meta-analysis," *Public Health.* (2013) 127(7):607-613; Tio M, Andrici J, Cox MR, Eslick GD, "Folate intake and the risk of upper gastrointestinal cancers: a systematic review and meta-analysis," *J. Gastroenterol. Hepatol.* (2014) 29(2):250-258; Liu W, Zhou H, Zhu Y, Tie C, "Associations between dietary folate intake and risks of esophageal, gastric and pancreatic cancers: an overall and dose-response meta-analysis," *Oncotarget* (2017) 8(49):86828-86842.

(3) Vitamin C

Meta-analyses have also reported decreased risk of pancreatic cancer with use of Vitamin C. Fan H, Kou J, Han D, Li P, Zhang D, Wu Q, He Q, "Association between vitamin C intake and the risk of pancreatic cancer: a meta-analysis of observational studies," *Sci. Rep.* (2015) 5:13973; Hua YF, Wang GQ, Jiang W, Huang J, Chen GC, Lu CD, "Vitamin C Intake and Pancreatic Cancer Risk: A Meta-Analysis of Published Case-Control and Cohort Studies," *PLoS One* (2016) 11(2):e0148816.

(4) Vitamin D

Meta-analyses have likewise reported decreased risk of pancreatic cancer in association with use of Vitamin D. Wolpin BM, Ng K, Bao Y, Kraft P, Stampfer MJ, Michaud DS, Ma J, Buring JE, Sesso HD, Lee IM, Rifai N, Cochrane BB, Wactawski-Wende J, Chlebowski RT, Willett WC, Manson JE, Giovannucci EL, Fuchs CS, "Plasma 25-hydroxyvitamin D and risk of pancreatic cancer," *Cancer Epidemiol. Biomarkers Prev.* (2012) 21(1):82-91; Zhang X, Huang XZ, Chen WJ, Wu J, Chen Y, Wu CC, Wang ZN, "Plasma 25-hydroxyvitamin D levels, vitamin D intake, and pancreatic cancer risk or mortality: a meta-analysis," *Oncotarget.* (2017) 8(38):64395-64406.

(5) Vitamin E

One Meta-analysis has reported decreased risk of pancreatic cancer with use of Vitamin E. Peng L, Liu X, Lu Q, Tang T, Yang Z, "Vitamin E intake and pancreatic cancer risk: a meta-analysis of observational studies," *Med. Sci. Monit.* (2015) 21:1249-1255.

g. Trace Elements

Meta-analyses have reported decreased pancreatic risk with some trace elements, including selenium (Wang L, Wang J, Liu X, Liu Q, Zhang G, Liang L, "Association between selenium intake and the risk of pancreatic cancer: a meta-analysis of observational studies," *Biosci. Rep.* (Oct. 14, 2016) 36(5). pii: e00395) and zinc. Li L, Gai X, "The association between dietary zinc intake and risk of pancreatic cancer: a meta-analysis," *Biosci Rep.* (Jun3 8, 2017) 37(3). pii: BSR20170155.

4. Reproductive Factors

Meta-analyses have reported decreased risks of pancreatic cancer in association with parity. Guan HB, Wu L, Wu QJ, Zhu J, Gong T, "Parity and pancreatic cancer risk: a dose-response meta-analysis of epidemiologic studies," *PLoS One.* (2014) 9(3):e92738; Zhu B, Zou L, Han J, Chen W, Shen N, Zhong R, Li J, Chen X, Liu C, Shi Y, Miao X, "Parity and pancreatic cancer risk: evidence from a meta-analysis of twenty epidemiologic studies," *Sci. Rep.* (June 17, 2014) 4:5313; Lujan-Barroso L, Zhang W, Olson SH, Gao YT, Yu H, Baghurst PA, Bracci PM, Bueno-de-Mesquita HB, Foretová L, Gallinger S, Holcatova I, Janout V, Ji BT, Kurtz RC, La Vecchia C, Lagiou P, Li D, Miller AB, Serraino D, Zatonski W, Risch HA, Duell EJ, "Menstrual and Reproductive Factors, Hormone Use, and Risk of Pancreatic Cancer: Analysis From the International Pancreatic Cancer Case-Control Consortium (PanC4)," *Pancreas* (2016) 45(10):1401-1410.

5. Allergies and Asthma

Meta-analyses have reported decreased risks of pancreatic cancer in association with allergies and asthma. Gandini S, Lowenfels AB, Jaffee EM, Armstrong TD, Maisonneuve P, "Allergies and the risk of pancreatic cancer: a meta-analysis with review of epidemiology and biological mechanisms," *Cancer Epidemiol. Biomarkers Prev.* (2005) 14(8):1908-1916; Olson SH, Hsu M, Satagopan JM, Maisonneuve P, Silverman DT, Lucenteforte E, Anderson KE, Borgida A, Bracci PM, Bueno-de-Mesquita HB, Cotterchio M, Dai Q, Duell EJ, Fontham EH, Gallinger S, Holly EA, Ji BT, Kurtz RC, La Vecchia C, Lowenfels AB, Luckett B, Ludwig E, Petersen GM, Polesel J, Seminara D, Strayer L, Talamini R; Pancreatic Cancer Case-Control Consortium, "Allergies and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Case-Control Consortium," *Am. J. Epidemiol.* (2013) 178(5):691-700; Gomez-Rubio P, Zock JP, Rava M, Marquez M, Sharp L, Hidalgo M, Carrato A, Ilzarbe L, Michalski C, Molero X, Farré A, Perea J, Greenhalf W, O'Rorke

M, Tardón A, Gress T, Barberà V, Crnogorac-Jurcevic T, Domínguez-Muñoz E, Muñoz-Bellvís L, Alvarez-Urturi C, Balcells J, Barneo L, Costello E, Guillén-Ponce C, Kleeff J, Kong B, Lawlor R, Löhr M, Mora J, Murray L, O'Driscoll D, Peláez P, Poves I, Scarpa A, Real FX, Malats N; PanGenEU Study Investigators, "Reduced risk of pancreatic cancer associated with asthma and nasal allergies," *Gut* (2017) 66(2):314-322.

6. Blood Group

A reduced risk of pancreatic cancer has also been observed in association with Blood Group O. Zhang BL, He N, Huang YB, Song FJ, Chen KX, "ABO blood groups and risk of cancer: a systematic review and meta-analysis," *Asian Pac. J. Cancer Prev.* (2014) 15(11):4643-4650.

7. Conclusion

According to IARC, to find *evidence suggesting lack of carcinogenicity,* "bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up." However, nowhere in its discussion regarding coffee and pncreatic cancer does IARC indicate whether the Working Group was able to rule out bias and confounding with reasonable confidence or whether there was adequate follow-up in the pancreatic cancer studies.

The IARC Monograph does not mention that meta-analyses have reported significantly decreased risks of pancreatic cancer in association with multiple factors, including physical activity, medications (aspirin and metformin), dietary factors (including the Mediterranean diet, fruits and vegetables, whole grains, other dietary factors (including nuts, unsaturated fatty acids, green tea, and plasma adiponectin), vitamins (including Vitamin A, folate, Vitamin C, Vitamin D, and Vitamin E, trace elements (selenium and zinc), reproductive factors (parity), medical conditions (allergies and asthma), and Type O blood group.

It is therefore doubtful that IARC considered these negative confounders of the association between coffee consumption and pancreatic cancer, and it is unclear whether IARC was able to and did actually rule them out with reasonable confidence in reaching its conclusion regarding coffee consumption and pancreatic cancer.

E. Prostate Cancer

In summarizing the studies regarding coffee consumption and prostate cancer, IARC wrote: "Evidence from ten cohort studies and four case-control studies of the association between coffee drinking and cancer of the prostate was evaluated. The greatest weight was given to studies of aggressive and fatal prostate cancer to reduce the potential for bias from screening. No case-control or cohort studies found positive associations with the risk of total prostate cancer. Recent met-analyses of cohort and case-control studies estimated inverse associations for fatal prostate cancer and no association for advanced prostate cancer. Studies conducted worldwide consistently indicated no increased risk of prostate cancer associated with coffee drinking, with inverse or null associations observed in all studies." (IARC Monograph at pp. 417-418) IARC concluded that there was *evidence suggesting lack of carcinogenicity* of drinking coffee for in humans for cancers of the . . . prostate." (IARC Monograph at p. 425).

1. Inconsistency of Studies

Epidemiologic studies regarding consumption of coffee and prostate cancer report inconsistent results.

a. Case-Control Studies

At least 14 case-control studies regarding coffee consumption and prostate cancer have been published. Slattery ML, West DW, "Smoking, alcohol, coffee, tea, caffeine, and theobromine: risk of prostate cancer in Utah (United States)," *Cancer Causes Control* (1993) 4(6):559-563; Grönberg H, Damber L, Damber JE, "Total food consumption and body mass index in relation to prostate cancer risk: a case-control study in Sweden with prospectively collected exposure data," *J. Urol.* (1996) 155(3):969-974; Jain MG, Hislop GT, Howe GR, Burch JD, Ghadirian P, "Alcohol and other beverage use and prostate cancer risk among Canadian men," *Int. J. Cancer.* (1998) 78(6):707-711; Villeneuve PJ, Johnson KC, Kreiger N, Mao Y, "Risk factors for prostate cancer: results from the Canadian National Enhanced Cancer Surveillance System. The Canadian Cancer Registries Epidemiology Research Group," *Cancer Causes Control* (1999) 10(5):355-367; Hsieh CC, Thanos A, Mitropoulos D, Deliveliotis C, Mantzoros CS, Trichopoulos D, "Risk factors for prostate cancer: a case-control study in Greece," *Int. J. Cancer* (1999) 80(5):699-703; Sharpe CR, Siemiatycki J, "Consumption of non-alcoholic beverages and prostate cancer risk," *Eur. J. Cancer Prev.* (2002) 11(5):497-501; Chen YC, Chiang CI, Lin RS, Pu YS, Lai MK, Sung FC, "Diet, vegetarian food and prostate carcinoma among men in Taiwan," *Br. J. Cancer* (2005) 93(9):1057-1061; Gallus S, Foschi R, Talamini R, Altieri A, Negri E, Franceschi S, Montella M, Dal Maso L, Ramazzotti V, La Vecchia C, "Risk factors for prostate cancer in men aged less than 60 years: a case-control study from Italy," *Urology* (2007) 70(6):1121-1126; Ganesh B, Saoba SL, Sarade MN, Pinjari SV, "Risk factors for prostate cancer: An hospital-based case-control study from Mumbai, India," *Indian J. Urol.* (2011) 27(3):345-350; De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Acosta G, "Alcohol Drinking, Non-alcoholic Beverages and Risk of Advanced Prostate Cancer among Uruguayan Men," *J. Cancer Sci. Ther.* (2011) S1; Polesel J, Zucchetto A, Talamini R, Dal Maso L, Serraino D, La Vecchia C, Franceschi S, "Re: coffee consumption and prostate cancer risk and progression in the health professional follow-up study," *J. Natl. Cancer Inst.* (2012) 104(21):1684-

1686; Wilson KM, Bälter K, Möller E, Adami HO, Andrén O, Andersson SO, Grönberg H, Mucci LA, "Coffee and risk of prostate cancer incidence and mortality in the Cancer of the Prostate in Sweden Study," *Cancer Causes Control* (2013) 24(8):1575-1581; Geybels MS, Neuhouser ML, Wright JL, Stott-Miller M, Stanford JL, "Coffee and tea consumption in relation to prostate cancer prognosis," *Cancer Causes Control* (2013) 24(11):1947-1954; Russnes KM, Möller E, Wilson KM, Carlsen M, Blomhoff R, Smeland S, Adami HO, Grönberg H, Mucci LA, Bälter K, "Total antioxidant intake and prostate cancer in the Cancer of the Prostate in Sweden (CAPS) study. A case control study," *BMC Cancer* (2016) 16:438.

Most of these studies reported increased risks, with four of the studies reporting significantly increased risks of prostate cancer in association with coffee consumption.. Villeneuve PJ, Johnson KC, Kreiger N, Mao Y, "Risk factors for prostate cancer: results from the Canadian National Enhanced Cancer Surveillance System. The Canadian Cancer Registries Epidemiology Research Group," *Cancer Causes Control* (1999) 10(5):355-367; Chen YC, Chiang CI, Lin RS, Pu YS, Lai MK, Sung FC, "Diet, vegetarian food and prostate carcinoma among men in Taiwan," *Br. J. Cancer* (2005) 93(9):1057-1061; Gallus S, Foschi R, Talamini R, Altieri A, Negri E, Franceschi S, Montella M, Dal Maso L, Ramazzotti V, La Vecchia C, "Risk factors for prostate cancer in men aged less than 60 years: a case-control study from Italy," *Urology* (2007) 70(6):1121-1126; De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Acosta G, "Alcohol Drinking, Non-alcoholic Beverages and Risk of Advanced Prostate Cancer among Uruguayan Men," *J. Cancer Sci. Ther.* (2011) S1.

The most recent study reported no association between coffee consumption total prostate cancer, but a significantly decreased risk for "high grade" prostate cancer and an increased risk for the more common low grade prostate cancer. Total anti-oxidant intake was not associated with prostate cancer. Russnes KM, Möller E, Wilson KM, Carlsen M, Blomhoff R, Smeland S, Adami HO, Grönberg H, Mucci LA, Bälter K, "Total antioxidant intake and prostate cancer in the Cancer of the Prostate in Sweden (CAPS) study. A case control study," *BMC Cancer* (2016) 16:438.

b. Cohort Studies

At least 15 cohort studies regarding coffee consumption and prostate cancer have been published. These studies report both increased and decreased risks of prostate cancer, with the more recent studies report decreased risks of prostate cancer that are statistically significant in two recent studies. The most recent cohort study is of the EPIC cohort, which reported risks slightly above unity for three consumption categories. [See Report of Dr. Peter Infante for the Phase 2 trial in the *CERT v. Starbucks* case].

c. Meta-Analyses

Ten meta-analyses regarding coffee consumption and prostate cancer have been published.

The earliest meta-analysis, published in 2010, based on 8 case-control studies and 4 cohort studies, reported a significantly increased risk of prostate cancer comparing highest to lowest consumption (RR 1.16, 95% CI 1.01 - 1.33). The increased risk was greater in the analysis based on the case-control studies (RR 1.21, 95% CI 1.03 - 1.43) than the analysis based on the cohort studies (RR 1.06, 95% CI 0.83 - 1.35). Park CH, Myung SK, Kim TY, Seo HG, Jeon YJ, Kim Y; Korean Meta-Analysis (KORMA) Study Group, "Coffee consumption and risk of prostate cancer: a meta-analysis of epidemiological studies," *BJU Int.* (2010) 106(6):762-769.

Several subsequent meta-analyses reported decreased risks of prostate cancer. Yu X, Bao Z, Zou J, Dong J, "Coffee consumption and risk of cancers: a meta-analysis of cohort studies," *BMC Cancer* (2011) 11:96; Discacciati A, Orsini N, Wolk A, "Coffee consumption and risk of nonaggressive, aggressive and fatal prostate cancer--a dose-response meta-analysis," *Ann. Oncol.* (2014) 25(3):584-591; Cao S, Liu L, Yin X, Wang Y, Liu J, Lu Z, "Coffee consumption and risk of prostate cancer: a meta-analysis of prospective cohort studies," *Carcinogenesis.* (2014) 35(2):256-261; Lu Y, Zhai L, Zeng J, Peng Q, Wang J, Deng Y, Xie L, Mo C, Yang S, Li S, Qin X, "Coffee

consumption and prostate cancer risk: an updated meta-analysis," *Cancer Causes Control* (2014) 25(5):591-604; Huang TB, Guo ZF, Zhang XL, Zhang XP, Liu H, Geng J, Yao XD, Zheng JH, "Coffee consumption and urologic cancer risk: a meta-analysis of cohort studies," *Int. Urol Nephrol.* (2014) 46(8):1481-1493. Liu H, Hu GH, Wang XC, Huang TB, Xu L, Lai P, Guo ZF, Xu YF, "Coffee consumption and prostate cancer risk: a meta-analysis of cohort studies," *Nutr Cancer* (2015) 67(3):392-400; Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and cancer risk: A meta-analysis of prospective observational studies," *Sci. Rep.* (2016) 6:33711.

A meta-analysis published in 2014, based on 12 case-control studies and 12 cohort studies reported a nonsignificant decrease in risk comparing highest and non-lowest consumption for all studies (RR 0.94, 95% CI 0.85 - 1.05), but a statistically significant increased risk for the hospital-based case-control studies (RR 1.29, 95% CI 1.01 - 1.65). Zhong S, Chen W, Yu X, Chen Z, Hu Q, Zhao J, "Coffee consumption and risk of prostate cancer: an up-to-date meta-analysis," *Eur. J. Clin. Nutr.* (2014) 68(3):330-337.

The most recent meta-analyses, based on 14 cohort and 14 case-control studies, reported a nonsignificantly increased risk of prostate cancer for high versus non/lowest consumption (RR 1.07, 95% C: 0.96-1.18). In subgroup meta-analysis by study design, risk of prostate cancer was significantly increased in the case-control studies (RR 1.19, 95% CI 1.05-1.35) but not in the cohort studies (RR 0.97, 95% CI 0.84-1.12). Xia J, Chen J, Xue JX, Yang J, Wang ZJ, "An Up-to-date Meta-analysis of Coffee Consumption and Risk of Prostate Cancer," *Urol. J.* (2017) 14(5):4079-4088.

2. Negative Confounders

The IARC Monograph does not mention that meta-analyses have reported significantly decreased risks of prostate cancer in association with multiple factors other than consumption of

coffee, including medical conditions (Type 2 diabetes, Parkinson's disease, Schizophrenia, and spinal cord injury) medications (aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), beta-blockers, and metformin), physical activity, dietary factors (Mediterranean diet, fruits and vegetables, lycopene and tomatoes, phytoestrogens, fish and omega-3 fatty acids, soy and soy flavones, tea (especially green tea), wine (moderate consumption) certain vitamin precursors (α-carotene and α-tocopherol), and selenium.

a. Medical Conditions

Several medical conditions, including Type 2 diabetes, Parkinson's disease, Schizophrenia, and spinal cord injury, have been reported to decrease the risk of prostate cancer in meta-analyses of observational epidemiological studies:.

(1). Type 2 Diabetes

Several meta-analyses have reported that Type 2 diabetes substantially decreases the risk of prostate cancer. Bonovas S, Filioussi K, Sitaras NM, "Statin use and the risk of prostate cancer: A metaanalysis of 6 randomized clinical trials and 13 observational studies," *Int. J. Cancer* (2008) 123(4):899-904; Kasper JS, Giovannucci E, "A meta-analysis of diabetes mellitus and the risk of prostate cancer," *Cancer Epidemiol. Biomarkers Prev.* (2006) 15(11):2056-2062; Bansal D, Bhansali A, Kapil G, Undela K, Tiwari P, "Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies," *Prostate Cancer Prostatic Dis.* (2013) 16(2):151-158; Zhang F, Yang Y, Skrip L, Hu D, Wang Y, Wong C, Qiu J, Lei H, "Diabetes mellitus and risk of prostate cancer: an updated meta-analysis based on 12 case-control and 25 cohort studies," *Acta Diabetol.* (2012) 49 Suppl 1:S235-S246; Xu H, Mao SH, Ding GX, Ding Q, Jiang HW, "Diabetes Mellitus Reduces Prostate Cancer Risk - No Function of Age at Diagnosis or Duration of Disease," *Asian Pac. J.*

Cancer Prev. (2013) 14(1):441-447; Jian Gang P, Mo L, Lu Y, Runqi L, Xing Z, "Diabetes mellitus and the risk of prostate cancer: an update and cumulative meta-analysis," *Endocr. Res.* (2015) 40(1):54-61; Jayedi A, Djafarian K, Rezagholizadeh F, Mirzababaei A, Hajimohammadi M, Shab-Bidar S, "Fasting blood glucose and risk of prostate cancer: A systematic review and meta-analysis of dose-response," *Diabetes Metab.* (October 23, 2017) pii: S1262-3636(17)30516-5.

(2). Parkinson's Disease

One meta-analysis has reported a decreased risk of prostate cancer associated with Parkinson's Disease. Chen C, Zheng H, Hu Z, "Association between Parkinson's disease and risk of prostate cancer in different populations: An updated meta-analysis," *Sci. Rep.* (2017) 7(1):13449.

(3). Schizophrenia

One meta-analysis has reported that schizophrenia reduces the risk of prostate cancer. Li H, Li J, Yu X, Zheng H, Sun X, Lu Y, Zhang Y, Li C, Bi X, "The incidence rate of cancer in patients with schizophrenia: A meta-analysis of cohort studies," *Schizophr. Res.* (2018) 195:519-528.

(4). Spinal cord injury

One meta-analysis has reported a decreased risk of prostate cancer with spinal cord injury. Barbonetti A, D'Andrea S, Martorella A, Felzani G, Francavilla S, Francavilla F, "Risk of prostate cancer in men with spinal cord injury: A systematic review and meta-analysis," *Asian J. Androl.* (June 26, 2018) doi: 10.4103/aja.aja_31_18. [Epub ahead of print]

b. Medications

(1). Statins and Non-Steroidal Anti-Inflammatory Drugs

Meta-analyses have consistently reported that the use of statins and non-steroidal anti-inflammatory drugs, especially aspirin, significantly reduce the risk of prostate cancer. Mahmud S, Franco E, Aprikian A, "Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis," *Br. J. Cancer* (2004) 90(1):93-99; Jafari S, Etminan M, Afshar K, "Nonsteroidal anti-inflammatory drugs and prostate cancer: a systematic review of the literature and meta-analysis," *Can. Urol. Assoc. J.* (2009) 3(4):323-330; Mahmud SM, Franco EL, Aprikian AG, "Use of nonsteroidal anti-inflammatory drugs and prostate cancer risk: a meta-analysis," *Int. J. Cancer.* (2010) 127(7):1680-1691; Bansal D, Undela K, D'Cruz S, Schifano F, "Statin use and risk of prostate cancer: a meta-analysis of observational studies," *PLoS One* (2012) 7(10):e46691; Liu Y, Chen JQ, Xie L, Wang J, Li T, He Y, Gao Y, Qin X, Li S, "Effect of aspirin and other non-steroidal anti-inflammatory drugs on prostate cancer incidence and mortality: a systematic review and meta-analysis," *BMC Med.* (2014) 12:55; Huang TB, Yan Y, Guo ZF, Zhang XL, Liu H, Geng J, Yao XD, Zheng JH, "Aspirin use and the risk of prostate cancer: a meta-analysis of 24 epidemiologic studies," *Int. Urol. Nephrol.* (2014) 46(9):1715-1728; Wang X, Lin YW, Wu J, Zhu Y, Xu XL, Xu X, Liang Z, Hu ZH, Li SQ, Zheng XY, Xie LP, "Meta-analysis of nonsteroidal anti-inflammatory drug intake and prostate cancer risk," *World J. Surg. Oncol.* (2014) 12:304; Vidal AC, Howard LE, Moreira DM, Castro-Santamaria R, Andriole GL, Freedland SJ, "Aspirin, NSAIDs, and risk of prostate cancer: results from the REDUCE study," *Clin. Cancer Res.* (2015) 21(4):756-762; Meng Y, Liao YB, Xu P, Wei WR, Wang J, "Statin use and mortality of patients with prostate cancer: a meta-analysis," *Onco Targets Ther.* (2016) 9:1689-1696; Tan P, Wei S, Tang Z, Gao L, Zhang C, Nie P, Yang L, Wei Q, "LDL-lowering therapy and the risk of prostate cancer: a meta-analysis of 6 randomized controlled trials and 36 observational studies," *Sci. Rep.* (2016) 6:24521;

Tan P, Wei S, Yang L, Tang Z, Cao D, Liu L, Lei J, Fan Y, Gao L, Wei Q, "The effect of statins on prostate cancer recurrence and mortality after definitive therapy: a systematic review and meta-analysis," *Sci. Rep.* (2016) 6:29106; Zhou CK, Daugherty SE, Liao LM, Freedman ND, Abnet CC, Pfeiffer R, Cook MB, "Do Aspirin and Other NSAIDs Confer a Survival Benefit in Men Diagnosed with Prostate Cancer? A Pooled Analysis of NIH-AARP and PLCO Cohorts," *Cancer Prev. Res.* (2017) 10(7):410-420; Qiao Y, Yang T, Gan Y, Li W, Wang C, Gong Y, Lu Z, "Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies," *BMC Cancer* (2018) 18(1):288.

(2). Beta-Blockers

One meta-analysis has reported a decreased risk of prostate cancer with use of beta blockers. Lu H, Liu X, Guo F, Tan S, Wang G, Liu H, Wang J, He X, Mo Y, Shi B, "Impact of beta-blockers on prostate cancer mortality: a meta-analysis of 16,825 patients, *Onco Targets Ther.* (2015) 8:985-990.

(3). Metformin

A few meta-analyses have reported decreased risks of prostate cancer in association with metformin use. Yu H, Yin L, Jiang X, Sun X, Wu J, Tian H, Gao X, He X, "Effect of metformin on cancer risk and treatment outcome of prostate cancer: a meta-analysis of epidemiological observational studies," *PLoS One.* (2014) 9(12):e116327; Hwang IC, Park SM, Shin D, Ahn HY, Rieken M, Shariat SF, "Metformin association with lower prostate cancer recurrence in type 2 diabetes: a systematic review and meta-analysis," *Asian Pac. J. Cancer Prev.* (2015) 16(2):595-600. Deng D, Yang Y, Tang X, Skrip L, Qiu J, Wang Y, Zhang F, "Association between metformin

therapy and incidence, recurrence and mortality of prostate cancer: evidence from a meta-analysis," *Diabetes Metab. Res. Rev.* (2015) 31(6):595-602

c. Physical Activity

Meta-analyses have reported decreased risks of prostate cancer with physical activity. Liu Y, Hu F, Li D, Wang F, Zhu L, Chen W, Ge J, An R, Zhao Y, "Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis," *Eur. Urol.* (2011) 60(5):1029-1044; Shephard RJ, "Physical Activity and Prostate Cancer: An Updated Review," *Sports Med.* (2017) 47(6):1055-1073; Kruk J, Aboul-Enein H, "What Are the Links of Prostate Cancer with Physical Activity and Nutrition? : A Systematic Review Article," *Iran J. Public Health.* (2016) 45(12):1558-1567; Benke IN, Leitzmann MF, Behrens G, Schmid D, "Physical activity in relation to risk of prostate cancer: a systematic review and meta-analysis," *Ann. Oncol.* (2018) 29(5):1154-1179.

d. Dietary Factors

Several dietary factors have been reported to reduce prostate cancer risk in meta-analyses.

(1). Mediterranean Diet

Several meta-analyses have reported that the Mediterranean diet reduces the risk of prostate cancer. Schwingshackl L, Hoffmann G, "Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies," *Int. J. Cancer* (2014) 135(8):1884-1897; Schwingshackl L, Hoffmann G. "Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies," *Cancer Med.* (2015) 4(12):1933-1947; Capurso C, Vendemiale G, "The Mediterranean Diet Reduces the Risk and

Mortality of the Prostate Cancer: A Narrative Review," *Front. Nutr.* (2017) 4:38; Schwingshackl L, Schwedhelm C, Galbete C, Hoffmann G, "Adherence to Mediterranean Diet and Risk of Cancer: An Updated Systematic Review and Meta-Analysis," *Nutrients* (Sept. 26, 2017) 9(10). pii: E1063.

(2). Fruits and Vegetables

Several meta-analyses have reported significantly reduced risks of prostate cancer in association with consumption of fruits and, especially, of vegetables. Liu B, Mao Q, Cao M, Xie L,"Cruciferous vegetables intake and risk of prostate cancer: a meta-analysis," *Int. J. Urol.* (2012) 19(2):134-141; Zhou XF, Ding ZS, Liu NB, "Allium vegetables and risk of prostate cancer: evidence from 132,192 subjects," *Asian Pac. J. Cancer Prev.* (2013) 14(7):4131-4134; Xu X, Cheng Y, Li S, Zhu Y, Xu X, Zheng X, Mao Q, Xie L, "Dietary carrot consumption and the risk of prostate cancer," *Eur. J. Nutr.* (2014) 53(8):1615-1623; Li J, Mao QQ, "Legume intake and risk of prostate cancer: a meta-analysis of prospective cohort studies," *Oncotarget* (2017) 8(27):44776-44784

(3). Lycopene and Tomatoes

Lycopene and consumption of tomatoes has been strongly associated with decreased risks of prostate cancer in several meta-analyses. Etminan M, Takkouche B, Caamaño-Isorna F, "The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies," *Cancer Epidemiol. Biomarkers Prev.* (2004) 13(3):340-345; Chen J, Song Y, Zhang L, "Lycopene/tomato consumption and the risk of prostate cancer: a systematic review and meta-analysis of prospective studies," *J. Nutr. Sci. Vitaminol.* (2013) 59(3):213-223; Chen P, Zhang W, Wang X, Zhao K, Negi DS, Zhuo L, Qi M, Wang X, Zhang X, "Lycopene and Risk of Prostate Cancer: A Systematic Review and Meta-Analysis," *Medicine* (2015) 94(33):e1260; Xu X, Li J, Wang X, Wang S, Meng S, Zhu Y, Liang Z, Zheng X, Xie L, "Tomato consumption and prostate

cancer risk: a systematic review and meta-analysis," *Sci. Rep.* (2016) 6:37091; Rowles JL 3rd, Ranard KM, Smith JW, An R, Erdman JW Jr, "Increased dietary and circulating lycopene are associated with reduced prostate cancer risk: a systematic review and meta-analysis," *Prostate Cancer Prostatic Dis.* (2017) 20(4):361-377; Rowles JL 3rd, Ranard KM, Applegate CC, Jeon S, An R, Erdman JW Jr., "Processed and raw tomato consumption and risk of prostate cancer: a systematic review and dose-response meta-analysis," *Prostate Cancer Prostatic Dis.* (January 9, 2018) doi: 10.1038/s41391-017-0005-x. [Epub ahead of print]; Cataño JG, Trujillo CG, Caicedo JI, Bravo-Balado A, Robledo D, Mariño-Alvarez AM, Pedraza A, Arcila MJ, Plata M, "[Efficacy of lycopene intake in primary prevention of prostate cancer: a systematic review of the literature and meta-analysis]," *Arch. Esp. Urol.* (2018) 71(2):187-197.

(4). Phytoestrogens

Two meta-analyses report that phytoestrogens reduce the risk of prostate cancer. He J, Wang S, Zhou M, Yu W, Zhang Y, He X, "Phytoestrogens and risk of prostate cancer: a meta-analysis of observational studies," *World J. Surg. Oncol.* (2015) 13:231; Zhang Q, Feng H, Qluwakemi B, Wang J, Yao S, Cheng G, Xu H, Qiu H, Zhu L, Yuan M, "Phytoestrogens and risk of prostate cancer: an updated meta-analysis of epidemiologic studies," *Int. J. Food Sci. Nutr.* (2017) 68(1):28-42

(5). Fish and Omega-3 Fatty Acids

Several meta-analyses have reported decreased risks of prostate cancer with consumption of fish and omega-3 fatty acids. Szymanski KM, Wheeler DC, Mucci LA, "Fish consumption and prostate cancer risk: a review and meta-analysis," *Am. J. Clin. Nutr.* (2010) 92(5):1223-1233; Carayol M, Grosclaude P, Delpierre C, "Prospective studies of dietary alpha-linolenic acid intake and prostate cancer risk: a meta-analysis," *Cancer Causes Control.* (2010) 21(3):347-355; Chua

ME, Sio MC, Sorongon MC, Dy JS, "Relationship of dietary intake of omega-3 and omega-6 Fatty acids with risk of prostate cancer development: a meta-analysis of prospective studies and review of literature," *Prostate Cancer* (2012) 2012:826254; Chua ME, Sio MC, Sorongon MC, Morales ML Jr., "The relevance of serum levels of long chain omega-3 polyunsaturated fatty acids and prostate cancer risk: A meta-analysis," *Can. Urol. Assoc. J.* (2013) 7(5-6):E333-E343; Crowe FL, Appleby PN, Travis RC, Barnett M, Brasky TM, Bueno-de-Mesquita HB, Chajes V, Chavarro JE, Chirlaque MD, English DR, Gibson RA, Giles GG, Goodman GE, Henning SM, Kaaks R, King IB, Kolonel LN, Kristal AR, Neuhouser ML, Park SY, Severi G, Siddiq A, Stampfer MJ, Stattin P, Tangen CM, Tjønneland A, Trichopoulos D, Tumino R, Wilkens LR, Key TJ, Allen NE; Endogenous Hormones, Nutritional Biomarkers and Prostate Cancer Collaborative Group, "Circulating fatty acids and prostate cancer risk: individual participant meta-analysis of prospective studies," *J. Natl. Cancer Inst.* (September 10, 2014) 106(9). pii: dju240; Fu YQ, Zheng JS, Yang B, Li D, "Effect of individual omega-3 fatty acids on the risk of prostate cancer: a systematic review and dose-response meta-analysis of prospective cohort studies," *J. Epidemiol.* (2015) 25(4):261-274.

(6). Soy and Soy Isoflavones

Several meta-analyses have reported decreased prostate cancer risk from soy and soy isoflavones. Yan L, Spitznagel EL, "Meta-analysis of soy food and risk of prostate cancer in men," *Int. J. Cancer* (2005) 117(4):667-669; Yan L, Spitznagel EL, "Soy consumption and prostate cancer risk in men: a revisit of a meta-analysis," *Am. J. Clin. Nutr.* (2009) 89(4):1155-1163; Hwang YW, Kim SY, Jee SH, Kim YN, Nam CM, "Soy food consumption and risk of prostate cancer: a meta-analysis of observational studies," *Nutr Cancer* (2009) 61(5):598-606; van Die MD, Bone KM, Williams SG, Pirotta MV, "Soy and soy isoflavones in prostate cancer: a systematic review and meta-analysis of randomized controlled trials," *BJU Int.* (2014) 113(5b):E119-130; Applegate CC,

Rowles JL, Ranard KM, Jeon S, Erdman JW, "Soy Consumption and the Risk of Prostate Cancer: An Updated Systematic Review and Meta-Analysis," *Nutrients* (2018) 10(1). pii: E40.

(7). Tea and Green Tea

Meta-analyses have reported decreased risks of prostate cancer with consumption of tea, especially green tea. Zheng J, Yang B, Huang T, Yu Y, Yang J, Li D, "Green tea and black tea consumption and prostate cancer risk: an exploratory meta-analysis of observational studies," *Nutr. Cancer* (2011) 63(5):663-672; Lin YW, Hu ZH, Wang X, Mao QQ, Qin J, Zheng XY, Xie LP, "Tea consumption and prostate cancer: an updated meta-analysis," *World J. Surg. Oncol.* (2014) 12:38; Fei X, Shen Y, Li X, Guo H, "The association of tea consumption and the risk and progression of prostate cancer: a meta-analysis," *Int. J. Clin. Exp. Med.* (2014) 7(11):3881-3891; Guo Y, Zhi F, Chen P, Zhao K, Xiang H, Mao Q, Wang X, Zhang X, "Green tea and the risk of prostate cancer: A systematic review and meta-analysis," *Medicine* (2017) 96(13):e6426

(8). Wine

One meta-analyses observed a decreased risk of prostate cancer with moderate consumption of wine. Vartolomei MD, Kimura S, Ferro M, Foerster B, Abufaraj M, Briganti A, Karakiewicz PI, Shariat SF, "The impact of moderate wine consumption on the risk of developing prostate cancer," *Clin. Epidemiol.* (2018) 10:431-444.

e. Vitamins and Vitamin Precursors

Meta-analyses have reported decreased risks of prostate cancer with intake of Vitamin C (Bai XY, Qu X, Jiang X, Xu Z, Yang Y, Su Q, Wang M, Wu H, "Association between Dietary

Vitamin C Intake and Risk of Prostate Cancer: A Meta-analysis Involving 103,658 Subjects," *J. Cancer* (2015) 6(9):913-921) and Vitamin E (Alkhenizan A, Hafez K, "The role of vitamin E in the prevention of cancer: a meta-analysis of randomized controlled trials," *Ann. Saudi Med.* (2007) 27(6):409-414; Major JM, Yu K, Weinstein SJ, Berndt SI, Hyland PL, Yeager M, Chanock S, Albanes D, "Genetic variants reflecting higher vitamin e status in men are associated with reduced risk of prostate cancer," *J. Nutr.* (2014) 144(5):729-733

Meta-analyses have noted decreased risks of prostate cancer with vitamin precursors. Wang Y, Cui R, Xiao Y, Fang J, Xu Q, "Effect of Carotene and Lycopene on the Risk of Prostate Cancer: A Systematic Review and Dose-Response Meta-Analysis of Observational Studies," *PLoS One.* (2015) 10(9):e0137427; Cui R, Liu ZQ, Xu Q, "Blood α-tocopherol, γ-tocopherol levels and risk of prostate cancer: a meta-analysis of prospective studies," *PLoS One.* (2014) 9(3):e93044; Key TJ, Appleby PN, Travis RC, Albanes D, Alberg AJ, Barricarte A, Black A, Boeing H, Bueno-de-Mesquita HB, Chan JM, Chen C, Cook MB, Donovan JL, Galan P, Gilbert R, Giles GG, Giovannucci E, Goodman GE, Goodman PJ, Gunter MJ, Hamdy FC, Heliövaara M, Helzlsouer KJ, Henderson BE, Hercberg S, Hoffman-Bolton J, Hoover RN, Johansson M, Khaw KT, King IB, Knekt P, Kolonel LN, Le Marchand L, Männistö S, Martin RM, Meyer HE, Mondul AM, Moy KA, Neal DE, Neuhouser ML, Palli D, Platz EA, Pouchieu C, Rissanen H, Schenk JM, Severi G, Stampfer MJ, Tjønneland A, Touvier M, Trichopoulou A, Weinstein SJ, Ziegler RG, Zhou CK, Allen NE; Endogenous Hormones Nutritional Biomarkers Prostate Cancer Collaborative Group, "Carotenoids, retinol, tocopherols, and prostate cancer risk: pooled analysis of 15 studies," *Am. J. Clin. Nutr.* (2015) 102(5):1142-1157

f. Selenium

Several meta-analyses have reported decreased risks of prostate risk from selenium. Etminan M, FitzGerald JM, Gleave M, Chambers K, "Intake of selenium in the prevention of prostate cancer: a systematic review and meta-analysis," *Cancer Causes Control* (2005) 16(9):1125-1131; Hurst R, Hooper L, Norat T, Lau R, Aune D, Greenwood DC, Vieira R, Collings R, Harvey LJ, Sterne JA, Beynon R, Savović J, Fairweather-Tait SJ, "Selenium and prostate cancer: systematic review and meta-analysis," *Am. J. Clin. Nutr.* (2012) 96(1):111-122; Kim Y, Wei J, Citronberg J, Hartman T, Fedirko V, Goodman M, "Relation of Vitamin E and Selenium Exposure to Prostate Cancer Risk by Smoking Status: A Review and Meta-Analysis," *Anticancer Res.* (2015) 35(9):4983-4996; Cai X, Wang C, Yu W, Fan W, Wang S, Shen N, Wu P, Li X, Wang F, "Selenium Exposure and Cancer Risk: an Updated Meta-analysis and Meta-regression," *Sci. Rep.* (2016) 6:19213; Cui Z, Liu D, Liu C, Liu G, "Serum selenium levels and prostate cancer risk: A MOOSE-compliant meta-analysis," *Medicine* (2017) 96(5):e5944; Sayehmiri K, Azami M, Mohammadi Y, Soleymani A, Tardeh Z, "The association between Selenium and Prostate Cancer: a Systematic Review and Meta-Analysis," *Asian Pac. J. Cancer Prev.* (2018) 19(6):1431-1437.

g. Adiponectin

One meta-analyses reported a decreased risk of prostate cancer with adiponectin. Liao Q, Long C, Deng Z, Bi X, Hu J, "The role of circulating adiponectin in prostate cancer: a meta-analysis," *Int. J. Biol. Markers* (2015) 30(1):e22-31.

h. Urinary Estrogen.

One meta-analysis reported a decreased risk of prostate cancer with urinary estrogen metabolites. Barba M, Yang L, Schünemann HJ, Sperati F, Grioni S, Stranges S, Westerlind KC, Blandino G, Gallucci M, Lauria R, Malorni L, Muti P, "Urinary estrogen metabolites and prostate cancer: a case-control study and meta-analysis," *J. Exp. Clin. Cancer Res.* (2009) 28:135.

i. Reproductive Factors

Meta-analyses have reported decreased risks of prostate cancer in childless men (Mao Y, Xu X, Zheng X, Xie L, "Reduced risk of prostate cancer in childless men as compared to fathers: a systematic review and meta-analysis," *Sci. Rep.* (2016) 6:19210) and in association with circumcision. Pabalan N, Singian E, Jarjanazi H, Paganini-Hill A, "Association of male circumcision with risk of prostate cancer: a meta-analysis,"*Prostate Cancer Prostatic Dis.* (2015) 18(4):352-357; Li YD, Teng Y, Dai Y, Ding H, "The Association of Circumcision and Prostate Cancer: A Meta-Analysis," *Asian Pac. J. Cancer Prev.* (2016) 17(8):3823-3827.

j. Sun Exposure

One meta-analysis reported a reduced risk of prostate cancer with increased sun exposure. Gilbert R, Metcalfe C, Oliver SE, Whiteman DC, Bain C, Ness A, Donovan J, Hamdy F, Neal DE, Lane JA, Martin RM, "Life course sun exposure and risk of prostate cancer: population-based nested case-control study and meta-analysis," *Int. J. Cancer* (2009) 125(6):1414-1423

k. Conclusion

According to IARC, to find *evidence suggesting lack of carcinogenicity,* "bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up." However, nowhere in its discussion regarding coffee and prostate cancer does IARC indicate whether the Working Group was able to rule out bias and confounding with reasonable confidence. It does not appear that IARC considered confounding of the association between coffee consumption and prostate cancer by the numerous factors that have been reported to decrease the risk of prostate cancer in meta-analyses of observational studies.

The most important study regarding coffee consumption and prostate cancer is the Mendelian randomization study by researchers from Bristol and Seattle, who found a small significantly increased risk of nonlocalized prostate cancer compared to localized stage disease (OR 1.03, 95% CI 1.01 - 1.06). They concluded that their study did not support a causal role of coffee consumption in prostate cancer incidence and suggested that observational findings that coffee consumption is associated with reduced risk of prostate cancer may be due to confounding by other lifestyle factors. Taylor AE, et al.,"Investigating the possible causal role of coffee consumption with prostate cancer risk and progression using Mendelian randomization analysis," *Int. J. Cancer* (2017) 140(2):322-328. In light of this study which post-dates IARC's review, it cannot be concluded that the classification *evidence suggesting lack of carcinogenicity* is valid for the association between coffee consumption and prostate cancer.

IX. OEHHA'S CLAIM THAT ANTIOXIDANTS IN COFFEE PREVENT CANCER IS SCIENTIFICALLY UNSUBSTANTIATED AND UNFOUNDED AND LACKS RELEVANCE TO THE MECHANISM OF ACRYLAMIDE-INDUCED CANCER

A. The Spandidos Publications Article

In support of the proposed new regulation, OEHHA asserts that "coffee contains . . . numerous chemicals with biological activities associated with protective, anti-carcinogenic effects." (Page 7 of Initial Statement of Reasons). In support of this assertion, OEHHA cites but a single aticle: Priftis A, Stagos D, Konstantinopoulos K, Tsitsimpikou C, Spandidos DA, Tsatsakis AM, Tzatzarakis MN, Kouretas D, "Comparison of antioxidant activity between green and roasted coffee beans using molecular methods," *Mol. Med. Rep.* (2015) 12:7293-7302. This is an obscure article published in an obscure journal. According to the website for this journal, *Molecular Medicine Reports* it is one of several "Spandidos publications," i.e. journals owned by the Spandidos family in Greece. The Editor in Chief of this journal is Demetrios A. Spandidos, who, perhaps not so coincidentally, is one of the authors of the article. The Deputy Editors of the journal are Athanasia Spandidos and Nikiforos A. Spandidos. Since the editors of the journal are comprised of one of the authors of the article and members of his family, it is questionable whether the article was properly peer-reviewed by disinterested scientists. The journal has an impact factor of 1.617, which is at the lower end of the spectrum. (The *New England Journal of Medicine* has an impact factor of 72.406).

As mentioned above, OEHHA cites the Priftis article for the proposition that "coffee contains . . . numerous chemicals with biological activities associated with protective, anti-carcinogenic effects." However, no such statement appears in the article. Indeed, the word "anticarcinogenic" does not appear in the article, except in the Acknowledgment section at the end of the article which states: "The present study was funded by a grant (no. 5042; 'Assessment of antioxidant and anticarcinogenic activity of green and roasted coffee varieties') awarded to Professor D. Kouretas."

It is noteworthy that although the research grant was for the assessment of "anticarcinogenic activity" of coffee, the authors chose not to use the word "anticarcinogenic" in their article. Since the word "anticarcinogenic" doesn't even appear in the text of the article, OEHHA's assertion that the article establishes that "coffee contains . . . numerous chemicals with biological activities associated with . . . anti-carcinogenic effects" is plainly not a conclusion of the article.

OEHHA's conclusion that carcinogens formed in the process of roasting coffee beans pose no significant risk of cancer appears to be premised, at least in part, on the notion that roasting coffee beans produces antioxidants that may confer health benefits. However, in the Priftis study, in 5 out of 13 varieties of coffee tests, roasting reduced the antioxidant activity.

Since the Priftis article does not mention any anticarcinogenic effects let alone attribute any such effects to coffee, and since it is the only article that OEHHA cites in support of its assertion that "coffee contains . . . numerous chemicals with biological activities associated with . . . anti-carcinogenic effects," OEHHA's conclusion that antioxidants in coffee are anticarcinogenic, i.e., prevent cancer, is unsupported. No study has demonstrated a causal reduction in the incidence of human cancer from any single antioxidant chemical or any combination of antioxidant chemicals in coffee. In fact, the hypothesis that dietary antioxidants prevent human cancer is at best controversial, and to date remains untested and unsubstantiated.

B. Studies Questioning the Antioxidant-Cancer Prevention Hypothesis

Numerous scientific articles have questioned the hypothesis that antioxidants, including polyphenols and other dietary antioxidants, prevent human cancer. See, e.g., Zhao CN, Li Y, Meng X, Li S, Liu Q, Tang G-Y, Gan R-Y, Li H-B," "Insight into the roles of vitamins C and D against cancer: Myth or truth? *Cancer Lett.* (2018) 431:151-170; Azzi A, "Antioxidants: Wonder drugs or quackery?" *Biofactors* (2017) 43(6):785-788; Sauer S, Plauth A, "Health-beneficial nutraceuticals – myth or reality?" *Appl. Microbiol. Biotechnol.* (2017) 101(3):951-961; Kaisar, MA, Cucullo L,

"OTC Antioxidant Products for the Treatment of Cardiovascular and other Disorders: Popular Myth or Fact?" *Pharmacovigil.* (2015) 3(2): pii: e136; Potter JD, "The failure of cancer chemoprevention," *Carcinogenesis* (2014) 35:974-982; Teixeira MC, Braghiroli MI, Sabbaga J, Hoff PM, "Primary prevention of colorectal cancer: Myth or reality?" *World J Gastroenterol.* (2014) 20(41):15060–15069; Bast A, Haenen GRMM, "Ten misconceptions about antioxidants," *Trends Pharmacolog. Sci.* (2013) 34(8):430-436; Moyer MW, "The Myth of Antioxidants," *Sci. Am.* (2013) February: 64-67; Berger RG, Lunkenbein S, Ströhle A, Hahn A, "Antioxidants in Food: Mere Myth or Magic Medicine?" *Crit. Rev. Food Sci. Nutr.* (2012) 52(2):162-171; Ricciardiello L, Bazzoli F, Fogliano V, "Phytochemicals and colorectal cancer prevention—myth or reality? *Nature Rev. Gastroenterol. Hepatol.* (2011) 8:592-596; Serafini M, "Rise and falls of dietary antioxidants for disease prevention: Magic bullets, false myth or scarce knowledge?" *Eur. J. Pharmacol.* (2011) 668(Suppl.1):e5; Talaulikar VS, Manyonda IT, "Vitamin C as an antioxidant supplement in women's health: a myth in need of urgent burial," *Eur. J. Obstetr. Gynecol. Reprod. Biol.* (2011) 157(1):10-13; Gutteridge JMC, Halliwell B, "Antioxidants: Molecules, medicines, and myths," *Biochem. Biophys. Res. Comm.* (2010) 393:561–564; Haidara MA, Yassin HZ, Zakula Z, Mikhailidis DP, Isenovic ER, "Diabetes and Antioxidants: Myth or Reality?" *Current Vascular Pharmacol.* (2010) 8:611-672; Rodriguez O, "Is Soy Safe? Busting the Myths of a Nutritional Powerhouse *Life Ext. Mag.* (July 2010); Vanden Berghe W, Haegeman G, "Epigenetic Remedies by Dietary Phyto-chemicals Against Inflammatory Skin Disorders: Myth or Reality?" *Curr. Drug Metabol.* (2010) 11(5):436-450; Wu PA, Stern RS, "Topical Tretinoin, Another Failure in the Pursuit of Practical Chemoprevention for Non-Melanoma Skin Cancer," *J. Invest. Dermatol.* (2012) 132:1532-1535; Espin JC, Garcia-Conesa MT, Tomás-Barberán FA, "Nutraceuticals: facts and fiction," *Phytochemistry* (2007) 68(22-24):2986-3008; Melton L, "The antioxidant myth: a medical fairy tale," *New Scientist* (Aug. 5, 2006); Núñez-Sellés AJ, "Antioxidant Therapy: Myth or Reality?" *J. Braz. Chem. Soc.* (2005) 16(4): 699-710; Mann JR, DuBois RN, "Cancer chemoprevention: myth or reality?" *Drug Discovery Today: Therap. Strategies* (2004) 1(4):403-409; Gescher AJ, Sharma

RA, Steward WP, "Cancer chemoprevention by dietary constituents: a tale of failure and promise," *Lancet Oncol.* (2001) 2(6):371-379; Löw-Baselli A, Huber WW, Käfer M, Bukowska K, Schulte-Hermann R, Grasl-Kraupp B, "Failure to demonstrate chemoprevention by the monoterpene perillyl alcohol during early rat hepatocarcinogenesis: a cautionary note," *Carcinogenesis* (2000) 21(10):1869-1877; Herbert V, "The antioxidant supplement myth," (1994) *Am. J. Clin. Nutr.* 60(2):157-158; Bright-See E "Diet and Cancer Prevention: Separating Fact from Myth," *Can. Fam. Physician* (1985) 31:1293–1296.

C. Meta-Analyses of Randomized Controlled Trials of Antioxidants and Cancer Do Not Show Reduced Risk; They Show Increased Cancer Risk

Several meta-analyses of randomized controlled trials studies have evaluated associations between antioxidant intake and human cancers. These studies do not report reduced risks of cancer from increased antioxidant intake, but rather report possible increased risks of cancer from antioxidant intake. See, e.g., Moradi-Joo M, Heidari S, Seyed-Nezhad M, Akbari ME, Moosavi A, Davoodi SH, "Antioxidant Supplements and breast Cancer: A Systematic Review and Meta-Analysis," *Int. J. Cancer Manag.* (2018) 11(4):e10082 ["The current meta-analysis of randomized controlled trials suggests that there is no clinical evidence to support the efficacy of vitamin and antioxidant supplements in reducing the risk or preventive effect of breast cancer."]; Park SJ, Myung SK, Lee Y, Lee YJ, "Effects of Vitamin and Antioxidant Supplements in Prevention of Bladder Cancer: a Meta-Analysis of Randomized Controlled Trials," *J. Korean Med. Sci.* (2017) 32:628-635 ["The current meta-analysis found that vitamin and antioxidant supplements have no preventive effect against bladder cancer. . . . Instead, subgroup meta-analyses showed that beta-carotene supplementation marginally increased the risk of bladder cancer."]; Pais R, Dumitraşcu DL, "Do antioxidants prevent colorectal cancer? A meta-analysis," *Rom. J. Intern. Med.* (2013) 51(3-4):152-163 ["This meta-analysis found no evidence in favor of a protective effect of the studied antioxidant supplements in the prevention of colorectal cancer or cancer related mortality."]; Myung SK, Yang

HJ, "Efficacy of Vitamin and Antioxidant Supplements in Prevention of Esophageal Cancer: Meta-analysis of Randomized Controlled Trials," *J. Cancer Prev.* (2013) 18(2):135-143 ["Unlike observational epidemiological studies, this meta-analysis of RCTs suggests that there is no clinical evidence to support the efficacy of vitamin and antioxidant supplements in the prevention of esophageal cancer."]; Papaioannou D, Cooper KL, Carroll C, Hind D, Squires H, Tappenden P, Logan RF, "Antioxidants in the chemoprevention of colorectal cancer and colorectal adenomas in the general population: a systematic review and meta-analysis," *Colorectal Dis.* (2011) 13(10):1085-1099 ["The review demonstrates that antioxidants (vitamin A, C and E, selenium and β-carotene), as single agents, in combination with other antioxidants or in combination with other agents, are not effective in the chemoprevention of colorectal neoplasia in the general population."]; Chang YJ, Myung SK, Chung ST, Kim Y, Lee EH, Jeon YJ, Park CH, Seo HG, Huh BY, "Effects of vitamin treatment or supplements with purported antioxidant properties on skin cancer prevention: a meta-analysis of randomized controlled trials," *Dermatology* (2011) 223(1):36-44 ["The current meta-analysis of RCTs indicated that there is no clinical evidence to support an overall primary and secondary preventive effect of vitamin treatment or supplements with purported antioxidant properties on skin cancer."]; Myung SK, Kim Y, Ju W, Choi HJ, Bae WK, "Effects of antioxidant supplements on cancer prevention: meta-analysis of randomized controlled trials," *Ann. Oncol.* (2010) 21:166-179 ["The meta-analysis of randomized controlled trials indicated that there is no clinical evidence to support an overall primary and secondary preventive effect of antioxidant supplements on cancer. The effects of antioxidant supplements on human health, particularly in relation to cancer, should not be overemphasized because the use of those might be harmful for some cancer."]; Jiang L, Yang KH, Tian JH, Guan QL, Yao N, Cao N, Mi DH, Wu J, Ma B, Yang SH, "Efficacy of antioxidant vitamins and selenium supplement in prostate cancer prevention: a meta-analysis of randomized controlled trials," *Nutr. Cancer* (2010) 62(6):719-727 ["Our findings indicate that antioxidant vitamins and selenium supplement did not reduce the incidence and mortality of prostate cancer; these data provide no support for the use of these supplements for the prevention

of prostate cancer."]; Bardia A, Tleyjeh IM, Cerhan JR, Sood AK, Limburg PJ, Erwin PJ, Montori VM, "Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis," *Mayo Clin. Proc.* (2008) 83(1):23-34 [B eta carotene supplementation appeared to increase cancer incidence and cancer mortality among smokers, whereas vitamin E supplemental had no effect."]; Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C, "Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases," *Cochrane Database Syst. Rev.* (2008) 2:CD007176; Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C, "Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention: Systematic Review and Meta-analysis," *J. Am. Med. Assn.* (2007) 297(8):842-857 ["Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study."]; Coulter ID, Hardy ML, Morton SC, Hilton LG, Tu W, Valentine D, Shekelle PG, "Antioxidants vitamin C and vitamin e for the prevention and treatment of cancer," *J. Gen. Intern. Med.* (2006) 21(7):735-744 ["The systematic review of the literature does not support the hypothesis that the use of supplements of vitamin C or vitamin E in the doses tested helps prevent and/or treat cancer in the populations tested."]; Bjelakovic G, Nagorni A, Nikolova D, Simonetti RG, Bjelakovic M, Gluud C, "Meta-analysis: antioxidant supplements for primary and secondary prevention of colorectal adenoma," *Aliment. Pharmacol. Ther.* (2006) 24:281-291 ["We found no convincing evidence that antioxidant supplements have significant beneficial effect on primary or secondary prevention of colorectal adenoma."]; Bjelakovic G, Nikolova D, Simonetti RG, Gluud C, "Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis," *Lancet* (2004) 364:1219-1228. ["We could not find evidence that antioxidant supplements can prevent gastrointestinal cancers; on the contrary, they seem to increase overall mortality."]

D. The Studies Regarding Antioxidant Effects of Coffee are Inconsistent

In its Initial Statement of Reasons, OEHHA cites human studies suggesting that antioxidants in coffee may confer potential health benefits. However, such studies do not measure cancer effects, but instead measure biochemical markers, which may be correlated with cancer, but do not reflect true cancer risk and often yield misleading information that results in erroneous conclusions. See. e..g., Grimes DA, Schulz KF, "Surrogate end points in clinical research: hazardous to your health," *Obstet. Gynecol.* (2005) 105(5 Pt 1):1114-1118; Schatzkin A, "Problems with using biomarkers as surrogate end points for cancer: a cautionary tale," *Recent Results Cancer Res.* (2005) 166:89-98; Cooper R, Kaanders JH, "Biological surrogate end-points in cancer trials: potential uses, benefits and pitfalls," *Eur. J. Cancer* (2005) 41(9):1261-1266; Holloway RG, Dick AW, "Clinical trial end points: on the road to nowhere?" *Neurology* (2002) 58(5):679-686; Schatzkin A, Gail M, "The promise and peril of surrogate end points in cancer research," *Nat. Rev. Cancer.* (2002) 2(1):19-27; Schatzkin A, Freedman LS, Dorgan J, McShane LM, Schiffman MH, Dawsey SM, "Surrogate End Points in Cancer Research: A Critique," *Cancer Epidemiol. Biomarkers Prev.* (1996) 5:947-953. See also Schatzkin A, Freedman LS, Dorgan J, McShane L, Schiffman MH, Dawsey SM, "Using and interpreting surrogate end-points in cancer research," *IARC Sci Publ.* (1997) 142:265-271.

The studies also do not consistently report reductions in markers of oxidative stress. Indeed, several of the studies regarding coffee consumption found no positive antioxidant effect at all.

In 2010, a controlled intervention trial with a cross-over design was conducted in which 38 participants consumed 800 ml coffee or water daily over 5 days. Several biochemical parameters of redox status were measured: malondialdehyde, 3-nitrotyrosine and total antioxidant levels in plasma, glutathione concentrations in blood, intracellular reactive oxygen species levels, and activities of superoxide dismutase and glutathione peroxidase in lymphocytes. None of these markers of oxidative stress were significantly changed, although oxidative DNA damage, as measured by the comet assay, was significantly decreased. Mišík M, Hoelzl C, Wagner KH, Cavin

C, Moser B, Kundi M, Simic T, Elbling L, Kager N, Ferk F, Ehrlich V, Nersesyan A, Dušinská M, Schilter B, Knasmüller S, "Impact of paper filtered coffee on oxidative DNA-damage: results of a clinical trial," *Mutat. Res.* (2010) 692(1-2):42-48.

In another study published in 2010, consumption of 800 mL of instant coffee enriched with chlorogenic acid did not significantly reduce DNA damage, as measured by the comet assay, but plasma 3-NT and urinary PGF2α were significantly decreased. Hoelzl C, Knasmüller S, Wagner KH, Elbling L, Huber W, Kager N, Ferk F, Ehrlish V, Nersesyan A Neubauer O, Desmarchelier A, Marin-Kuan M, Delatour T, Vergnet C, Bezençon C, Besson A, Grathwohl D, Simic T, Kundi M, Schilter B, Cavin C, "Instant coffee with high clorogenic acid levels protects humans against oxidative damage of macromolecules," *Mol. Nutr. Food Res.* (2010) 54(12):1722-1733.

In 2011, Thai researchers conducted a study to evaluate the short term effect of coffee drinking on energy utilization in men. Twenty-six healthy sedentary men were randomized into three groups (control, decaffeinated and caffeinated). After drinking coffee for 1 hour, they did an exercise test. Before and after the exercise test, complete blood count, glucose, antioxidant capacity, lipid peroxide and caffeine in blood were evaluated. The caffeine group showed significant changes in all parameters. Glucose and lipid peroxide levels significantly increased after exercise test, but antioxidant capacity did not change significantly after the exercise test. Leelarungrayub D, Sallepan M, Charoenwattana S, "Effects of acute caffeinated coffee consumption on energy utilization related to glucose and lipid oxidation from short submaximal treadmill exercise in sedentary men," *Nutr. Metab. Insights* (2011) 4:65-72.

In a 2012 clinical trial, on three different occasions, 16 men and women consumed a high-fat milk shake followed by either 16 ounces of caffeinated or decaffeinated coffee or bottled water. Blood samples were collected before and at 2 and 4 hours following intake and analyzed for triglycerides, malondialdehyde, hydrogen peroxide, and Trolox equivalent antioxidant capacity. The results showed that coffee had no impact on any of these markers of oxidative stress, which led the investigators to conclude that acute coffee consumption has no impact on postprandial oxidative

stress. Bloomer RJ, Trepanowski JF, Farney TM, "Influence of acute coffee consumption on postprandial oxidative stress," *Nutr. Metabol. Insights* (2013) 6:35-42.

A 2012 randomized cross-over study investigated antioxidant effects of single and multiple doses of coffee by consumption and by enema in 11 adult males. Blood samples were collected at specific time points for the determination of serum levels of glutathione, malondialdehyde, and trolox equivalent antioxidant capacity. The findings showed that single and multiple doses of orally consumed coffee or administrations of the coffee enema did not produce any beneficial effects to enhance serum glutathione levels or to decrease serum malondialdehyde levels. Serum trolox equivalent antioxidant capacity levels at days 5 and 12 after oral coffee consumption and at day 12 after the coffee enema were significantly reduced. The investigators concluded that the results showed no beneficial effects with respect to enhancement of serum glutathione or trolox equivalent antioxidant capacity levels or a decrease in serum malondialdehyde levels from orally consumed ready-to-drink coffee or coffee enema. Teekachunhatean S, Tosri N, Sangdee C, Wongpoomchai R, Ruangyuttikarn W, Puaninta C, Srichairatanakool S, ""Antioxidant effects after coffee enema or oral coffee consumption in healthy Thai male volunteers," *Hum. Exp. Toxicol.* (2012) 31(7):643-651.

In a study published in 2013, Japanese researchers evaluated the extent of oxidative stress in 9,877 subjects (mean age 59.2) who underwent medical screening, by measuring derivatives of reactive oxygen metabolites and biological antioxidant potential. By univariate analysis (ANOVA), coffee consumption showed a graded negative association with levels of reactive oxygen metabolites in men, but not in women. Notably, coffee consumption was not related to biological antioxidant potential in both men and women. Ishizaka Y, Yamakado M, Toda A, Tani M, Ishizaka N, "Relationship between coffee consumption, oxidant status, and antioxidant potential in the Japanese general population," *Clin. Chem. Lab. Med.* (2013) 51(10):1951-1959.

In a crossover trial that compared consumption of 4 cups of coffee per day with abstinence in 37 patients with chronic hepatitis, coffee significantly decreased 8-OhdG, but advanced protein oxidation products (AOPP) were not changed. Cardin R, Piciocchi M, Martines D, Scribano L,

Petracco M, Farinati F, "Effects of coffee consumption in chronic hepatitis C: a randomized controlled trial," *Dig. Liver Dis.* (2013) 45(6):499-504.

In its monograph, IARC commented that in a 2009 intervention study by Japanese investigators, hydroxyhydroquinone-reduced coffee significantly increased glutathione (GSH) and also decreased lipid peroxidation (F2-isoprostanes), IARC Monograph at p. 379. However, this study was done using a specially prepared beverage in which the level of hydroxyhydroquinone , a product of roasting coffee beans, was reduced by an adsorption treatment from typical levels of 0.1 - 1.7 mg to just 0.03 mg per 184 ml coffee, and in which the amount of chlorogenic acids was adjusted to 300 mg per 184 ml, although a cup of coffee typically contains 40 - 350 mg of chlorogenic acids. While this study involving this unusual test beverage did observe a significant increase in glutathione and a significant decrease in urinary isoprostane over the course of 8 weeks, the increase in glutathione was not statistically significant when compared to the placebo group. Ochiai R, Chikama A, Kataoka K, Tokimitsu I, Maekawa Y, Ohishi M, Rakugi H, Mikami H, "Effects of hydroxyhydroquinone-reduced coffee on vasoreactivity and blood pressure," *Hypertension Res.* (2009) 32:969-974. The results of this study are likely not generalizable to commercially available coffee because a study by Brazilian researchers that compared commercially available light and medium roast paper-filtered coffees observed no significant differences in lipid peroxidation biomarkers (PGF2α and oxLDL) and total antioxidant capacity, as measured by both DPPH (1,1,-diphenyl-2-picryl-hydrazyl-hydrate) scavenging capacity and ORAC (oxygen radical absorbance capacity) between medium and light roast coffee. Corrêa TA, Monteiro MP, Mendes TM, Oliveira DM, Rogero MM, Benites CI, Vinagre CG, Mioto BM, Tarasoutchi D, Tuda VL, César LA, Torres EA, "Medium light and medium roast paper-filtered coffee increased antioxidant capacity in healthy volunteers: results of a randomized trial," *Plant Foods Hum. Nutr.* (2012) 67(3):277-282.

IARC also commented that "[i]n a crossover trial of 64 healthy subjects, coffee (1 L/day) did not change the activity of GST in the mucosa, but increased GSH in mucosa and plasma." This study by Dutch researchers evaluated the effect of unfiltered coffee on putative biomarkers for colon

cancer risk. They assessed the effect of unfiltered coffee consumption on colonic cell hyperproliferation in colorectal biopsies, fecal soluble bile acids and colorectal mucosal glutathione S-transferase activity, as well as glutathione content in colorectal mucosae and in plasma. They considered colonic cell hyperproliferation to be a superior marker of colorectal carcinogenesis because it is thought to be an early event in the multi-step process of the colonic adenocarcinoma sequence. However, their study showed no effect of unfiltered coffee on colorectal cell proliferation assayed by estimating the Proliferating Cell Nuclear Antigen labelling index and no effects were seen on the concentrations of fecal soluble bile acids and colorectal mucosal glutathione S-transferase activity. However, they did observe an 8% increase of glutathione content in the colorectal mucosa and a 15% increase of glutathione content in plasma. These researchers concluded that their results "do not reinforce the hypothesis that coffee consumption reduces the risk of colon cancer." Moreover, the study is not generalizable to coffee generally consumed in the United States, where most coffee is filtered, which removes diterpenes that are present in unfiltered coffee. Grubben MJ, Van Den Braak CC, Broekhuizen R, De Jong R, Van Rijt L, De Ruijter E, Peters WH, Katan MB, Nagengast FM, "The effect of unfiltered coffee on potential biomarkers for colonic cancer risk in healthy volunteers: a randomized trial," *Aliment.. Pharmacol. Ther.* (2000) 14(9):1181-1190.

A review of human intervention studies regarding coffee consumption and oxidative stress was published by Italian investigators a few months after the IARC Working Group on Coffee met in May 2016. This review summarized the main findings on the effect of coffee consumption on protection against lipid, protein and DNA damage, as well as on the modulation of antioxidant capacity and antioxidant enzymes in human studies. They considered 26 dietary intervention studies involving acute and chronic coffee intake. While these researchers concluded that overall, the results suggest that coffee consumption can increase glutathione levels, the effects of coffee on plasma antioxidant capacity and antioxidant enzymes, as well as on protein and lipid damage, are unclear following both acute and chronic exposure. These researchers also concluded that heterogeneity among the studies was high and that more robust and well-controlled intervention studies are

necessary for a thorough understanding of the effect of coffee on oxidative stress markers in humans. Martini D, Del Bo' C, Tassotti M, Riso P, Del Rio D, Brighenti F, Porrini M, "Coffee Consumption and Oxidative Stress: A Review of Human Intervention Studies," *Molecules* (2016) 21(8). pii: E979.

E. The Coffee Industry's Expert Admitted The Theory Lacked Scientific Proof

The antioxidant theory of cancer prevention has been fully embraced by the coffee industry in touting supposed health benefits of coffee. Indeed, during the Phase 1 trial of *CERT v. Starbucks*, the coffee industry's toxicology expert, Dr. F. Jay Murray, opined that "that the antioxidant constituents of coffee do impact the carcinogenic potential of acrylamide and acrylamide in coffee." (Reporter's Transcript of Proceedings, September 9, 2014 a.m. at p. 21, lines 16-18). However, on cross-examination Dr. Murray was asked whether he could identify any chemical constituents of coffee that had been proven to inhibit the carcinogenicity of acrylamide. Dr. Murray answered, "No, not acrylamide specifically." (Reporter's Transcript of Proceedings, September 9, 2014 p.m. at p. 206, lines 1-5). Dr. Murray was then asked whether he could identify any constituent of coffee that has been proven to inhibit the carcinogenicity of any other carcinogen in coffee. Dr. Murray answered, "I don't think anybody has done those studies, so no, I can't identify that." (Reporter's Transcript of Proceedings, September 9, 2014 p.m. at p. 207, lines 7-12). Thus, even the coffee industry's own expert toxicologist acknowledged that no study has shown that antioxidants in coffee inhibit the carcinogenicity of any carcinogens in coffee.

F. EFSA Has Rejected Health Claims for Antioxidants in Coffee

It should also be noted that the FDA has never authorized any health claims for antioxidants in coffee and that the European Food Safety Authority (EFSA) has evaluated, but rejected, three separate applications for coffee health claims based on antioxidants in coffee in the last several years.

The first application for health claims that EFSA considered were for coffee, *Coffea Arabica* L., chlorogenic acids from coffee, and antioxidants in coffee. The health claims were for the protection of DNA, proteins and lipids from oxidative damage, maintenance of normal blood glucose concentrations, and contribution to the maintenance or achievement of a normal body weight. EFSA concluded (1) that a cause and effect relationship had not been established between the consumption of chlorogenic acids from coffee and protection of DNA, lips or proteins from oxidative damage; (2) that a cause and effect relationship had not been established between the consumption of chlorogenic acids in coffee and maintenance of normal blood glucose concentrations; and (3) that a cause and effect relationship had not been established between the consumption of chlorogenic acids from coffee and contribution to the maintenance or achievement of a normal body weight. EFSA, Scientific Opinion on the substantiation of health claims related to coffee, including chlorogenic acids from coffee, and protection of DNA, proteins and lipids from oxidative damage (ID 1099, 3152, 4301), maintenance of normal blood glucose concentrations (ID 1100, 1962), and contribution to the maintenance or achievement of a normal body weight (ID 2031, 4326) pursuant to Article 13(1) of Regulation (EC) No 1924/2006, *EFSA Journal* (2011) 9(4):2057.

The second application that EFSA considered was for coffee C21 and reduction of spontaneous DNA strand breaks. EFSA concluded that a cause and effect relationship had not been established between the consumption of coffee C21 and a reduction of spontaneous DNA strand breaks. EFSA, Scientific Opinion on the substantiation of a health claim related to coffee C21 and reduction of spontaneous DNA strand breaks pursuant to Article 13(5) of Regulation (EC) No 1924/2006, *EFSA Journal* (2011) 9(12):2465.

The third application the EFSA considered was for coffee C21 and reduction of DNA damage by decreasing spontaneous DNA strand breaks. Although this application was based on six intervention studies, EFSA nevertheless concluded that a cause and effect relationship had not been established between the consumption of coffee C21, a coffee standardized by its content of caffeoylquinic acids, trigonelline and NMP, and a reduction of DNA damage by decreasing spontaneous DNA strand breaks. EFSA, Scientific Opinion on the substantiation of a health claim related to coffee C21, a coffee standardised by its content of caffeoylquinic acids, trigonelline and *N*-methylpridinhium, and reduction of DNA damage by decreasing spontaneous DNA strand breaks pursuant to Article 13(5) of Regulation (EC) No 1924/2006, *EFSA Journal* (2015) 13(5):4099.

G. Antioxidants In Coffee Health Benefit Claim: An Unproven Hypothesis

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. (CERT's Submission No. 8).

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.

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 ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R, "Association of coffee drinking with total and cause-specific mortality," *New Engl J. Med.* (2012) 366(20):1891-1904. 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.

Coffee consumption is correlated with smoking, alcohol consumption, and less physical activity. Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R, "Association of coffee drinking with total and cause-specific mortality," *New Engl J. Med.* (2012) 366(20):1891-1904. 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 heath-protective effect from coffee.

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. In one study, the antioxidant activity of whole coffee fruit extracts was found to be up to 25-fold higher than the final product. Mullen W, Nemzer B, Ou B, Stalmach A, Hunter J, Clifford MN, Combet E, "The antioxidant and chlorogenic acid profiles of whole coffee fruits are influenced by the extraction procedures," *J. Agric. Food Chem.* (2011) 59(8):3754-3762.

Despite having antioxidant properties, the aromatic hydrocarbons, cafestol and kahweol, in coffee beverages (Liang N, Kitts DD, "Antioxidant property of coffee components: assessment of methods that define mechanisms of action," *Molecules* (2014) 19(11):19180-19208) are known to increase serum total cholesterol in consumers. Corrêa TA, Rogero MM, Mioto BM, Tarasoutchi D, Tuda VL, César LA, Torres EA, "Filtered coffee increases cholesterol and inflammation biomarkers independent of roasting degree: A clinical trial," *Nutr.* (2013) 29(7-8):977-981; Strandhagen E, Tehlle Ds, "filtered coffee raises serum cholesterol: results from a controlled study," *Eur. J. Clin. Nutr.* (2003) 57:1164-1168.

The net health effect , if any, from antioxidant constituents of coffee remains unknown. [Report of Dr. Jack James - CERT's Submission No.8).

H. Antioxidant Hypothesis: A Hypothetical Mechanism In Search Of An Effect

Although the Initial Statement of Reasons does not expressly state as much, it appears that OEHHA's purpose in discussing antioxidants in coffee is to provide a mechanistic basis for what OEHHA suspects may be an anti-carcinogenic effect of such chemicals in coffee that might explain the inverse associations between coffee consumption and certain cancers reported in some observational epidemiological studies. This inference is supported by OEHHA's citation of the landmark paper by Professor Martyn T. Smith and colleagues from IARC and other institutions: Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Rucher JR, Stewart BW, Baan RA, Cogliano JV, Straif K, "Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis," *Environ. Health Perspect.* (2016) 124(6):713-721. If this is OEHHA's purpose, its purpose is not accomplished because, as explained above, recent Mendelian randomization studies indicate that the inverse associations between coffee consumption and certain cancers are not causal, no antioxidant in coffee has ever been proven to prevent any type of human cancer, and the European Food Safety Authority has denied three applications for antioxidant-related health claims for coffee in the last several years. Thus, OEHHA's discussion of supposed "anti-carcinogenic" effects of antioxidants in coffee appears to be nothing more than a hypothetical mechanism in support of a hypothetical (and recently disproven) anticarcinogenic effect. OEHHA's rationale simply isn't the stuff on which scientific conclusions may properly be based, and it provides no scientific basis at all for OEHHA's proposed regulation.

I. The Mechanism of Acrylamide Carcinogenicity Should Be Considered

Acrylamide was classified by IARC as a probable human carcinogen based on data showing that this chemical induces tumors at multiple sites in experimental animals, is metabolized to glycidamide (an epoxide intermediate that forms covalent bonds with DNA in rats and mice and covalent hemoglobin adducts in humans and rats), and because it induces gene mutations and chromosomal aberrations in somatic cells and germ cells of rodents *in vivo*. International Agency for Research on Cancer, "Acrylamide," *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* 60:389-433 (IARC 1994).

The metabolism of acrylamide to glycidamide is catalyzed primarily by CYP2E1, Ghanayem BI, McDaniel LP, Churchwell MI, Twaddle NC, Snyder R, Fennell TR, Doerge DR, "Role of CYP2E1 in the epoxidation of acrylamide to glycidamide and formation of DNA and hemoglobin adducts," *Toxicol. Sci.* (2005) 88(2):311-318, an enzyme that is present at variable levels in humans and is the major enzyme involved in the epoxidation of several chemical carcinogens including benzene, vinyl chloride, and 1,3-butadiene. Guengerich FP, Kim DH, Iwasaki M, "Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects," *Chem. Res. Toxicol.* (1991) 4(2):168-179. Reaction of acrylamide or glycidamide with glutathione yields inactive conjugates that are ultimately excreted in urine as cysteine conjugates. The finding of glycidamide-hemoglobin adducts as well as unchanged glycidamide in urine of exposed humans, Fennell TR, Sumner SC, Snyder RW, Burgess J, Spicer R, Bridson WE, Friedman MA, "Metabolism and hemoglobin adduct formation of acrylamide in humans," *Toxicol. Sci.* (2005) 85(1):447-459, indicates that this DNA-reactive intermediate is distributed systemically in humans. Coffee consumption is also associated with increased glycidamide-hemoglobin adducts in non-smoking women. Outzen M, Egeberg R, Dragsted L, Christensen J, Olesen PT, Frandsen H, Overvad K, Tjønneland A, Olsen A, "Dietary determinants for Hb-acrylamide and Hb-glycidamide adducts in Danish non-smoking women," *Br. J. Nutr.* (2011) 105(9):1381-1387. This finding indicates that

glycidamide, a genotoxic carcinogen formed from acrylamide, can be systemically distributed in coffee drinkers.

Both acrylamide and glycidamide are multi-site carcinogens in rats and mice, and "based upon the concordance of tumor sites between the two bioassays, the data also indicate that carcinogenic activity of acrylamide is due to its metabolic conversion to glycidamide." National Toxicology Program, *Toxicology and Carcinogenesis Studies of Acrylamide (CAS No. 79-06-1) in F344/N Rats and B6C3F1 Mice (Feed and Drinking Water Study)* (NTP 2012); National Toxicology Program. *Toxicology and Carcinogenesis Studies of Glycidamide (CAS No. 5694-00-8) in F344/N Nctr Rats and B6C3F1/Nctr Mice (Drinking Water Study)* NTP 2013). There was also concordance in sites of tumor induction by acrylamide or glycidamide with other epoxide and epoxide-forming chemicals, e.g. lung, mammary gland, and harderian gland of mice (acrylamide, glycidamide, vinyl fluoride or vinyl chloride, 1,3-butadiene, ethylene oxide, chloroprene, isoprene, benzene, glycidol); other common sites include mammary gland in rats (acrylamide, glycidamide, 1,3-butadiene, vinyl chloride, chloroprene, isoprene, glycidol), brain of rats (glycidamide, vinyl chloride, 1,3-butadiene, ethylene oxide, glycidol), thyroid gland of rats (acrylamide, glycidamide, 1,3-butadiene, chloroprene, glycidamide), ovary of mice (acrylamide and 1,3-butadiene), and forestomach of rats or mice (acrylamide, glycidamide, vinyl chloride, 1,3-butadiene, benzene, glycidamide, chloroprene, isoprene). Melnick RL, "Carcinogenicity and mechanistic insights on the behavior of epoxides and epoxide-forming chemicals," *Ann. N. Y. Acad. Sci.* (2002) 982:177-189. Thus, it is apparent that acrylamide and/or glycidamide induce tumors in experimental animals at organ sites in common with other epoxide and epoxide-forming chemicals, including several that have been classified as known human carcinogens. From a public health perspective, it would be inappropriate to dismiss the cancer risk from these DNA-reactive epoxide chemicals that induce tumors at multiple organ sites.

J. Inapplicability of Oxidative Stress to Dietary Acrylamide Cancer Risk

One reason that the Initial Statement of Reasons appears to justify the statements that "the carcinogens in this particular mixture [coffee] should be viewed differently" and that "OEHHA has determined that exposure to listed carcinogens in coffee……do not pose a significant cancer risk under Proposition 65" is that "coffee has antioxidant effects….that are related to reductions in cancer risk" and that "protect against oxidative stress." While it is true that oxidative stress is a key characteristic of some carcinogens and that coffee contains antioxidants, these factors have little impact on the carcinogenicity of epoxide-forming chemicals such as acrylamide. In his deposition and trial testimony during Phase 1 of the *CERT v. Starbucks* case, Dr. Ronald L. Melnick testified that the mechanism of acrylamide carcinogenicity does not involve oxidative stress and therefore is not ameliorated by the presence of antioxidants in coffee. (CERT's Submission No. 11)

The epoxide metabolites of acrylamide, vinyl chloride, 1,3-butadiene, chloroprene, glycidol, and other epoxide-forming chemicals react with DNA to form covalent adducts. The carcinogenicity of acrylamide involves a genotoxic mechanism based on its metabolism to glycidamide and subsequent DNA adduct formation. Bowyer JF, Latendresse JR, Delongchamp RR, Muskhelishvili L, Warbritton AR, Thomas M, Tareke E, McDaniel LP, Doerge DR, "The effects of subchronic acrylamide exposure on gene expression, neurochemistry, hormones, and histopathology in the hypothalamus-pituitary-thyroid axis of male Fischer 344 rats," *Toxicol. Appl. Pharmacol.* (2008) 230(2):208-215. Glycidamide-specific DNA adducts are different than the major DNA adduct formed by reactive oxygen species (8-Oxo-deoxyguanosine). The finding that DNA damage induced by glycidamide in male mouse germ cells and in mouse and human lymphocytes was not affected by hOGG1 (a DNA repair enzyme that excises 8-oxoguanine, a mutagenic base formed by reactive oxygen species) shows that alkylation rather than oxidation of DNA is involved in producing DNA lesions by this reactive epoxide metabolite. Hansen SH, Olsen AK, Soderlund EJ, Brunborg G, "In

vitro investigations of glycidamide-induced DNA lesions in mouse male germ cells and in mouse and human lymphocytes," *Mutat. Res.* (2010) 696(1):55-61.

At concentrations of glycidamide that induced the formation of micronuclei by glycidamide in human mammary cells (MCF10A) there was no increase in reactive oxygen species, and antioxidants did not protect these cells from glycidamide-induced cytotoxicity, indicating that these effects occurred by mechanisms not involving oxidative stress. Bandarra S, Fernandes AS, Magro I, Guerreiro PS, Pingarillo M, Churchwell MI, Gil OM, Batinic-Haberle I, Gonçalves S, Rueff J, Miranda JP, Marques mm, Beland FA, Castro M, Gaspar JF, Oliveira NG, "Mechanistic insights into the cytotoxicity and genotoxicity induced by glycidamide in human mammary cells," *Mutagenesis* (2013) 28(6):721-729. In those studies, linear dose-dependent formation of glycidamide-specific DNA adducts was observed. Thus, the formation of glycidamide-DNA adducts and the genotoxicity of this epoxide do not involve oxidative stress.

Studies that suggest acrylamide is associated with oxidative stress used very high concentrations of this chemical. For example, Chinese researchers observed increased oxidative damage and glutathione depletion in rats treated for 12 days with acrylamide at daily doses of 40 mg/kg. Pan X, Zhu L, Lu H, Wang D, Lu Q, Yan H, "Melatonin Attenuates Oxidative Damage Induced by Acrylamide In Vitro and In Vivo," *Oxid. Med. Cell Longev.* (2015) 2015:703709. However, this dose is at least 10 times greater than the doses of acrylamide that produced clear evidence of carcinogenicity in NTP's 2-year study in rats (doses ranged from 0.33 to 4.0 mg/kg/day). As mentioned above, the elimination of acrylamide and glycidamide includes conjugation of these chemicals with glutathione. At high acrylamide levels, these reactions can deplete cellular glutathione levels and thereby decrease the effectiveness of this antioxidant in reducing reactive oxygen species. Thus, depletion of glutathione at high acrylamide levels can result in increased cellular levels of reactive oxygen species. However, at low concentrations of acrylamide where glutathione depletion is minimal, this indirect effect on oxidative stress is essentially zero. Because the mechanism of carcinogenicity caused by acrylamide does not involve induction of oxidative

stress, it is extremely unlikely that the presence of antioxidants in coffee impacts the cancer risk of acrylamide among consumers of this beverage.

Two diterpenes found in coffee, cafestol and kahweol, are cholesterol raising factors that have also been suggested as potential cancer preventing agents by inhibiting certain cytochrome P450 enzymes (but not CYP2E1) and decreasing sulfotransferase 1A1 activity. Huber WW, Rossanith W, Grusch M, Haslinger E, Prustomersky S, Peter-Vörösmarty B. Pazefall W, Scharf G, Schulte-Hermann R, "Effects of coffee and its chemopreventive components kahweol and cafestol on cytochrome P450 and sulfotransferase in rat liver," *Food Chem. Toxicol.* (2008) 46(4):1230-1238. These effects have little bearing on acrylamide cancer risk since these agents do not inhibit CYP2E1, and sulfotransferase activity is not involved in the activation of acrylamide to glycidamide. However, furfuryl alcohol, which is also produced during the coffee roasting process, is metabolically activated by sulfate conjugation catalyzed by sulfotransferase 1A1/1A2. Sachse B, Meinl W, Glatt H, Monien BH, "Ethanol and 4-methylpyrazole increase DNA adduct formation of furfuryl alcohol in FVB/N wild-type mice and in mice expressing human sulfotransferases 1A1/1A2," *Carcinogenesis* (2016) 37(3):314-319. Thus, cafestol and kahweol might reduce cancer risk of furfuryl alcohol, but not of acrylamide.

K. Why Acrylamide Should Actually Be Viewed Differently in Coffee

Perhaps the presence of acrylamide in coffee should be viewed differently than other carcinogens in this mixture, but for reasons different than those indicated in the Initial Statement of Reasons: (1) acrylamide in coffee provides no health benefit, (2) acrylamide is not essential to the function and quality of coffee, (3) levels of acrylamide in coffee can be reduced by 90%, (4) the acrylamide levels in coffee can be reduced without negatively affecting the palatability of this beverage, and (5) there is no data showing that other constituents in coffee provide any protection against the carcinogenicity of acrylamide and its metabolite glycidamide.

In his reports and testimony in the *CERT v. Starbucks* case, Dr. Melnick described several methodologies that are currently available and effective in reducing acrylamide levels in coffee.

For example, treatment of unroasted coffee beans with asparaginase, the enzyme that metabolizes free asparagine (the acrylamide precursor) to aspartate, was effective in reducing acrylamide levels in roasted coffee by 70-90%. Dria GJ, Zyzak DV, Gutwein RW, Villagran FV, et al., "Method for reduction of acrylamide in roasted coffee beans, roasted coffee beans roasted coffee beans having reduced levels of acrylamide, and article of commerce," US 2004/0081724 A1. (The Proctor & Gamble Company, 2004); Dria GJ, Zyzak DV, Gutwein RW, Villagran FV, et al., "Method for reduction of acrylamide in roasted coffee beans, roasted coffee beans roasted coffee beans having reduced levels of acrylamide, and article of commerce. US 7,220,440 B2," (The Proctor & Gamble Company, 2007); Stadler R, "Food process contaminants: Industry perspectives and update on mitigation," (2013) Euro Food Chem XVII, Istanbul, Turkey; Navarini L, Del Terra L, Colomban S, Lonzarich V, Suggi Liverani F, "Method for reducing the content of acrylamide in a roasted coffee. WO 2013/005145 A1 (Illy Café' SPA, 2013).

In Germany, more than 200 tons of coffee beans that had been treated with asparaginase on industrial scale has been sold to the market. Confidential documents produced in *CERT v Starbucks.*

Supercritical CO_2 extraction, a method that is used to remove caffeine from coffee beans, is also effective in reducing levels of acrylamide by approximately 80% from roasted coffee beans. Banchero M, Pellegrino G, Manna L, "Supercritical fluid extraction as a potential mitigation strategy for the reduction of acrylamide level in coffee," *J. Food Engineering* (2013) 115:292-297.

Even storage of roasted ground coffee under vacuum or under a nitrogen atmosphere at room temperature was effective in reducing acrylamide by 20-30% after storage for 16 weeks or by 40-50% after storage for 48 weeks. Baum M, Bohm N, Gorlitz J, Lantz I, et al., "Fate of ^{14}C-acrylamide in roasted and ground coffee during storage," *Mol. Nutr. Food Res.* (2008) 52:600-608. The decline in acrylamide during storage has been attributed largely to covalent binding to nucleophilic groups by Michael addition to other compounds in coffee grounds. Illy claims that due to its inert gas

pressurization packaging technology, "the flavor and freshness of the unopened Illy coffee can be fully preserved for a long period of 2 years," while Starbucks specifies a shelf of up to 60 weeks for ground and whole bean roasted coffee. Acrylamide levels were also reduced 66% by heat curing of roasted coffee beans for 16 hours at 100ºC under an inert atmosphere. In each of these examples, the authors reported no significant impact on organoleptic properties. It is likely that combinations of these methods could effectively reduce acrylamide levels in roasted coffee by greater than 90%.

In contrast to the assertion in the Initial Statement of Reasons that carcinogens in coffee should be viewed differently and that exposures to these chemicals in coffee do not pose a significant cancer risk, the US EPA maintains that "environmental exposures ... to a mixture with a known carcinogenic component may pose a cancer risk in spite of negative results from a whole-mixture study." U.S. Environmental Protection Agency, *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (US EPA, 2000). There is no basis for viewing the cancer risk of acrylamide differently when it is present in coffee compared to any other source. Consequently, the fact that acrylamide is present in coffee at levels above its NSRL indicates that exposure to this carcinogen in coffee poses a significant cancer risk as defined under Proposition 65. Rather than simply declaring exposures to listed carcinogens in coffee do not pose a significant cancer risk, OEHHA should encourage coffee companies to apply available methodologies to reduce acrylamide to levels below its NSRL.

IX. OEHHA'S CLAIM THAT COFFEE CONFERS HEALTH BENEFITS

In its Initial Statement of Reasons, OEHHA touts supposedly beneficial ("chemopreventive") chemicals in coffee, but ignores the many carcinogenic and other toxic chemicals in coffee.

A. Coffee Contains Harmful, Rather than Beneficial, Constituents

1. Acrylamide

Coffee contains high levels of acrylamide. The concentration of acrylamide in brewed coffee is 2.22 micrograms in an average cup of coffee, which is about eleven times the Safe Harbor level of acrylamide of 0.2 micrograms. [Testimony of Dr. Steven Bayard, October 27, 2014 p.m. at 190:13-27 (Exhibit "27")].

Community Coffee Co., H.N. Fernandez, and Reily Foods Company sell coffee products containing chicory, which has high levels of acrylamide and increases acrylamide exposure. Thus, according to Defendants' very low exposure assessment, the average consumer's daily acrylamide intake from Riley Foods' French Market Chicory Blend Coffee is 22.85 ug/day, whereas average intake from its dark roast is just 1.76 ug/day - a 13-fold difference. Testimony of Dr. Carolyn Scrafford, September 18, 2017 p.m. at 195:8 - 197:5 (Exhibit "149"); Brand-Specific Exposure Assessment (Exhibit "254") (Defendants' Trial Exhibit 73540); Deposition of Burton E. Benrud, March 21, 2017 at 17:7-9, 27:14-28:12 (Exhibit "255")].

2. Other Carcinogenic Chemicals

Coffee also contains several other carcinogenic chemicals. Of the more than 1,000 chemicals in coffee, about 50 have been evaluated for carcinogenicity in long-term bioassays. Of the

approximately 50 chemicals that are present in coffee that have been tested for carcinogenicity, approximately two-thirds to three-fourths have shown carcinogenic activity in animals. [Testimony of Dr. James Huff, October 22, 2014 at 161:5-23 (Exhibit "25"); Testimony of Dr. William Ristenpart, September 6, 2017 a.m. at 26:2-62:28 (Exhibit "119")]

Coffee also contains numerous clastogenic chemicals - chemicals that break chromosomes and cause structural chromosome aberrations that are predictive of human cancer. Acrylamide is one of those numerous chemical constituents of coffee that are clastogenic. [Testimony of Dr. Martyn Smith, October 10, 2014 at 18:20 - 32:28 (Exhibit "20")].

3. Caffeine

Coffee contains caffeine, a drug that causes various adverse psychological and physiological effects, including recognized medical disorders such as caffeine intoxication, caffeine withdrawal syndrome, anxiety, sleep disorders and problematic caffeine use. [Testimony of Dr. Laura Juliano, September 19, 2017 p.m. at 191:6 - 192:19; 182:18 - 190:19; 197:2 - 198:17; 200:26 - 204:10; 204:12 - 208:13; 178:12 - 179:20. (Exhibit "113")].

There is no question that caffeine is a pharmacological agent that has "minuses." [Testimony of Dr. David Kessler, September 11, 2017 a.m. at 43:7-9. (Exhibit "114")]. "People drink coffee because of caffeine." If people don't get caffeine from coffee, "they're going to want their caffeine from other sources." [Testimony of Dr. David Kessler, September 11, 2017 a.m. at 43:15-16. (Exhibit "114")].

Consumption of more than 100 mg/day of caffeine was significantly associated reduction in birth weight of 34-59g in 1st trimester; 24-74 g in 2nd trimester; 66-89 g in 3rd trimester. This reduction in birth weight as a result of caffeine intake by the mother was confirmed in a second propsective cohort study. Sengpiel V, Elind E, Bacelis J, Nilsson S, Grove J, "Maternal Caffeine Intake during Pregnancy Is Associated with Brith Weight but Not with Gestational Length: Results

from a Large Prospective Observational Cohort," *BMC Med.* (2013) 11:42. Caffeine therefore not only causes spontaneous abortions but also has been shown to retard the growth of the fetus in humans in very well-designed cohort studies.

4. Sugar, Fat and Other Unhealthy Additives

Food that is hijacked by sugar and fat, including sugar-sweetened beverages, is not healthy. [Testimony of Dr. David Kessler, September 11, 2017 a.m. at 76:21-27; 77:18-28; 78:2-8. (Exhibit "114")]. The Defendants' coffee products contain sugars, sweeteners, creamers, whiteners, flavorings, and other additives. [Testimony of David Kessler, September 11, 2017 a.m. at 78:2-8 (Exhibit "114")]; Food Composition Report submitted by Brad Barry Company to the United States Department of Agriculture (Exhibit "240"); Food Composition Report submitted by Caribou Coffee Company to the United States Department of Agriculture (Exhibit "241"); Food Composition Report submitted by Copper Moon Coffee LLC to the United States Department of Agriculture (Exhibit "242"); Food Composition Report submitted by The Folgers Coffee Company to the United States Department of Agriculture (Exhibit "243"); Food Composition Report submitted by Illy Caffe North America, Inc. to the United States Department of Agriculture (Exhibit "244"); Food Composition Report submitted by Keurig Green Mountain Coffee Roasters Inc. to the United States Department of Agriculture (Exhibit "245"); Food Composition Report submitted by The Kroger Company to the United States Department of Agriculture (Exhibit "246"); Food Composition Report submitted by Massimo Zanetti Beverage USA, Inc. to the United States Department of Agriculture (Exhibit "247"); Food Composition Report submitted by Peet's Operating Company, Inc. to the United States Department of Agriculture (Exhibit "248"); Food Composition Report submitted by Safeway, Inc. to the United States Department of Agriculture (Exhibit "249"); Food Composition Report submitted by Sam's West, Inc. to the United States Department of Agriculture (Exhibit "250"); Food Composition Report submitted by Starbucks to the United States Department of

Agriculture (Exhibit "251"); Food Composition Report submitted by Wal-Mart Stores, Inc. to the United States Department of Agriculture (Exhibit "252"); Food Composition Report submitted by Whole Foods Market California, Inc. to the United States Department of Agriculture (Exhibit "253").

Sweeteners and creamers are the largest ingredients in products that are the subject of Food Composition Reports, as they are the first or second listed ingredients in the reports, establishing that these products are "hijacked by sugar and fat" and are therefore not healthy beverages. [Testimony of Dr. David Kessler, September 11, 2017 a.m. at 76:21-27; 77:18-28; 78:2-8. (Exhibit "114")]

Numerous products of other Defendants also contain sweeteners, creamers, and other additives. Deposition of James Seiple, Person Most Knowledgeable for Albertsons, LLC and Safeway, Inc. February 14, 2017 at 37:19-20 (Exhibit "170"); Deposition of Jeff Teter, Person Most Knowledgeable for Allegro Coffee Company, March 2, 2017 at 15:7-13 (Exhibit "171"); Deposition of Michael Rogers, Person Most Knowledgeable for Apffels Coffee Company, February 1, 2017 at 66:24-25 (Exhibit "172"); Deposition of Pamela Boyer, Person Most Knowledgeable for Boyer Coffee Company, July 27, 2017 at 16:8-16 (Exhibit "173"); Deposition of Kathleen Mejia, Person Most Knowledgeable for BP West Coast Products, LLC, March 10, 2017 at 9:23 - 10:10; 49:4-15 (Exhibit "174"); Deposition of Jerome Patrick Greener, Person Most Knowledgeable for Brad Barry Company, LTD., February 9, 2017 at 11:15-25; 15:3-8; 46:10-20 (Exhibit "175"); Deposition of Arnie Holt, Person Most Knowledgeable for Caffe Calabria Roasting Company, February 23, 2017 at 13:16-22 (Exhibit "176"); Deposition of Lesa Lynn Wilson, Person Most Knowledgeable for Caffe Ibis, Inc., February 9, 2017 at 14:22 - 15:12 (Exhibit "177"); Deposition of Richard Paul Turek, Person Most Knowledgeable for Caribou Coffee Company, Inc., February 10, 2017 at 17:13 - 18:3 (Exhibit "178"); Deposition of Greg Thayer, Person Most Knowledgeable for Cascade Coffee, Inc., February 8, 2017 at 19:16-23 (Exhibit "179"); Deposition of Julie Ann Galloway and Chris Eric Galloway, Persons Most Knowledgeable for Central Coast Coffee Roasting Company, Inc., April 7, 2017 at 17:24 - 18:24 (Exhibit "180"); Deposition of Tik The, Person Most Knowledgeable for

The Coca-Cola Company, February 21, 2017 at 20:7 - 28:6 (Exhibit "181"); Deposition of Edward A. Oscarson, Person Most Knowledgeable for Coffee Bean International, February 7, 2017 at 63:1 - 64:23 (Exhibit "182"); Deposition of Ann Hall, Person Most Knowledgeable for Arizona Coffee Roasters, Inc., March 10, 2017 at 12:8 - 13:3 (Exhibit "183"); Deposition of James R. Leblanc, Person Most Knowledgeable for Community Coffee Company, February 22, 2017 at 12:19-25 (Exhibit "184"); Deposition of Cary Gutwein, Person Most Knowledgeable for Copper Moon Coffee, February 23, 2017 at 15:9-19 (Exhibit "185"); Deposition of David M. Allen, Person Most Knowledgeable for Eight O'clock Coffee Company, February 6, 2017 at 31:8-24 (Exhibit "186"); Deposition of Ted Stachura, Person Most Knowledgeable for Equator Coffee and Tea Company, February 16, 2017 at 10:12-18 (Exhibit "187"); Deposition of Jose A Gavina, Person Most Knowledgeable for F. Gavina & Sons, Inc., March 21, 2017 at 14:9 - 15:23 (Exhibit "188"); Deposition of Hugh Campbell, Person Most Knowledgeable for Gold Medal Products Company, March 9, 2017 at 11:21-23 (Exhibit "189"); Deposition of John Isais, Person Most Knowledgeable for International Coffee & Tea, LLC, February 22, 2017 at 16:21 - 17:20 (Exhibit "190"); Deposition of James C. Cannell, Person Most Knowledgeable for James C. Cannell Coffees, Inc. dba Jim's Organic Coffee, February 27, 2017 at 11:22 - 12:1 (Exhibit "191"); Deposition of James Rogers, Person Most Knowledgeable for JBR, Inc. dba Rogers Family Company, February 13, 2017 at 11:22-25 (Exhibit "192"); Deposition of Colin Neidert, Person Most Knowledgeable for The J.M. Smucker Company, January 20, 2017 at 31:3 - 32:25 (Exhibit "193"); Deposition of Liam Hughes, Person Most Knowledgeable for Kerry Inc., dba Kerry Ingredients, Inc., April 18, 2017 at 26:8-16; 29:18-25 (Exhibit "194"); Deposition of Michael V. Cramer, Person Most Knowledgeable for Keurig Green Mountain, Inc., January 18, 2017 at 97:19 - 98:22 (Exhibit "195"); Deposition of Matthew Plumb, Person Most Knowledgeable for Kraft Heinz Company, January 13, 2017 at 31:5 - 36:1 (Exhibit "196"); Deposition of John Boyle, Person Most Knowledgeable for Massimo Zanetti Beverage Company USA and Kauai Coffee Company, January 30, 2017 at 46:13 - 47:2; 61:19-24 (Exhibit "197"); Deposition of Alberto Martin Mayorga, Person Most Knowledgeable for Mayorga Coffee,

LLC, March 1, 2017 at 12:4-9 (Exhibit "198"); Deposition of Fred H Lueck, Person Most Knowledgeable for Melitta U.S.A., Inc., February 6, 2017 at 42:19 - 44:5 (Exhibit "199"); Deposition of Beth Beall, Person Most Knowledgeable for Montana Coffee Traders, Inc., February 27, 2017 at 12:13-24 (Exhibit "200"); Deposition of Sean Bredt, Person Most Knowledgeable for Mother Parkers Tea and Coffee, Inc., February 6, 2017 at 35:14-15 (Exhibit "201"); Deposition of Michael Mountanos, Person Most Knowledgeable for Mountanos Brothers Coffee Company, February 13, 2017 at 13:12 -14:20 (Exhibit "202"); Deposition of Ben Sange, Person Most Knowledgeable for Napa Valley Coffee Roasting Company, February 15, 2017 at 13:25 - 14:12 (Exhibit "203"); Deposition of Patti Kimi Yasuda Motoyasu, Person Most Knowledgeable for Nestle, U.S.A., March 7, 2017 at 15:17 - 16:12 (Exhibit "204"); Deposition of James Kaloyanides, Person Most Knowledgeable for New England Tea & Coffee Company, Inc., February 24, 2017 at 14:13 - 15:12 (Exhibit "205"); Deposition of Randy Jae Chung, Person Most Knowledgeable for Paradise Beverages dba Hawaii Coffee Company, February 10, 2017 at 15:17 - 17:1 (Exhibit "206"); Deposition of Doug Welsh, Person Most Knowledgeable for Peet's Coffee and Tea, Inc., February 14, 2017 at 13:15-20 (Exhibit "207"); Deposition of Roger Scheumann, Person Most Knowledgeable for Quartermaine Coffee Roasters, March 9, 2017 at 11:25 - 12:17 (Exhibit "208"); Deposition of Joseph Apuzzo, Person Most Knowledgeable for Regal Commodities, February 1, 2017 at 17:18 - 19:1 (Exhibit "209"); Deposition of David Thomas Darragh, Person Most Knowledgeable for Reily Foods Company, March 8, 2017 at 12:21 - 13:22 (Exhibit "210"); Deposition of Tracy Lynn Ging, Person Most Knowledgeable for S & D Coffee & Tea, March 9, 2017 at 14:12-21 (Exhibit "211"); Deposition of Robert E. Burns, Person Most Knowledgeable for Sam's West Inc., February 28, 2017 at 35:6 - 38:16 (Exhibit "212"); Deposition of Jeff Emme, Person Most Knowledgeable for Sara Lee Corporation, February 3, 2017 at 62:20 - 63:8 (Exhibit "213"); Deposition of Mark Lee Ballering, Person Most Knowledgeable for Steep & Brew, Inc., February 10, 2017 at 24:2 - 25:7 (Exhibit "214"); Deposition of Matthew D. Sloan, Person Most Knowledgeable for Trader Joe's Company, March 6, 2017 at 46:17-19 (Exhibit "215"); Deposition of Mike Eyer, Person Most Knowledgeable

for Verve Pacific Avenue Café, February 16, 2017 at 13:6-19 (Exhibit "216"); Deposition of Scott Gerhartz, Person Most Knowledgeable for Victor Allen's Coffee, LLC, February 8, 2017 at 24:16 - 25:25 (Exhibit "217"); Deposition of Juan Mena, Person Most Knowledgeable for Vilore Foods Company, Inc., January 31, 2017 at 26:15-25 (Exhibit "218"); Deposition of Creighton T. Kiper, Person Most Knowledgeable for Wal-Mart Stores, Inc., February 28, 2017 at 53:4-19 (Exhibit "219"); Deposition of Quintana Kardel, Person Most Knowledgeable for Whole Foods Market California, Inc., February 13, 2017 at 44:2 - 45:5 (Exhibit "220"); Deposition of Jose Antonio Camolina, Person Most Knowledgeable for Yum Yum Donut Shops, Inc., March 2, 2017 at 37:16 - 38:13 (Exhibit "221"); Deposition of Fritz Kugler, Person Most Knowledgeable for Zavida Coffee, February 21, 2017 at 14:20-25 (Exhibit "222").

B. Human Exposure to Coffee and Caffeine

Humans are exposed to caffeine from consumption of, or exposure to, coffee at all stages of life.

1. Exposure of the Fetus

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. Many women spontaneously reduce caffeine intake during pregnancy because they report a loss of taste for caffeine during pregnancy. 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. The level of caffeine in fetal blood approximates that of the mother. James JE, Paull I, "Caffeine and human reproduction," *Rev. Environ. Health* (1985) 5(2):151-167; James JE, *Caffeine and Health* (1991) Academic Press,

London; James JE, *Understanding Caffeine: A Biobehavioral Analysis* (1997) Sage Publications, Thousand Oaks, CA; James JE, "Higher caffeine intakes during pregnaancy increases risk of low birth weight (Invited commentary), *Evid.-Based Nursing* (2015) 18, doi:10.1136/eb-2014-102027.

A substantial portion of newborns have pharmacologically active levels of caffeine in blood, which occurs transplacentally through maternal consumption. The major source of fetal caffeine exposure is maternal consumption of coffee. The fetus is dependent on the mother to metabolize caffeine. 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. James JE, Paull I, "Caffeine and human reproduction," *Rev. Environ. Health* (1985) 5(2):151-167.

2. Exposure of Children and Adolescents

At a young age children become exposed to caffeine primarily in the form of caffeinated sugar-sweetened beverages. 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 behavior. This is consistent with evidence that caffeine is a common source of sleep disruption for adolescents. Studies show that about 75% of adolescents consume caffeine daily, primarily from soft drinks, followed by coffee, tea, and energy drinks. James JE, Kristjánsson ÁL, Sigfúsdóttir ID, "Adolescent substance use, sleep, and academic achievement: evidence of harm due to caffeine," *J. Adolescence* (2011) 34(4):665-673; James JE, Kristjansson AL, Sigfusdottir ID, "A gender-specific analysis of adolescent dietary caffeine, alcohol consumption, anger, and violent behavior," *Substance Use Misuse* (2015) 50(2):257-267; Kristjansson AL, Sigfusdottir ID, Allegrante JP, James JE. Adolescent caffeine consumption, daytime sleepiness, and anger. *J. Caffeine Res..* (2011) 1(1):75-82; Kristjansson AL, Sigfusdottir ID, Frost SS, James JE, "Adolescent caffeine consumption and

self-reported violence and conduct disorder," *J. Youth Adolescence* (2013) 42(7):1053-1062; Kristjansson AL, Sigfusdottir ID, Mann MJ, James JE, "Caffeinated sugar-sweetened beverages and common physical complaints in Icelandic children aged 10–12 years," *Prev. Med.*(2014) 58:40-44; Kristjansson AL, Mann MJ, Sigfusdottir ID, James JE, "Mode of daily caffeine consumption among adolescents and the practice of mixing alcohol with energy drinks: relationships to drunkenness," *J. Studies Alcohol Drugs* (2015) 76(3):397-405.

3. Exposure of Adults and the Elderly

By adulthood caffeine consumption patterns are established. 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. More than 80% of the adult population consumes caffeine daily, and in some communities the proportion is close to 100%. De Leon J, Diaz FJ, Rogers T, Browne D, Dinsmore L, Ghosheh OH, Dwoskin LP, Crooks PA, "A pilot study of plasma caffeine concentrations in a US sample of smoker and nonsmoker volunteers,". *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* (2003) 27(1):165-171. 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. Patterns of adult caffeine consumption remain relatively stable as people age, with some modest reduction in older age. 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. James JE, *Caffeine and Health* (1991) Academic Press, London; James JE, *Understanding Caffeine: A Biobehavioral Analysis* (1997) Sage Publications, Thousand Oaks, CA.

Coffee is the major source of caffeine in the adult population. Caffeine is a drug. [Testimony of Dr. Laura M. Juliano in *CERT v. Starbucks* trial, September 19, 2018 p.m. at p . 168, lines 11-15].

"[I]n order to understand caffeine exposure, one needs to understand coffee consumption. And also being that caffeine is a primary reinforcing ingredient in coffee, people consumer coffee because of the caffeine. It's a reinforcer. Most people consume caffeinated coffee. So to fully understand coffee consumption, one needs to understand the primary reinforcing ingredient in coffee, which is caffeine." [Testimony of Dr. Laura M. Juliano September 19, 2018 p.m. at 196:11-15].

C. Adverse Non-Cancer Effects in Humans

1. Adverse Psychological and Physiological Effects

a. Caffeine Intoxication

Caffeine can cause a caffeine intoxication syndrome that consists of symptoms including restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, inexhaustibility, and psychomotor agitation. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* Washington DC (2013). The DSM-5 includes a diagnosis of caffeine intoxication syndrome. *Id.* The International Classification of Diseases - Tenth revision (ICD-10) includes a diagnosis of acute caffeine intoxication. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization (1992).

b. Caffeine Withdrawal

Caffeine produces physical dependence in habitual consumers, which manifests as a characteristic withdrawal syndrome upon acute abstinence. Juliano LM, Griffiths RR, "A critical

review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features," *Psychopharmacology* (2004) 176(1):1-29.

Caffeine withdrawal is characterized by symptoms including but not limited to headache, fatigue or drowsiness, difficulty concentrating, dysphoric mood, depressed mood or irritability, flu-like symptoms, nausea, vomiting, muscle pain or stiffness. Juliano LM, Griffiths RR, "A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features," *Psychopharmacology* (2004) 176(1):1-29; Juliano LM, Huntley ED, Harrell PT, Westerman AT, "Development of the caffeine withdrawal symptom questionnaire: caffeine withdrawal symptoms cluster into 7 factors," *Drug Alcohol Dependence* (2012) 124(3):229-234; American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* Washington DC (2013).

Daily doses of caffeine as low as 100 mg have been shown to produce physical dependence in humans. Evans SM, Griffiths RR, "Caffeine withdrawal: a parametric analysis of caffeine dosing conditions. *J. Pharmacol. Exper. Therap.* (1999) 289(1):285-294; Griffiths RR, Evans SM, Heishman SJ, Preston KL, Sannerud CA, Wolf B, Woodson PP, "Low-dose caffeine physical dependence in humans," *J. Pharmacol. Exper. Therap.* (1990) 255(3):1123-1132..

Caffeine withdrawal syndrome can persist for 2 to 9 days. Griffiths RR, Evans SM, Heishman SJ, Preston KL, Sannerud CA, Wolf B, Woodson PP, "Low-dose caffeine physical dependence in humans," *J. Pharmacol. Exper. Therap.* (1990) 255(3):1123-1132; Juliano LM, Griffiths RR, "A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features," *Psychopharmacology* (2004) 176(1):1-29; van Dusseldorp M, Katan MB, " Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial," *Br. Med. J.* (1990) 300(6739):1558-1559; Höfer I, Bättig K, "Cardiovascular, behavioral, and subjective effects of caffeine under field conditions," *Pharmacol. Biochem. Behavior* (1994) 48(4):899-908.

Caffeine withdrawal syndrome is a clinically important phenomenon that can cause significant distress and impairment in completing one's normal daily activities. Juliano LM, Evatt DP, Richards, BD, Griffiths RR, "Characterization of individuals seeking treatment for caffeine dependence," *Psychol. Addict. Behaviors* (2012) 26(4):948-954; Strain EC, Mumford G, Silverman K, Griffiths RR, "Caffeine dependence syndrome: Evidence from case histories and experimental evaluations," *J. Am. Med. Assn.* (1994) 272(13):1043–1048.

Caffeine withdrawal headache has been described as diffuse, throbbing, severe, and sensitive to movement. Juliano LM, Griffiths RR, "A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features," *Psychopharmacology* (2004) 176(1):1-29.

Caffeine consumers who abstain from caffeine for medical procedures are at high risk of experiencing caffeine withdrawal including post-operative headache. Fennelly M, Purdie GI, "Is Caffeine Withdrawal the Mechanism of Postoperative Headache?" *Anesthesia Analgesia* (1991) 72(4):449-453; Hampl KF, Schneider MC, Rüttimann U, Ummenhofer W, Drewe J," Perioperative administration of caffeine tablets for prevention of postoperative headaches," *Canadian J. Anesthesia* (1995) 42(9):789-792; Weber JG, Ereth MH, Danielson DR, "Perioperative ingestion of caffeine and postoperative headache," *Mayo Clinic Proc.* (1993) 68(9):842-845.

In addition to physical symptoms coffee/caffeine withdrawal is associated with decrements in mood and psychomotor/cognitive performance. James JE, "Acute and chronic effects of caffeine on performance, mood, headache, and sleep," *Neuropsychobiology* (1998) 38(1):32-41; James JE, Gregg ME, Kane M, Harte F, "Dietary caffeine, performance and mood: enhancing and restorative effects after controlling for withdrawal reversal," *Neuropsychobiology* (2005) 52(1):1; James JE, Rogers PJ, "Effects of caffeine on performance and mood: withdrawal reversal is the most plausible explanation," *Psychopharmacology* (2005) 182(1):1-8; James JE, "Caffeine-induced enhancement of cognitive performance: Confounding due to reversal of withdrawal effects," *Australian J. Psychol.* (2005) 57(3):197-200; Rogers PJ, Martin J, Smith C, Heatherley SV, Smit HJ, "Absence of

reinforcing, mood and psychomotor performance effects of caffeine in habitual non-consumers of caffeine," *Psychopharmacology* (2003) 167(1):54-62; Rogers PJ, Heatherley SV, Mullings EL, Smith JE, "Faster but not smarter: effects of caffeine and caffeine withdrawal on alertness and performance," *Psychopharmacology* (2013) 226(2):229-240; Yeomans MR, Ripley T, Davies LH, Rusted JM, Rogers PJ, "Effects of caffeine on performance and mood depend on the level of caffeine abstinence," *Psychopharmacology* (2002) 164(3):241-249.

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 SV, Hayward RC, Seers HE, Rogers PJ, "Cognitive and psychomotor performance, mood, and pressor effects of caffeine after 4, 6 and 8 h caffeine abstinence," *Psychopharmacology.* (2005) 178(4):461-470.

Negative withdrawal effects (e.g., dysphoric mood, inattention, lethargy) are commonplace within the general population of coffee consumers. Griffiths RR, Evans SM, Heishman SJ, Preston KL, Sannerud CA, Wolf B, Woodson PP, "Low-dose caffeine physical dependence in humans," *J. Pharmacol. Exp. Ther.* (1990) 255(3):1123-1132; Hughes JR, Higgins ST, Bickel WK, Hunt WK, Fenwick JW, Gulliver SB, Mireault GC, "Caffeine self-administration, withdrawal, and adverse effects among coffee drinkers," *Arch. Gen. Psychiatry* (1991) 48(7):611-617; Hughes JR, "Clinical importance of caffeine withdrawal," *New Engl. J. Med.* (1992) 327(16):1160; Hughes JR, Oliveto AH, Bickel WK, Higgins ST, Badger GJ, "Caffeine self-administration and withdrawal: incidence, individual differences and interrelationships," *Drug Alcohol Depend.* (1993) 32(3):239-246; Hughes JR, Hale KL, "Behavioral effects of caffeine and other methylxanthines on children," *Exp, Clin. Psychopharmacol.* (1998) 6(1):87-95; Juliano LM, Griffiths RR. A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology*. (2004) 176(1):1-29.

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. [Report of Dr. Jack E. James]

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 SV, Hayward RC, Seers HE, Rogers PJ, "Cognitive and psychomotor performance, mood, and pressor effects of caffeine after 4, 6 and 8 h caffeine abstinence," *Psychopharmacology* (2005) 178(4):461-470; James JE, "Does caffeine enhance or merely restore degraded psychomotor performance?" *Neuropsychobiology* (1994) 30(2-3):124-125; James JE, "Acute and chronic effects of caffeine on performance, mood, headache, and sleep," *Neuropsychobiology* (1998) 38(1):32-41; James JE, Gregg ME, Kane M, Harte F, "Dietary caffeine, performance and mood: enhancing and restorative effects after controlling for withdrawal reversal," *Neuropsychobiology* (2005) 52(1):1; James JE, Rogers PJ, "Effects of caffeine on performance and mood: withdrawal reversal is the most plausible explanation," *Psychopharmacology* (2005) 182(1):1-8; James JE, Caffeine-induced enhancement of cognitive performance: Confounding due to reversal of withdrawal effects," *Australian J. Psychol*. (2005) 57(3):197-200; Judelson DA, Armstrong LE, Sökmen B, Roti MW, Casa DJ, Kellogg MD, "Effect of chronic caffeine intake on choice reaction time, mood, and visual vigilance," *Physiology Behavior* (2005) 85(5):629-34; Rogers JE, "Effects of caffeine on performance and mood: withdrawal reversal is the most plausible explanation," *Psychopharmacology* (2005) 182:1-8.

Most reports of reputed coffee-induced enhancement of psychomotor/cognitive performance failed to control for reversal of abstinence-induced negative withdrawal effects. James JE, "Does caffeine enhance or merely restore degraded psychomotor performance?" *Neuropsycholobiology* (1994) 30(2-3):124-125; James JE, Gregg ME, "Effects of dietary caffeine on mood when rested and sleep restricted," *Human Psychoharmacol. Clin. Exp.* (2004) 19(5):331-341; James JE, "Critical review of dietary caffeine and blood pressure: a relationship that should be

taken more seriously," *Psychosomatic Med.* (2004) 66(1):63-71. 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 JE, "Acute and chronic effects of caffeine on performance, mood, headache, and sleep," *Neuropsychobiology* (1998) 38(1):32-41; James JE, Gregg ME, Kane M, Harte F, "Dietary caffeine, performance and mood: enhancing and restorative effects after controlling for withdrawal reversal," *Neuropsychobiology* (2005) 52(1):1; James JE, Rogers PJ, "Effects of caffeine on performance and mood: withdrawal reversal is the most plausible explanation," *Psychopharmacology* (2005) 182(1):1-8; James JE, Caffeine-induced enhancement of cognitive performance: Confounding due to reversal of withdrawal effects," *Australian J. Psychol*. (2005) 57(3):197-200; Judelson DA, Armstrong LE, Sökmen B, Roti MW, Casa DJ, Kellogg MD, "Effect of chronic caffeine intake on choice reaction time, mood, and visual vigilance," *Physiology Behavior* (2005) 85(5):629-634; Rogers JE, " Effects of caffeine on performance and mood: withdrawal reversal is the most plausible explanation," *Psychopharmacology* (2005) 182:1-8) or children. Heatherley SV, Hancock KM, Rogers PJ, "Psychostimulant and other effects of caffeine in 9- to 11-year-old children," *J. Child Psychol. Psychiatgry* (2006) 47(2):135-142.

The DSM-5 includes a diagnosis of caffeine withdrawal syndrome. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, Washington DC (2013). The IDC-10 includes a diagnosis of caffeine withdrawal syndrome. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization (1992).

c. Anxiety

Caffeine increases anxiety in humans. Alsene K, Deckert J, Sand P, de Wit H, "Association between A2a receptor gene polymorphisms and caffeine-induced anxiety," *Neuropsycho-*

pharmacology (2003) 28(9):1694-1702; Boulenger, JP, Salem N, Marangos PJ, Uhde TW, "Plasma adenosine levels: measurement in humans and relationship to the anxiogenic effects of caffeine," *Psychiatry Res.* (1987) 21(3):247-255; Charney DS, Galloway MP:, Heninger GR, "The effects of caffeine on plasma MHPG, subjective anxiety, autonomic symptoms and blood pressure in healthy humans," *Life Sci.* (1984) 35(2:135-144; Orlikov A, Ryzov I, "Caffeine-induced anxiety and increase of kynurenine concentration in plasma of healthy subjects: a pilot study," *Biolog. Psychiatry* (1991) 29(4):391-396; Shanahan MP, Hughes RN, "Potentiation of performance-induced anxiety by caffeine in coffee," *Psychological Rep.* (1986) 59(1):83-86; Veleber, DM, Templer DI, "Effects of caffeine on anxiety and depression," *J. Abnormal Psychol.* (1984) 93(1):120-122.

Caffeine can trigger panic attacks, especially among individuals prone to anxiety. Klein E, Zohar J, Geraci MF, Murphy DL, Uhde TW, "Anxiogenic effects of m-CPP in patients with panic disorder: comparison to caffeine's anxiogenic effects," *Biological Psychiatry* (1991) 30(10):973-984; Masdrakis VG, Papakostas YG, Vaidakis N, Papageorgiou C, Pehlivanidis A, "Caffeine challenge in patients with panic disorder: baseline differences between those who panic and those who do not," *Depression Anxiety* (2008) 25(9):E72-E79; Nardi Ae, Lopes fl, Valença AM, Freire RC, Veras, AB, de-Melo-Neto VL, Zin WA, "Caffeine challenge test in panic disorder and depression with panic attacks," *Comprehensive Psychiatry* (2007) 48(3):257-263; Nardi AE, Lopes FL, Freire RC, Veras AB, Nascimento I, Valença AM, Mezzasalma MA, "Panic disorder and social anxiety disorder subtypes in a caffeine challenge test," *Psychiatry Res.* (2009) 169(2):149-153; Vilarim MM, Rocha Araujo DM, Nardi AE, "Caffeine challenge test and panic disorder: a systematic literature review," *Expert Rev. Neurotherapeutics* (2011) 11(8):1185-1195.

The DSM-5 includes a diagnosis of caffeine induced anxiety disorder. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, Washington DC (2013).

d. Sleep Disorders

Caffeine disrupts planned sleep. Clark I, Landolt HP, "Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials," *Sleep Med. Rev.* (2017) 31:70-78; Cousins J, Bell IR, Bootzin RR, "Coffee-Related Insomnia," In *Coffee in Health and Disease Prevention*. (Elsevier Inc. 2015); Roehrs T, Roth T, "Caffeine: sleep and daytime sleepiness," *Sleep Med. Rev.* (2008) 12(2):153-162.

Caffeine increases the latency to sleep, decreases total sleep time, and increases nighttime awakenings, and decreases the perceived quality of sleep. Březinová V, "Effect of caffeine on sleep: EEG study in late middle age people," *Br. J. Clin. Pharmacol.* (1974) 1(3):203-208; Clark I, Landolt HP, "Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials," *Sleep Med. Rev.* (2017) 31:70-78; Cousins J, Bell IR, Bootzin RR, "Coffee-Related Insomnia," In *Coffee in Health and Disease Prevention*. (Elsevier Inc. 2015); Drapeau C, Hamel-Hébert I, Robillard R, Selmaoui B, Filipini D, Carrier J, "Challenging sleep in aging: the effects of 200 mg of caffeine during the evening in young and middle-aged moderate caffeine consumers," *J. Sleep Res.* (2006) 15(2):133-141; Hindmarch I, Rigney U, Stanley N, Quinlan P, Rycroft J, Lane J, "A naturalistic investigation of the effects of day-long consumption of tea, coffee and water on alertness, sleep onset and sleep quality," *Psychopharmacology* (2000) 149(3):203-216; LaJambe CM, Kamimori GH, Belenky G, Balkin TJ, "Caffeine effects on recovery sleep following 27 h total sleep deprivation," *Aviation Space Environ. Med.* (2005) 76(2):108-113; Shilo L, Sabbah H, Hadari R, Kovatz S, Weinberg U, Doley S, Shenkman L, "The effects of coffee consumption on sleep and melatonin secretion," *Sleep Med.* (2002) 3(3):271-273; Smith A, Maben A, Brockman P, Effects of evening meals and caffeine on cognitive performance, mood and cardiovascular functioning," *Appetite* (1994) 22(1):57-65.

Coffee consumption and caffeine use is associated with higher risk of insomnia and sleep problems. Chaudhary NS, Grandner MA, Jackson NJ, Chakravorty S, "Caffeine consumption, insomnia, and sleep duration: Results from a nationally representative sample," *Nutr.* (2016) 32(11): 1193-1199; Cousins J, Bell IR, Bootzin RR, "Coffee-Related Insomnia," In *Coffee in Health and Disease Prevention*. (Elsevier Inc. 2015); Fabsitz R, Sholinsky P, Goldberg J, "Correlates of sleep problems among men: the Vietnam Era Twin Registry, " J. *Sleep Res.* (1997) 6(1):50-56; Shirlow MJ, Mathers CD, "A study of caffeine consumption and symptoms: indigestion, palpitations, tremor, headache and insomnia," *Int. J. Epidemiol.* (1985) 14(2):239-248; Singareddy R, Vgontzas AN, Fernandez-Mendoza J, Liao D, Calhoun S, Shaffer ML, Bixler EO, "Risk factors for incident chronic insomnia: a general population prospective study," *Sleep Med.* (2012) 13(4):346-353.

Caffeine abstinence increases sleep time and improves sleep quality. Juliano LM, Griffiths RR, "A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features," *Psychopharmacology* (2004) 176(1):1-29; Sin CW, Ho JS, Chung JW, "Systematic review on the effectiveness of caffeine abstinence on the quality of sleep," *J. Clin. Nursing* (2009) 18(1):13-21.

The DSM-5 includes a diagnosis of caffeine induced sleep disorder. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, Washington DC (2013).

e. Problematic Caffeine Use

Caffeine use can result in a cluster of problematic symptoms that characterize a substance use disorder. Addicott MA, "Caffeine use disorder: a review of the evidence and future implications," *Current Addiction Rep.* (2014) 1(3):186-192; Bernstein GA, Carroll ME, Thuras PD, Cosgrove KP, Roth ME, "Caffeine dependence in teenagers,"*Drug Alcohol Dependence* (2002) 66(1):1-6; Budney AJ, Lee DC, Juliano LM, "Evaluating the validity of caffeine use disorder,"

Current Psychiatry Rep. (2015) 17(9):74; Jones HA, Lejuez CW, "Personality correlates of caffeine dependence: the role of sensation seeking, impulsivity, and risk taking," *Exp. Clin. Psycho-pharmacol.* (2005) 13(3):259-266; Juliano, LM, Evatt DP, Richards BD, Griffiths RR, "Characterization of individuals seeking treatment for caffeine dependence," *Psychol. Addict. Behaviors* (2012) 26(4):948-954; Meredith Se, Juliano LM, Hughes JR, Griffiths RR, "Caffeine use disorder: a comprehensive review and research agenda," *J. Caffeine Res.* (2013) 3(3):114-130; Oberstar JV, Bernstein GA, Thuras PD, Caffeine use and dependence in adolescents: one-year follow-up," *J. Child Adolescent Psychopharmacol.* (2002) 12(2):127-135; Ogawa N, Ueki H "Clinical importance of caffeine dependence and abuse," *Psychiatry Clin. Neurosci.* (2007) 61(3):263-268; Strain EC, Mumford G, Silverman K, Griffiths RR, "Caffeine dependence syndrome: Evidence from case histories and experimental evaluations," *J. Am. Med. Assn.* (1994) 272(13):1043-1048; Striley CL, Griffiths RR, Cottler LB, "Evaluating dependence criteria for caffeine," *J. Caffeine Res.* (2011) 1(4):219-225; Svikis SA, Berger N, Haug, NA, Griffith RR, "Caffeine dependence in combination with a family history of alcoholism as a predictor of continued use of caffeine during pregnancy," *Am. J. Psychiatry* (2005) 162(12):2344-2351.

Problematic caffeine use is characterized by symptoms including but not limited to unsuccessful attempts to quit or cut down, withdrawal symptoms upon acute abstinence, and continued use despite physical or psychological harm. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5),* Washington DC (2013); Budney AJ, Lee DC, Juliano LM, "Evaluating the validity of caffeine use disorder," *Current Psychiatry Rep.* (2015) 17(9):74.

A wide range of daily doses of caffeine have been found to be associated with problematic caffeine use. Bernstein GA, Carroll ME, Thuras PD, Cosgrove KP, Roth ME, "Caffeine dependence in teenagers,"*Drug Alcohol Dependence* (2002) 66(1):1-6; Juliano LM, Evatt DP, Richards BD, Griffiths RR, "Characterization of individuals seeking treatment for caffeine dependence," *Psychology Addict. Behaviors* (2012) 26(4):948; Strain EC, Mumford G, Silverman K, Griffiths RR,

"Caffeine dependence syndrome: Evidence from case histories and experimental evaluations," *J. Am. Med. Assn.* (1994) 272(13):1043-1048.

A population of individuals who are interested in or who are seeking professional treatment for problematic caffeine use has been identified. Evatt DP, Juliano LM, Griffiths RR, "A brief manualized treatment for problematic caffeine use: A randomized control trial," *J. Consult. Clin. Psychol.* (2016) 84(2):113-121; Juliano LM, Evatt DP, Richards BD, Griffiths RR, "Characterization of individuals seeking treatment for caffeine dependence," *Psychol. Addict. Behav.* (2012) 26(4):948.

The DSM-5 includes caffeine use disorder as a condition for further study. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, Washington DC (2013). The ICD-10 includes a diagnosis of caffeine dependence syndrome. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization (1992).

The mechanism responsible for caffeine dependence is believed to involve adenosine upregulation resulting in hypersensitivity during abstinence. This hypothesis is consistent with the variety of symptoms experienced by habitual coffee/caffeine consumers during periods of abstinence. James JE, "Dietary caffeine:"unnatural" exposure requiring precaution?" *J. Substance Use*. (2014) 19(5):394-397.

2. Adverse Pregnancy Outcomes

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.

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.

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."

Reduced fetal blood flow has been demonstrated to result from caffeine exposure. Hoecker C, Nelle M, Beedgen B, Rengelshausen J, Linderkamp O, "Effects of a divided high loading dose of caffeine on circulatory variables in preterm infants," *Arch. Dis. Childhood-Fetal Neonatal Ed.* (2006) 91(1):F61-F64; Lane AJ, Coombs RC, Evans DH, Levin RJ, "Effect of caffeine on neonatal splanchnic blood flow," *Arch. Dis. Childhood-Fetal Neonatal Ed*. (1999) 80(2):F128-F129; Momoi N, Tinney JP, Liu LJ, Elshershari H, Hoffmann PJ, Ralphe JC, Keller BB, Tobita K, "Modest maternal caffeine exposure affects developing embryonic cardiovascular function and growth," Am. J. Physiol/ Heart Circul. Physiology. (2008) 294(5):H2248-56. Reduced fetal blood flow may be the principal mechanism of action for some adverse pregnancy outcomes (e.g., birth weight).

It was hypothesized that adverse pregnancy outcomes might be attributable to first trimester nausea. Stein Z, Susser M, "Miscarriage, caffeine, and the epiphenomena of pregnancy: the causal model," *Epidemiology* (1991) 2(3):163-167. 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 L, Eskenazi B, Windham GC, Swan SH, "Caffeine consumption during pregnancy and spontaneous abortion," *Epidemiology* (1991) 168-174; Giannelli M, Doyle P, Roman E, Pelerin M, Hermon C, "The effect of caffeine consumption and nausea on the risk of miscarriage," *Paediatr. Perinatal Epidemiology* (2003) 17(4):316-323.

a. Reduced Fetal Weight and Growth

Many studies have reported an association between coffee consumption during pregnancy and low birth weight. Several meta-analyses over the past two decades have evaluated the risk of low birth weight from maternal consumption of coffee during pregnancy. Fernandes O, Sabharwal M, Smiley T, Pastuszak A, Koren G, Einarson T, "Moderate to heavy caffeine consumption during pregnancy and relationship to spontaneous abortion and abnormal fetal growth: a meta-analysis," *Reprod. Toxicol.* (1998) 12(4):435-444; Santos IS, Victora CG, Huttly S, Carvalhal JB, "Caffeine intake and low birth weight: a population-based case-control study," *Am. J. Epidemiol.* (1998) 147(7):620-627; Chen LW, Wu Y, Neelakantan N, Chong MF, Pan A, van Dam RM, "Maternal caffeine intake during pregnancy is associated with risk of low birth weight: a systematic review and dose-response meta-analysis," *BMC Medicine.* (2014) 12(1):174; Greenwood DC, Thatcher NJ, Ye J, Garrard L, Keogh G, King LG, Cade JE, "Caffeine intake during pregnancy and adverse birth outcomes: a systematic review and dose-response meta-analysis," *Eur. J. Epidemiol.* (2014) 725-734; Rhee J, Kim R, Kim Y, Tam M, Lai Y, Keum N, Oldenburg CE, "Maternal caffeine consumption during pregnancy and risk of low birth weight: a dose-response meta-analysis of observational studies," *PLoS One*. (2015) 10(7):e0132334.

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 O, Sabharwal M, Smiley T, Pastuszak A, Koren G, Einarson T, "Moderate to heavy caffeine consumption during pregnancy and relationship to spontaneous abortion and abnormal fetal growth: a meta-analysis," *Reproduct. Toxicol.* (1998) 12(4):435-444.

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 IS, Victora CG, Huttly S, Morris S, "Caffeine intake and pregnancy outcomes: a meta-analytic review," *Cad. Saude Publica* (1998) 14(3):523-530.

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 LW, Wu Y, Neelakantan N, Chong MF, Pan A, van Dam RM, "Maternal caffeine intake during pregnancy is associated with risk of low birth weight: a systematic review and dose-response meta-analysis," *BMC Medicine.* (2014) 12(1):174.

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 DC, Thatcher NJ, Ye J, Garrard L, Keogh G, King LG, Cade JE, "Caffeine intake during pregnancy and adverse birth outcomes: a systematic review and dose-response meta-analysis," *Eur. J. Epidemiol.* (2014) 725-734;

Rhee found that the highest versus lowest level of caffeine intake during pregnancy resulted in a 38% increased risk of low birth weight. Rhee J, Kim R, Kim Y, Tam M, Lai Y, Keum N, Oldenburg CE, "Maternal caffeine consumption during pregnancy and risk of low birth weight: a dose-response meta-analysis of observational studies," *PLoS One*. (2015) 10(7):e0132334.

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.

b. Pregnancy Loss

The findings of studies concerning the association between maternal caffeine consumption during pregnancy and spontaneous abortion mirror those for low birth weight.

Four meta-analyses have evaluated the risk of spontaneous abortion from maternal consumption of coffee during pregnancy.

Fernandes found a 36% increased risk of spontaneous abortion for women who consumed caffeine during pregnancy. Fernandes O, Sabharwal M, Smiley T, Pastuszak A, Koren G, Einarson T, "Moderate to heavy caffeine consumption during pregnancy and relationship to spontaneous abortion and abnormal fetal growth: a meta-analysis," *Reproduct. Toxicol.* (1998) 12(4):435-444.

Greenwood reported a 14% increased risk of spontaneous abortion and a 19% increased risk of stillbirth among women who consumed caffeine during pregnancy. Greenwood DC, Thatcher NJ, Ye J, Garrard L, Keogh G, King LG, Cade JE, "Caffeine intake during pregnancy and adverse birth outcomes: a systematic review and dose-response meta-analysis," *Eur. J. Epidemiol.* (2014) 725-734.

Chen found a 7% increased risk of pregnancy loss among women who consumed 100 mg of caffeine per day. Chen LW, Wu Y, Neelakantan N, Chong MF, Pan A, van Dam RM, "Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose–response meta-analysis of prospective studies," *Public Health Nutr.* (2016) 19(7):1233-1244.

Li reported a dose-response relationship between maternal consumption of coffee/caffeine and pregnancy loss. Li J, Zhao H, Song JM, Zhang UJ, Tang YO, Xin CM, "A meta-analysis of risk of pregnancy loss and caffeine and coffee consumption during pregnancy," *Int. J. Gynaecol. Obstet.* (2015) 130(2):116-122.

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. [Report of Dr. Jack E. James]

c. Infertility and Infertility Treatment

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 KL, Domar AD, "The impact of lifestyle behaviors on infertility treatment outcome," *Curr. Opin. Obstetr. Gynecol*. (2014) 26(3):181-185; Tan SQ Huang Ey, Lau MSK, Viardot V, Teo S, Chan J, Tan HH, Nadarajah S, "Lifestyle Behaviours in Women Undergoing In Vitro Fertilizatoin (IVF) in Singapore: A Cross Sectional Survey," *Women's Health Gynecol.* (2016) 2(1):1-4.. It is routine clinical practice for couples seeking fertility treatment to be advised to abstain from caffeine beverages. *Id.* Adverse effects on fertility have been reported for both male and female fertility.

(1) Fertility effects in men

Coffee/caffeine consumption has been associated with sperm head and neck abnormalities. Jurewicz J, Radwan M, Sobala W, Ligocka D, Radwan P, Bochenek M, Hanke W, "Lifestyle and semen quality: role of modifiable risk factors," *Systems Biol. Reprod. Med.* (2014) 60(1):43-51.

Coffee/caffeine consumption has also been associated with chromosomal abnormalities in sperm. Robbins WA, Vine MF, Truong KY, Everson RB, "Use of fluorescence in situ hybridization (FISH) to assess effects of smoking, caffeine, and alcohol on aneuploidy load in sperm of healthy men," *Environ. Mol. Mutagen*. (1997) 30(2):175-183; Jurewicz J, Radwan M, Sobala W, Radwan P, Jakubowski L, Hawua W, Ulaska A, Hanke W, "Lifestyle factors and sperm aneuploidy," *Reprod. Biol*. (2014) 14(3):190-199.

Coffee intake was found to have an independent negative effect on sperm quality in more than 1600 male patients undergoing assistive reproductive technologies. Wogatzky J, Wirleitner B,

Stecher A, Vnderzwalmen P, Neyer A, Spitzer D, Schuff M, Schechinger B, Zech NH, "The combination matters--distinct impact of lifestyle factors on sperm quality: a study on semen analysis of 1683 patients according to MSOME criteria," *Reprod. Biol. Endocrinol.* 15:115.

(2) Fertility effects in women

Studies have repeatedly reported associations between coffee/caffeine consumption and delayed conception. Wilcox A, Weinberg C, Baird D, "Caffeinated beverages and decreased fertility," *Lancet* (1988);2(8626-8627):1453-1456.

An association between higher caffeine consumption and subfecundity was consistently observed for randomly selected samples of women in each of 5 European countries. Bolumar F, Olsen J, Rebagliato M, Bisanti L, "European Study Group on Infertility and Subfecundity. Caffeine intake and delayed conception: a European multicenter study on infertility and subfecundity," *Am. J. Epidemiol.* (1997) 145(4):324-334.

As an adenosine receptor antagonist, caffeine may contribute to delayed conception due to altered ovulation and menstrual characteristics. Wesselink AK, Wise LA, Rothman KJ, Han KA, Mikkelsen FM, Mahalingaiah S, Hatch EE, "Caffeine and caffeinated beverage consumption and fecundability in a preconception cohort," *Reprod. Toxicol.* 62:39-45.

3. Adverse Effects in Children and Adolescents

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 SM, Schaechter JL, Hershorin ER, Lipshultz SE, "Health effects of energy drinks on children, adolescents, and young adults," *Pediatrics* (2011) 127(3):511-528. 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 JE, "Dietary caffeine:"unnatural" exposure requiring precaution?" *J. Substance Use* (2014) 19(5):394-397; Pettit ML, DeBarr KA, "Perceived stress, energy drink consumption, and academic performance among college students," *J. Am. Coll. Health* (2011) 59(5):335-341; Schneider MB, Benjamin HJ, "Sports drinks and energy drinks for children and adolescents: are they appropriate?" *Pediatrics* (2011) 127(6):1182-1189; Temple JL, "Caffeine use in children: what we know, what we have left to learn, and why we should worry," *Neurosci. Biobehav Rev.* (2009) 33(6):793-806.

As an adenosine antagonist, caffeine counteracts the somnogenic effects of alcohol and alcohol may lessen the anxiogenic effects of caffeine. Seifert SM, Schaechter JL, Hershorin ER, Lipshultz SE, "Health effects of energy drinks on children, adolescents, and young adults," *Pediatrics* (2011) 127(3):511-528. 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 behavior. Brache K, Stockwell T, "Drinking patterns and risk behaviors associated with combined alcohol and energy drink consumption in college drinkers." *Addict. Behav.* (2011) 36(12):1133-1140; Ferré S, O'Brien MC, "Alcohol and caffeine: the perfect storm," *J. Caffeine Res.* (2011) 1(3):153-162; Howland J, Rohsenow DJ, "Risks of energy drinks mixed with alcohol," *J. Am. Med. Assn.* (2013) 309(3):245-246; Miller KE,."Energy drinks, race, and problem behaviors among college students,"

J. Adolescent Health. (2008) 43(5):490-497; O'Brien MC, McCoy TP, Rhodes SD, Wagoner A, Wolfson M, "Caffeinated cocktails: energy drink consumption, high-risk drinking, and alcohol-related consequences among college students," *Acad. Emergency Med*. (2008) 15(5):453-460.

In a series of large epidemiological studies of adolescent consumption of caffeine from all sources including coffee, James and colleagues reported:

(1) Associations between caffeine consumption and smoking, consumption of alcohol, in-class daytime sleepiness, and feelings of anger. Kristjansson AL, Sigfusdottir ID, Allegrante JP, James JE, "Adolescent caffeine consumption, daytime sleepiness, and anger," *J. Caffeine Res*. (2011) 1(1):75-82.

(2) An association between caffeine consumption and poorer academic performance, which was mediated by caffeine-induced daytime sleepiness. James JE, Kristjánsson ÁL, Sigfúsdóttir Id, "Adolescent substance use, sleep, and academic achievement: evidence of harm due to caffeine," *J. Adolescence*. (2011) 34(4):665-673);

(3) Higher rates of conduct disorders and violence among adolescents who consume more rather than less caffeine. Kristjansson AL, Sigfusdottir ID, Frost SS, James JE, "Adolescent caffeine consumption and self-reported violence and conduct disorder," *J. Youth Adolescence* (2013) 42(7):1053-1062.

(4) 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 AL, Sigfusdottir ID, Mann MJ, James JE, "Caffeinated sugar-sweetened beverages and common physical complaints in Icelandic children aged 10–12 years," *Prev. Med*. (2014) 58:40-44.

(5) 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 AL, Mann MJ, Sigfusdottir ID, James JE. Mode of daily caffeine consumption among

adolescents and the practice of mixing alcohol with energy drinks: relationships to drunkenness. *J. Studies Alcohol Drugs* (2015) 76(3):397-405.

(6) An association between caffeine consumption and adolescent violence, which was mediated by caffeine-induced anger. James JE, Kristjansson AL, Sigfusdottir ID, "A gender-specific analysis of adolescent dietary caffeine, alcohol consumption, anger, and violent behavior," *Substance Use Misuse* (2015) 50(2):257-267.

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 O, Morelli M, "Caffeine and the dopaminergic system," *Behavioural Pharmacology.* (2005) 16(2):63-77. 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 JE, Kristjánsson ÁL, Sigfúsdóttir ID, "Adolescent substance use, sleep, and academic achievement: evidence of harm due to caffeine," *J. Adolescence* (2011) 34(4):665-673; James JE, Kristjansson AL, Sigfusdottir ID, "A gender-specific analysis of adolescent dietary caffeine, alcohol consumption, anger, and violent behavior," *Substance Use Misuse* (2015) 50(2):257-267; Kristjansson AL, Sigfusdottir ID, Allegrante JP, James JE, "Adolescent caffeine consumption, daytime sleepiness, and anger," *J. Caffeine Res*. (2011) 1(1):75-82; Reissig CJ, Strain EC, Griffiths RR, "Caffeinated energy drinks—a growing problem,".*Drug Alcohol Dependence* (2009) 99(1-3):1-10; Temple JL, "Caffeine use in children: what we know, what we have left to learn, and why we should worry," *Neurosci. Biobehavior. Rev.* (2009) 33(6):793-806; Thombs DL, O'Mara RJ, Tsukamoto M, Rossheim ME, Weiler RM, Merves JL, Goldberger BA, "Event-level analyses of energy drink consumption and alcohol intoxication in bar patrons," *Addictive Behaviors* (2010) 35(4):325-330.

4. Chronic Diseases

a. Bone Disease

Numerous studies have been published regarding the effects of coffee consumption on bone density and the risk of resultant bone fractures.

A community-based cohort study of postmenopausal California women found a significant association between coffee intake and decreased bone mineral density of the hip and spine. The researchers concluded: "Lifetime caffeinated coffee intake equivalent to two cups per day is associated with decreased bone density in older women who do not drink milk on a daily basis." Barrett-Connor E, Chang JC, Edelstein SL, "Coffee-associated osteoporosis offset by daily milk consumption: the Rancho Bernardo Study," *J. Am. Med. Assn.* (1994) 271(4):280-283.

A cohort study of coffee consumption and CYP1A2 genotype, found that men who drank ≥4 cups of coffee/day had 4% lower bone mineral density at the proximal femur than low or nondrinkers, and that in high consumers of coffee, those with rapid metabolism of caffeine (C/C genotype) had lower bone mineral density at the femoral neck and at the trochanter. Hallström H, Melhus H, Glynn A, Lind L, Syvänen AC, Michaëlsson K, "Coffee consumption and CYP1A2 genotype in relation to bone mineral density of the proximal femur in elderly men and women: a cohort study," *Nutr. Metabol.* (2010) 7(1):12.

A meta-analysis of 10 prospective studies showed an overall 3.5% higher risk of fracture per cup of coffee per day (RR 1.05, 95% CI 1.02 - 1.08) and a dose-response relationship for consumption and risk of fractures for men and women combined and women specifically. Liu H, Yao K, Zhang W, Zhou J, Wu T, He C, "Coffee consumption and risk of fractures: a meta-analysis," *Arch. Med. Sci.* (2012) 8(5):776-783.

A meta-analysis of 6 case-control studies and 8 cohort studies reported an overall 30% increase in bone fracture in both sexes combined, with a greater than 50% excess from the 8 studies

in women (RR 1.55, 95% CI 1.15 - 2.08). The increased risk for coffee consumption was greatest among those above age 70 (RR 1.40, 95% CI 1.02 - 1.94), especially in North America (RR 1.49, 95% CI 1.49 - 1.90). Li XL, Xu JH, "Coffee consumption and hip fracture risk: a meta-analysis," *J. Nutr. Sci.* (2013) 2:e23.

A meta-analysis of 9 cohort and 8 case-control studies found an increased risk of fracture in women (RR 1.14, 95% CI 1.05 - 1.24) but not men, especially among women consuming 8 cups per day (RR 1.54, 95% CI 1.19 - 1.99). The risk of osteoporotic fracture was significantly increased in studies of both sexes (RR 1.35, 95% CI 1.06 - 1.73). Lee DR, Lee J, Rota M, Lee J, Ahn HS, Park SM, Shin D, "Coffee consumption and risk of fractures: A systematic review and dose–response meta-analysis,"*Bone* (2014) 63:20-28.

The most recent meta-analysis, based on 10 prospective cohort studies, reported nonsignificant increased risks of fracture for both sexes (RR 1.13, 95% CI 0.86 - 1.48), with higher risks among women (RR 1.27, 95% CI 0.94 - 1.72) and in both sexes when adjustment was made for calcium intake (RR 1.31, 95% CI 0.81 - 2.11). Li S, Dai Z, Wu Q, "Effect of coffee intake on hip fracture: a meta-analysis of prospective cohort studies," *Nutr.* (2015) 14(1):38.

b. Cardiovascular Diseases

Cardiovascular disease generally refers to conditions that involve narrowed or blocked blood vessels that can lead to a heart attack, chest pain (angina) or stroke. Cardiovascular disease includes coronary heart disease, myocardial infarction, stroke, congestive heart failure, and angina pectoris.

A meta-analysis regarding coffee consumption and cardiovascular disease was published by Harvard researchers in 2014. They reported risks of cardiovascular disease for different levels of coffee consumption. They found that the risk of cardiovascular disease was reduced 11% for people who drink 1½ cups of coffee per day (RR 0.89, 95% CI 0.84 - 0.94) and was reduced 15% for people who drink 3 cups of coffee per day (RR 0.85, 95% CI 0.80 - .090), but that the risk of cardiovascular

disease in people who drink 5.5 cups of coffee per day was reduced only 5% (RR 0.87 - 1.03). The absence of a linear dose-response between coffee consumption and cardiovascular disease renders the association between coffee and cardiovascular disease questionable and difficult to interpret. Moreover, since cardiovascular disease is a collection of different diseases with different causes and risk factors, it would be scientifically more appropriate to evaluate the effect of coffee consumption (and consumption of water) on cardiovascular diseases separately. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB, "Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies," *Circulation.* (2014) 129(6):643-659.

A recent systematic review concluded that studies showed that heavy, but not light, coffee consumption was associated with adverse cardiovascular disease effects. Lafortune L, Martin S, Kelly S, Kuhn I, Remes O, Cowan A, Brayne C, "Behavioural risk factors in mid-life associated with successful ageing, disability, dementia and frailty in later life: a rapid systematic review," *PLoS One*. (2016) 11(2):e0144405.

In a recently published prospective cohort study of 3,042 healthy adults followed for 10 years, Greek researchers reported a J-shaped relationship between coffee consumption and cardiovascular disease. Comparing those consuming more than 250 milliliters of coffee per day with those consuming no coffee, the risk of cardiovascular disease was more than doubled for each of three analytical models (Model 1: HR 2.81 (95% CI 1.84 - 4.23, Model 2: HR 2.62, 95% CI 1.67 - 4.09), Model 3 (HR 2.48, 95% CI 1.56 - 1.93). Kouli GM, Panagiotakos DB, Georgousopoulou EN, Mellor DD, Chrysohoou C, Zana A, Tsigos C, Tousoulis D, Stefanadis C, Pitsavos C, "J-shaped relationship between habitual coffee consumption and 10-year (2002–2012) cardiovascular disease incidence: the ATTICA study," *Eur. J. Nutr.* (2018) 57(4):1677-1685.

In Mendelian randomization analyses of coffee consumption and cardiovascular disease in 95,366 Danes and 223,414 individuals, U-shaped associations between coffee intake and cardiovascular disease and all-cause mortality were observed, confirming an increased risk of

cardiovascular disease for high consumption of coffee with a lower risk for medium consumption of coffee. Nordestgaard AT, Nordestgaard BG, "Coffee intake, cardiovascular disease and all-cause mortality: observational and Mendelian randomization analysis in 95 000 - 223 000 individuals," *Int. J. Epidemiol.* (2016) 45(6):1938-1952.

(1) Coronary Heart Disease

Coronary heart disease is a disease in which plaque builds up inside the coronary arteries. It distinguished from other heart conditions that affect the heart muscle, valves or rhythm, which are considered forms of heart disease.

"Coronary heart disease (CHD) is one of the leading causes of mortality in industrialized countries. CHD is responsible for about 19% of all deaths in the United States and UK in recent years, and is rapidly becoming a major cause of death worldwide." Wu JN, Ho SC, Zhou C, Ling Wh, Chen WQ, Wang CL, Chen YM, "Coffee consumption and risk of coronary heart diseases: a meta-analysis of 21 prospective cohort studies," *Int. J. Cardiol.* (2009) 137(3):216-225.

One meta-analysis of coffee consumption and coronary heart disease, based on 13 case-control studies and 10 cohort studies, reported a significantly increased risk of coronary heart disease for consumption of 3 to 4 cups of coffee per day (OR 1.33, 95% CI 1.04 - 1.71; $p < 0.0001$) with an even higher risk for consumption of more than 4 cups of coffee per day (OR 1.83, 95% CI 1.49 - 2.24; $p < 0.0001$). Sofi F, Conti AA, Gori Am, Eliana Luisi ML, Casini A, Abbate R, Gensini GF, "Coffee consumption and risk of coronary heart disease: a meta-analysis," *Nutr. Metab. Cardiovasc. Dis.* (2007) 17(3):209-223.

Another meta-analysis, based on 21 prospective cohort studies, reported lesser risks of coronary heart disease. As compared to light coffee consumption, under the random-effects model, the pooled relative risks for al; studies were 0.96 (95% CI 0.87 - 1.06) for moderate consumption, 1.04 (95% CI 0.92 - 1.17) for heavy consumption, and 1.07 (95% CI 0.87 - 1.32) for very heavy

consumption. Wu JN, Ho SC, Zhou C, Ling WH, Chen WQ, Wang Cl, Chen YM, "Coffee consumption and risk of coronary heart diseases: a meta-analysis of 21 prospective cohort studies," *Int. J. Cardiol.* (2009) 137(3):216-225.

Rather than demonstrating decreased risks of coronary heart disease from coffee consumption, these studies actually reflect increased risks of coronary heart disease with a dose-response.

Associations between fatal coronary heart disease and intake of water and fluids other than water were examined among the 8,280 male and 12,017 female participants aged 38-100 years who were without heart disease, stroke, or diabetes at baseline in 1976 in the Adventist Health Study, a prospective cohort study. Water was the fluid consumed in greatest amounts among the participants. Compared with the national averages, the Adventist Health Study population drank more water, milk, and fruit juices and less coffee, tea, and carbonated and alcoholic beverages. A total of 246 fatal coronary heart disease events occurred during the 6-year follow-up. High daily intake of water (five or more glasses) compared with low (two or fewer glasses) daily water intake was associated with a relative risk of 0.46 (95% CI 0.28 - 0.75; p trend = 0.001) in men, and a relative risk of 0.59 (95% CI: 0.36, 0.97) in women. A high versus low intake of fluids other than water was associated with a relative risk of 2.47 (95% CI: 1.04, 5.88) in women and of 1.46 (95% CI: 0.7, 3.03) in men. All associations remained virtually unchanged in multivariate analysis adjusting for age, smoking, hypertension, body mass index, education, and (in women only) hormone replacement therapy. Chan J, Knutsen SF, Blix GG, Lee JW, Fraser GE, "Water, other fluids, and fatal coronary heart disease: the Adventist Health Study," *Am. J. Epidemiol.* (2002) 155(9):827-833. This study shows an approximate 50% reduction of coronary heart disease for high water intake, but an approximate doubling of the risk of coronary heart disease from consumption of beverages other than water. This study provides strong evidence for a protective effect of high water intake on coronary heart disease in contrast to other beverages which included coffee.

(2) Myocardial Infarction

Myocardial infarction, commonly known as a "heart attack," occurs when blood flow stops to a part of the heart, causing damage (often necrosis) to the heart muscle.

In 1993 Sander Greenland published a meta-analysis of 22 studies of coffee consumption and myocardial infarction or coronary death. Eight of the included studies were case-control studies and fourteen of included studies were cohort studies. Comparing those who drank 5 cups per day with non-drinkers, a significantly increased risk of myocardial infarction or coronary death was found in the 8 case-control studies (RR 1.42, 95% CI 1.30 - 1.55) and a lesser, but significantly increased risk was found in the nine cohort studies published in 1986 or later (RR 1.27, 95% CI 1.17 - 1.39). Greenland S, "A meta-analysis of coffee, myocardial infarction, and coronary death," *Epidemiology* (1993) 366-374.

(3) Stroke

A stroke occurs when brain cells suddenly die to due to a lack of oxygen from obstructed blood flow, which can result from a blocked artery (ischemic stroke) or a ruptured blood vessel (hemorrhagic stroke). The two types of hemorrhagic stroke are intracerebral (within the brain) and subarachnoid, which results from bleeding into the subarachnoid space, usually due to a ruptured aneurysm.

Some case-control studies have reported increased risks of stroke associated with consumption of coffee or caffeine.

In a case-control study of 1,714 Americans diagnosed with intracerebral hemorrhage at age 18 to 49, the adjusted risk for intracerebral hemorrhage was significantly increased among those who consumed more than 5 caffeinated drinks per day (OR 1.73, 95% CI 1.08 - 2.79). Feldmann E, Broderick JP, Kernan WN, Viscoli CM, Brass LM, Brott T, Morgenstern LB, Wilterdink JL,

Horwitz RI, "Major risk factors for intracerebral hemorrhage in the young are modifiable," *Stroke* (2005) 36(9):1881-1885.

In a multicenter case-crossover study of 390 subjects, the relative risk of acute ischemic stroke in the hour after consuming coffee was doubled (RR 2.0, 95% CI 1.4 - 2.8, $p < 0.001$). The association between ischemic stroke in the hour after coffee consumption was only apparent among those consuming 1 cup of coffee per day or less, but not for patients who consumed coffee more regularly (*p*-trend = 0.002). The investigators concluded that coffee consumption transiently increases the risk of ischemic stroke onset, particularly among those who drink coffee infrequently. Mostofsky E, Schlaug G, Mukamal KJ, Rosamond WD, Mittleman MA, "Coffee and acute ischemic stroke onset: the Stroke Onset Study," *Neurology* (2010) 75(18):1583-1588.

In a multicenter case-control study in South Korea of 940 patients with acute hemorrhagic stroke aged 30 to 84 years without a history of stroke, those who consumed caffeine-containing medicines had more than double the risk of all hemorragic stroke (OR 2.23, 95% CI 1.41 - 3.69). Lee SM, Choi NK, Lee BC, Cho KH, Yoon BW, Park BJ, "Caffeine-Containing Medicines Increase the Risk of Hemorrhagic Stroke," *Stroke* (2013) 44(8):2139-2143.

Some cohort studies have reported increased risks of stroke in association with increased consumption of coffee.

In a cohort study of 37,514 Dutch adults who were followed for 13 years, on multivariate analysis, the risk of stroke increased with increasing coffee consumption: 1 to 3 cups/day (RR 0.86, 95% CI 0.39 - 1.87), 3.1 to 6 cups/day (RR 1.20, 95% CI 0.59 - 2.47), more than 6 cups per day (RR 1.34, 95% CI 0.49 - 3.64). de Koning Gans JM, Uiterwaal CS, van der Schouw YT, Boer JM, Grobbee DE, Verschuren WM, Beulens JW, "Tea and coffee consumption and cardiovascular morbidity and mortality," *Arterioscler. Thromb. Vasc. Biol.* (2010) 30(8):1665-1671.

In the Netherlands Cohort Study 120,852 adults aged 55-69 years were followed for 10 years. On multivariate analysis, consumption of more than 6 cups of coffee per day was associated with a slight increased of mortality from stroke among men (RR 1.15, 95% CI 0.74 - 1.77) and women

(RR1.10, 95% CI 0.63 - 1.90). Leurs LJ, Schouten LJ, Goldbohm RA, van den Brandt PA, "Total fluid and specific beverage intake and mortality due to IHD and stroke in the Netherlands Cohort Study," *Br. J. Nutr.*(2010) 104(8):1212-1221.

In a cohort study of Hawaiian men at high risk of cardiovascular disease who were followed for incident stroke over a 25-year period, the risk of thromboembolic stroke, adjusted for other factors, was more than doubled for men who consumed 3 cups of coffee per day compared to nondrinkers (RR 2.1, 95% CI 1.2 - 3.7). Hakim AA, Ross GW, Curb JD, Rodriguez BL, Burchfiel CM, Sharp DS, Yano K, Abbott RD, "Coffee consumption in hypertensive men in older middle-age and the risk of stroke: the Honolulu Heart Program," *J. Clin. Epidemiol.* (1998) 51(6):487-494.

While studies regarding coffee consumption and ischemic and hemorrhagic stroke are mixed, the risk of subarachnoid hemorrhagic stroke has been reported to be increased with consumption of coffee and/or caffeine in most studies. Isaksen J, Egge A, Waterloo K, Romner B, Ingebrigtsen T, "Risk factors for aneurysmal subarachnoid haemorrhage: the Tromsø study," *J. Neurol. Neurosurg. Psychiatry* (2002) 73(2):185-187: more than 5 cups of coffee per day (OR 3.86, 95% CI 1.01 - 14.73); Broderick JP, Viscoli CM, Brott T, Kernan WN, Brass LM, Feldmann E, Morgenstern LB, Wilterdink JL, Horwitz RI "Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable," *Stroke* (2003) 34(6):1375-1381 (5 or more caffeinated drinks per day (OR 1.94, $p < 0.0001$)); Jiménez-Yepes CM, Londoño-Fernández JL, "Risk of aneurysmal subarachnoid hemorrhage: the role of confirmed hypertension," *Stroke*.(2008) 39(4):1344-1346 (OR 1.48, 95% CI 0.86 - 2.55); Larsson SC, Männistö S, Virtanen MJ, Kontto J, Albanes D, Virtamo J, "Coffee and tea consumption and risk of stroke subtypes in male smokers," *Stroke* (2008) 39(6):1681-1687:8 or more cups of coffee per day in men (RR 1.18, 95% CI 0.63 - 2.20); Sugiyama K, Kuriyama S, Akhter M, Kakizaki M, Nakaya N, Ohmori-Matsuda K, Shimazu T, Nagai M, Sugawara Y, Hozawa A, Fukao A, Tsjui I, "Coffee consumption and mortality due to all causes-cardiovasuclar disease, and cancer in Japanese women," *J. Nutr.* (2010) 140(5):1007-1113: 1 cup of coffee per day (RR 1.32, 95% CI 0.44 - 3.95); Vlak MH, Rinkel GJ, Greebe P, van der mon JG, Algra A, "Trigger factors and

their attributable risk for rupture of intracranial aneurysms: a case-crossover study," *Stroke* (2011) 42(7):1878-1882 (RR 1.7, 95% CI 1.2 - 2.4); Larsson SC, Virtamo J, Wolk A, "Coffee Consumption and Risk of Stroke in Women," *Stroke* (2011) 42(4):908-912: 5 or more cups of coffee per day in women (RR 0.27, 95% CI 0.11 - 0.67); Lee SM, Choi NK, Lee BC, Cho KH, Yoon BW, Park BJ, "Caffeine-Containing Medicines Increase the Risk of Hemorrhagic Stroke," *Stroke* (2013) 44(8):2139-2143: caffeine-containing medicines (OR 2.24, 95% CI 1.08 - 4.66); Sakamaki T, Hara M, Kayaba K, Kotani K, Ishikawa S, "Coffee Consumption and Incidence of Subarachnoid Hemorrhage: The Jichi Medical School Cohort Study," *J. Epidemiol.* (2016) 26(2):71-75: 5 or more cups of coffee per day (RR 3.79, 95% CI 1.19 - 12.05).

(4) Heart Failure

Heart failure, often referred to as congestive heart failure, occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs.

In 2012 researchers from Boston published a meta-analysis of coffee consumption and the risk of heart failure that was based on five prospective cohort studies and included 6,522 heart failure events and 140,220 participants. They observed a statistically significant J-shaped relationship between coffee consumption and heart failure. Compared with no consumption, the pooled relative risk for heart failure was 0.96 (95% CI 0.90 - 0.99) for 1 to 2 servings per day, 0.93 (95% CI 0.86 - 0.99) for 2 to 3 servings per day, 0.90 (95% CI 0.82 - 0.99) for 3 to 4 servings per day, 0.89 (95% CI 0.81 - 0.99) for 4 to 5 servings per day, 0.91 (95% CI 0.83 - 1.01) for 5 to 6 servings per day, 0.93 (95% CI 0.85 - 1.02) for 6 to 7 servings per day, 0.95 (95% CI 0.87 - 1.05) for 7 to 8 servings per day, 0.97 (95% CI 0.89 - 1.07) for 8 to 9 servings per day, 0.99 (95% CI 0.90 - 1.10) for 9 to 10 servings per day, 1.01 (95% CI 0.90 - 1.14) for 10 to 11 servings per day, and 1.03 (95% CI 0.89 - 1.19) for 11 servings per day. Thus, dose-response was J-shaped with the strongest inverse association being seen for 4 servings per day. Mostofsky E, Rice MS, Levitan EB, Mittleman MA,

"Habitual Coffee Consumption and Risk of Heart Failure: A Dose-Response Meta-Analysis," *Circulation: Heart Failure* (2012) 5(4):401-405.

(5) Angina Pectoris

Angina pectoris is chest pain due to inadequate supply of oxygen to the heart muscle, usually resulting from , usually resulting from inadequate blood flow as a result of obstruction or spasm of the coronary arteries. The pain is typically severe and crushing, and is characterized by a feeling of pressure and suffocation behind the breastbone. Two studies published in 1995 evaluated the risk of angina pectoris in relation to consumption of coffee.

In a case-control study of nonfatal myocardial infarction among Massachusetts women aged 45-69 years, 858 cases with first infarctions were compared with 858 community controls matched on age and town precinct. Detailed information on coffee drinking, cigarette smoking, and other factors was obtained by telephone interview. On multivariate analysis, consumption of caffeinated coffee increased the risk of angina pectoris in a dose-response manner: 1-2 cups/day (RR 1.4, 95% CI 0.5 - 3.8), 3-4 cups/day (RR 2.9, 1.0 - 8.6), ≥5 cups/day (RR 4.0, 95% CI 1.2- 13). Palmer JR, Rosenberg L, Rao RS, Shapiro S, "Coffee consumption and myocardial infarction in women," *Am. J. Epidemiol.* (1995) 141(8):724-731.

The association between coffee consumption and angina pectoris and/or its symptoms was studied in 11635 men and 11785 women, aged 40-54 years. Angina pectoris was reported by 201 men and 102 women. Symptoms of angina pectoris were reported by 241 men and 395 women. The univariate analysis showed a positive association between number of cups of coffee and self-reported angina pectoris. After adjusting for major coronary risk factors, risk of angina pectoris was increased in men (RR 1.4, 95% CI 0.8 - 2.7) and women (RR 2.7, 95% CI 1.1 - 6.7). Stensvold I, Tverdal A, "The relationship of coffee consumption to various self-reported cardiovascular events in middle-aged Norwegian men and women," *Scand. J. Soc. Med.* (1995) 23(2):103-109.

c. Autoimmune Diseases

Autoimmune diseases include inherited and acquired disorders in which the body's normally protective immune system produces antibodies that target the body's own tissues for attack. These diseases include polymyositis and dermatomyositis, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic lupus erythematosus, and vasculidites - more than 20 conditions characterized by inflammation of blood vessels.

Studies regarding coffee consumption and autoimmune connective tissues diseases have been published regarding rheumatoid arthritis and systemic lupus erythematosus, and Type 1 Diabetes.

(1) Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disorder in which the immune system mistakenly attacks the synovium, a soft tissue that lines the joints, leading to inflammation.

In 2000, Finnish researchers published a study about coffee consumption and rheumatoid factor and rheumatoid arthritis. They assessed rheumatoid factor in a cross-sectional study and rheumatoid arthritis in a cohort study. In the former, daily coffee consumption was proportional to the prevalence of rheumatoid factor positivity. In the latter, the relative risk of rheumatoid factor-positive rheumatoid arthritis for consumption of 4 or more cups of coffer per day versus less coffee consumption was doubled. (RR 2.20, 95% CI 1.13 - 4.27). Heliövaara M, Aho K, Knekt P, Impivaara O, Reunanen A, Aromaa A, "Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis," *Ann. Rheum Dis.* (2000) 59(8):631-635.

In 2002, a prospective cohort study of women evaluating coffee consumption and rheumatoid arthritis was published. Compared with nondrinkers, women consuming 4 or more cups of of decaffeinated (but not caffeinated) coffee per day had a 2½ fold increased risk of rheumatoid arthritis (RR 2.58, 95% CI 1.63 - 4.06). Mikuls TR, Cerhan JR, Criswell LA, Merlino L, Mudano AS,

Burma M, Folsom AR, Saag KG, "Coffee, tea, and caffeine consumption and risk of rheumatoid arthritis: results from the Iowa Women's Health Study," *Arthritis Rheumatism* (2002) 46(1):83-91.

In 2006, Danish researchers published a case-control study of risk factors for serologic subtypes of rheumatoid arthritis. Risk of anti-CCP-positive rheumatoid arthritis was doubled among those drinking >10 cups/day coffee vs. none (OR 2.18, 95% CI 1.07 - 4.42). Pedersen M, Jacobsen S, Klarlund M, Pedersen BV, Wiik A, Wohlfahrt J, Frisch M, "Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides," *Arthritis Res. Ther*. (2006) 8:R133.

The following year the same researchers reported an extremely high (greater than 50-fold increased) risk of anti-CCP-positive rheumatoid arthritis in SE homozygotes who were heavy coffee drinkers (OR 53.3, 95% CI 15.5-183) compared with SE noncarriers who were not coffee drinkers. Pedersen M, Jacobsen S, Garred P, Madsen HO, Klarlund M, Svejgaard A, Pedersen BV, Wohlfahrt J, Frisch M, "Strong combined gene–environment effects in anti–cyclic citrullinated peptide–positive rheumatoid arthritis: a nationwide case–control study in Denmark," *Arthritis Rheumatism* (2007) 56(5):1446-1453.

In 2014, Korean researchers published a meta-analysis of studies regarding coffee and tea consumption and the development of rheumatoid arthritis. The analysis included five studies (three cohort studies and 2 case-control studies, including 134,901 participants (1,279 cases of rheumatoid arthritis and 133,622 non-cases). Meta-analysis of the cohort studies revealed a trend of an association between total coffee intake and rheumatoid arthritis incidence. Comparing the highest versus lowest exposure group, the risk was increased four-fold (RR 4.148, 95% CI 0.792 - 21.73, $p = 0.092$). Meta-analysis of case-control studies showed a significant association between total coffee intake and rheumatoid arthritis incidence (RR 1.217, 95% CI 1.088 - 1.368, $p = 0.001$). Combining the data of the cohort and case-control studies showed a significant association between total coffee intake and rheumatoid arthritis incidence (RR .426, 95% CI 1.060 - 5.554, $p = 0.036$). Meta-analysis stratified by seropositivity indicated a significant association between coffee

consumption and seropositive rheumatoid arthritis risk (RR 1.329, 95% CI 1.162 - 1.522, $p = 3.5 \times 10^{-5}$), but not seronegative rheumatoid arthritis risk (RR 1.093, 95% CI 0.884 - 1.350, $p = 0.411$). No association was found between tea intake and rheumatoid arthritis incidence (RR 0.880, 95% CI 0.624 - 1.239, $p = 0.463$). The authors concluded that their meta-analysis suggests that high coffee consumption is associated with an elevated risk of rheumatoid arthritis. The association between coffee and rheumatoid arthritis was found in seropositive rheumatoid arthritis, but not in seronegative rheumatoid arthritis. Lee YH, Bae SC, Song GG, "Coffee or tea consumption and the risk of rheumatoid arthritis: a meta-analysis," *Clin. Rheumatol*. (2014) 33(11):1575-1583.

(2) Systemic Lupus Erythematosus

Systemic lupus erythematosus is an autoimmune disorder that causes inflammation in many parts of the body, including the joints, skin, kidneys, blood, lungs, heart, and brain.

In 2013, Colombian researchers published a study of 310 Colombian patients with Systemic Lupus Erythematosus to determine the prevalence of and associated risk factors for cardiovascular disease. They found that the risk of cardio-vascular disease was almost doubled among Systemic Lupus Erythematosus patients who drink coffee (OR 1.94, 95% CI 1.19 - 3.18, $p = 0.019$). Amaya-Amaya J, Sarmiento-Monroy JC, Caro-Moreno J, Molano-González N, Mantilla RD, Rojas-Villarraga A, Anaya JM, "Cardiovascular disease in Latin American patients with systemic lupus erythematosus: a cross-sectional study and a systematic review," *Autoimmune Dis.* (2013) Article ID 794383.

In 2014, Japanese investigators reported the results of a study investigating the effects of alcoholic and caffeinated beverages on the risk of Systemic Lupus Erythematosus. They found an increased risk of Systemic Lupus Erythematosus in association with consumption of coffee (OR 1.57, 95% CI 0.95 - 2.61) and consumption of black tea (OR 1.88, 95% CI 1.03 - 3.41). Kiyohara C, Washio M, Horiuchi T, Asami T, Ide S, Atsumi T, Kobashi G, Takahashi H, Tada Y, Kyushu

Sapporo SLE (KYSS) Study Group, "Modifying Effect of N-Acetyltransferase 2 Genotype on the Association Between Systemic Lupus Erythematosus and Consumption of Alcohol and Caffeine-Rich Beverages," *Arthritis Care Res.* (2014) 66(7):1048-1056.

In 2016, Colombian researchers conducted a cross-sectional analysis on 319 Systemic Lupus Erythematosus patients using a structural model to characterize a severity construct of 17 variables. In addition, the model analyzed possible associations of the severity latent trait with other patient covariates including cardiovascular disease, age at onset of disease, and exposure factors. A total of 11 symptoms were included in the item response theory model showing three levels of disease severity. The only co-variate registered that reached an association with severity was coffee consumption. Molano-González N, Sarmiento-Monroy J, Rodríguez-Jiménez M, et al., "SAT0319-Severity in Systemic Lupus Erythematosus Patients: A Latent Trait Analysis," *Ann. Rheumatic Dis.* (2016) 75:783.

Interestingly, a connective tissue disease bearing features of Systemic Lupus Erythematosus and Periungual Telangiectasia (an autoimmune connective tissue disease that is a form of dermatomyositis) has been reported among coffee plantation workers in India. Narahari SR, Srinivas CR, Kelkar SK, "LE-like erythema and periungual telangiectasia among coffee plantation workers," *Contact Dermatitis* (1990) 22(5):296-297.

(3) Type 1 Diabetes

"Type 1 diabetes mellitus is a chronic disease resulting from autoimmune destruction of pancreatic beta cells responsible for insulin secretion and glucose hemostasis. The incidence of [Type 1 diabetes] is double-peaked, with the first peak being around the age of 5 to 7 years, and the second peak occurring near puberty. . . . [Type 1 diabetes] incidence has increased substantially during the last two decades, a phenomenon that could not be entirely explained by genetic factors

alone." Sharif K, Watad A, Bragazzi NL, Adawi M, Amital H, Shoenfeld Y, "Coffee and autoimmunity: More than a mere hot beverage!" *Autoimmun Rev.* (2017) 6(7):712-721.

In a Finnish case-control study of 600 children under age 15 with Type 1 diabetes, children who drank more than 2 cups of coffee per day had almost double the risk of the disease (OR 1.94, 95% CI 1.08 - 3.47). Virtanen SM, Räsänen L, Aro A, Ylönen K, Lounamaa R, Akerblom HK, Tuomilehto J, "Is Children's or Parents' Coffee or Tea Consumption Associated with the Risk for Type 1 Diabetes Mellitus in Children? Childhood Diabetes in Finland Study Group," *Eur. J. Clin. Nutr.* (1994) 48(4):279-285.

In a prospective randomized placebo-controlled double-blind study of 34 patients with type 1 diabetes, hypoglycemic episodes during the day were found to increase with higher consumption of caffeine ($p < 0.003$) and patients with higher coffee consumption had more severe warning symptoms ($p < 0.05$). Thus, disease development seems to increase with coffee consumption. Watson JM, Jenkins EJ, Hamilton P, Lunt MJ, Kerr D, "Influence of Caffeine on the Frequency and Perception of Hypoglycemia in Free-Living Patients with Type 1 Diabetes," *Diabetes Care* (2000) 23:455-459.

In a Swedish case-control study a slight nonsignificant risk of latent autoimmune diabetes in adults was found for coffee intake (OR 1.04, 95% CI 0.96 - 1.13), but stratifying according to the levels of autoantibody (glutamic acid decarboxylase), a significant association was found (OR 1.11, 95% CI 1.00 - 2.34) for consumption of 1 cup of coffee per day. Additionally, levels of glutamic acid decarboxylase showed a significant proportional increase with additional coffee consumption (> 6 cups per day), a result that was found to be significant after adjustment for multiple other factors. Löfvenborg JE, Andersson T, Carlsson PO, Dorkhan M, Groop L, Martinell M, Rasouli B, Storm P, Tuomi T, Carlsson S, "Coffee consumption and the risk of latent autoimmune diabetes in adults—results from a Swedish case–control study," *Diabetic Med.* (2014) 31(7):799-805.

In a recent population-based case-control study of 484 incident cases of latent autoimmune diabetes in adults and 885 healthy controls, coffee intake was positively associated with latent

autoimmune diabetes in adult carriers of high-risk HLA genotypes (OR 1.14 per cup per day, 95% CI 1.02 - 1.28), whereas no association was observed in non-carriers (OR 1.04, 95% CI 0.93 - 1.17). Subjects with both heavy coffee consumption (≥ 4 cups per day) and high-risk HLA genotypes had a substantially increased risk of latent autoimmune diabetes (OR 5.74, 95% Ci 3.34 - 9.88). The authors of the study concluded that their findings suggest that coffee consumption interats with HLA to promote latent autoimmune diabetes in adults. Rasouli B, Ahlqvist E, Alfredsson L, Andersson T, Carlsson PO, Groop L, Löfvenborg JE, Martinell M, Rosengren A, Tuomi T, Wolk A, Carlsson S, "Coffee consumption, genetic susceptibility and risk of latent autoimmune diabetes in adults: A population-based case-control study," *Diabetes Metab.* (May 17, 2018) pii: S1262-3636(18)30087-9.

d. Fibrocystic Breast Disease

Fibrocystic breast disease is a condition of breast tissue affecting an estimated 30-60% of women and at least 50% of women of childbearing age.

In 1981, American researchers reported that complete abstention from methylxanthine consumption resulted in resolution of Fibrocystic Breast Disease in 82.5% of women and significant improvement in 15% of women studied. Since 97.5% showed clinical benefit from methylxanthine abstention, the researchers concluded that methylxanthine intake is etiologically associated with Fibrocystic Breast Disease. Minton JP, Abou-Issa H, Reiches N, Roseman JM, "Clinical and biochemical studies on methylxanthine-related fibrocystic breast disease," *Surgery* (1981) 90(2):299-304.

In 1984, American researchers published a hospital-based case-control study of 634 women with Fibrocystic Breast Disease and 1,066 controls. Women who consumed 31-250 mg caffeine/day had a 1.5-fold increased risk of Fibrocystic Breast Disease; women who consumed >500 mg/day had a 2.3-fold increased risk. The association with caffeine consumption was especially high among women with atypical lobular hyperplasia and with sclerosing adenosis with concomitant

papillomatosis or papillary hyperplasia, both of which have been associated with increased breast cancer risk. The association was specific to Fibrocystic Breast Disease; there was no association of caffeine with fibroadenoma or other forms of benign breast disease. Boyle CA, Berkowitz GS, LiVolsi VA, Ort S, Merino MJ, White C, Kelsey JL, "Caffeine consumption and fibrocystic breast disease: a case-control epidemiologic study," *J. Natl. Cancer Inst.* (1984) 72(5):1015-1019.

In 1984, Kaiser Permanente physicians published a study of female twins, only one of whom had Fibrocystic Breast Disease. They found a positive association between coffee consumption and risk of Fibrocystic Breast Disease. Odenheimer DJ, Zunzunegui MV, King MC, Shipler CP, Friedman GD, "Risk factors for benign breast disease: a case-control study of discordant twins," *Am. J. Epidemiol*. (1984) 120(4):565-571.

In 1985, researchers from Buffalo, New York investigated the effect of theophylline therapy on fibrocystic breast disease in asthmatic women. They found clear evidence that total methylxanthines was a contributing factor in fibrocystic breast disease severity. Hindi-Alexander MC, Zielezny MA, Montes N, Bullough B, Middleton Jr E, Rosner DH, London WM, "Theophylline and fibrocystic breast disease," *J. Allergy Clin. Immunol.* (1985) 75(6):709-715.

In 1985, Italian researchers published a case-control study of 288 women with histologically confirmed benign breast lumps. The relative risk of fibrocystic disease for women who drank 1-2 or ≥3 cups of coffee/day were 4.1 and 6.4 based on hospital controls, and 2.0 and 3.7 based on outpatient controls. La Vecchia C, Franceschi S, Parazzini F, Regallo M, Decarli A, Gallus G, Di Pietro S, Tognoni G, "Benign breast disease and consumption of beverages containing methylxanthines," *J. Natl. Cancer Inst.* (1985) 74(5):995-1000.

In 1989, Australian researchers published a study of 383 cases of Benign Proliferative Epithelial Disorders (BPED) of the breast. They found a positive association with theobromine intake when cases were compared with biopsy controls. Total methylxanthine intake was associated with risk of BPED showing severe atypia, with a significant trend, using community controls. Rohan

TE, Cook MG, McMichael AJ, "Methylxanthines and benign proliferative epithelial disorders of the breast in women," *Int. J. Epidemiol.* (1989) 18(3):626-633.

In 2004, a study evaluating dietary factors found that high caffeine consumption increased risk of Benign Breast Disease (RR 2.46, 95% CI 1.11-5.49) for the highest quartile). Webb PM, Byrne C, Schnitt SJ, Connolly JL, Jacobs TW, Baer HJ, Willett WC, Colditz GA, "A prospective study of diet and benign breast disease," *Cancer Epidemiol/ Biomarkers Prev.* (2004) 13(7):1106-1113. There are, however, also some negative and null studies.

e. Gastrointestinal Disorders

"Gastrointestinal disorders affect an estimated 60 to 70 million Americans annual. In 2004, there were an estimated 4.6 million hospitalizations, 72 million ambulatory care visits, and 236,000 deaths attributable to gastrointestinal disease. Spending on gastrointestinal diseases in the United States has been estimated at $142 billion per year in direct and indirect costs." Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, "Burden of gastrointestinal disease in the United States: 2012 update," *Gastroenterology* (2012) 143(5):1179-1187.

"Coffee has been shown to have profound effects on the gastrointestinal system." Brown SR, Cann PA, Read NW, "Effect of coffee on distal colon function," *Gut* (1990) 31(4):450-453. Coffee reduces lower esophageal sphincter pressure (Dennish LG, Castell CD, "Caffeine and the lower esophageal sphincter," *Am. J. Dig. Dis.* (1972) 17(11):993-996) and stimulates secretion from the stomach (Debas HT, Cohen MM, Holubitsky IB, Harrison RC, "Caffeine-stimulated acid and pepsin secretion: dose-response studies," *Scand. J. Gastroenterol.* (1971) 6(5):453-457) and the small intestine. Wald A, Back C, Bayless TM, "Effect of caffeine on the human small intestine," *Gastroenterol.* (1976) 71(5):738-742. Coffee increases interdigestive exocrine pancreatic trypsin

secretion. Coffey RJ, Go VL, Zinsmeister AR, Dimagno EP, "The acute effects of coffee and caffeine on human interdigestive exocrine pancreatic secretion," *Pancreas* (1986) 1(1):55-61.

In a recent study of 3,426 subjects from three rural villages in India, consumption of coffee and tea significantly increased the risk of functional gastrointestinal disorders. Ghoshal UC, Singh R, "Frequency and risk factors of functional gastro-intestinal disorders in a rural Indian population," *J. Gastroenterol. Hepatol.* (2017) 32(2):378-387.

(1) Constipation

"Constipation is a significant problem in the United States with over 330 million dollars spent each year on over-the-counter laxatives." Sandler RS, Jordan MC, Shelton BJ, "Demographic and dietary determinants of constipation in the US population," *Am. J. Public Health* (1990) 80(2):185-189. In a prospective study of 1,064,004 men and women, 18.5% of men and 33.7% of women reported "constipation." Hammond EC, "Some preliminary findings on physical complaints from a prospective study of 1,064,004 men and women," *Am. J. Public Health Nations Health* (1964) 54(1):11-23.

In a study using data regarding 15,014 participants in the first Health and Nutrition Examination Survey, constipated individuals reported higher consumption of coffee and tea and lower consumption of other beverages. In the logistic regression model, the increased risk of constipation from coffee and tea was highly significant, as were decreased risks from other beverages ($p < 0.001$). Sandler RS, Jordan MC, Shelton BJ, "Demographic and dietary determinants of constipation in the US population," *Am. J. Public Health* (1990) 80(2):185-189.

In the Nurses' Health Study, a total of 62,036 women responses to questionnaires which assessed bowel movement frequency, dietary, and lifestyle choices. Constipation was defined as two or fewer bowel movements weekly. A total of 3,327 were classified as constipated. On multivariate analysis, the prevalence ratio of constipation was significantly increased among women who drank

the most coffee (≥ 6 cups per day) (PR 1.17, 95% CI 1.02 - 1.34, p-trend < 0.0001). Dukas L, Willett WC, Giovannucci EL, "Association between physical activity, fiber intake, and other lifestyle variables and constipation in a study of women," *Am. J. Gastroenterol.* (2003) 98(8):1790-1796.

(2) Gallstones

"Gallstones affect 10%-15% of adults in the Western world and, although often asymptomatic, can cause serious health complications." El-Sharkawy AM, Sahota O, Lobo DN, "Acute and chronic effects of hydration status on health," *Nutr. Rev.* (2015) 73:97-109.

A meta-analysis of epidemiologic studies regarding coffee consumption and gallstone disease, based on 1 case-control study and five prospective cohort studies (with 7 cohorts) was published by Chinese researchers in 2015. A significant nonlinear dose-response association was identified (*p* for nonlinearity = 0.106). Compared with the lowest level of consumption, risk of gallstone disease was decreased for consumption of 2 cups per day (RR 0.89, 95 % CI 0.79 - 0.99), 4 cups per day (RR 0.81, 95% CI 0.72 - 0.92) and 6 cups per day (RR 0.75, 95% CI 0.64 - 0.88). Zhang YP, Li WQ, Sun YL, Zhu RT, Wang WJ, "Systematic Review with Meta-Analysis: Coffee Consumption and the Risk of Gallstone Disease," *Aliment. Pharmacol. Ther.* (2015) 42(6):637-648.

(3) Gastroesophageal Reflux Disease

A meta-analysis of epidemiologic studies regarding coffee consumption and gastroesophageal reflux disease reported an increased risk of gastroesophageal reflux disease for studies where esophagitis was diagnosed by endoscopy (OR 1.17, 95% CI 1.08 - 1.26), but not in studies that only used symptoms to define GERD (OR 0.99, 95% CI 0.84 - 1.16). Kim J, Oh SW, Myung SK, Kwon H, Lee C, Yun JM, Lee HK, "Association between coffee intake and gastroesophageal reflux disease: a meta-analysis," *Dis. Esophagus* (2014) 27(4):311-317.

In a multi-center cross-sectional study, coffee consumption was found to increase the risk of atrophic chronic gastritis more than two-fold. Eurohepygast Study Group, "Risk Factors for Atrophic Chronic Gastritis in a European Population: Results of the Eurohepygast Study," *Gut* (2002) 50:779-785.

Risks greater than four-fold have been reported for gastroesophageal reflux symptoms from consumption of coffee. Castelo Vega JM, Olivera Hermoza R, Páucar Sotomayor H, Flores Aldea JC, ["Gastroesophageal Reflux: Clinical, Endoscopic Characteristics and Associated Risk Factors"], *Rev. Gastrenterol. Peru* (2003) 23(1):41-48 [article in Spanish].

One researcher reported: "Coffee ... commences the risk of gastroesophageal reflux, which may lead to gastric ulcers and increase the risk of gastric cancer." Fiebich BL, Valente P, Ferrer-Montiel A, Candelario-Jalil E, Menthe J, Luecker P., "Effects of coffees before and after special treatment procedure on cell membrane potentials in stomach cells," *Methods Findings Exp. Clini. Pharmacol.* (2006) 28(6):369-372.

Apparently only one study has compared the effects of coffee and water on gastroesophageal reflux. In 1994, German researchers published a study in which they evaluated gastroesophageal reflux induced by coffee and tea before and after a decaffeination process, and compared it with water and water-containing caffeine. Three-hour ambulatory pH-metry was performed in 16 healthy volunteers, who received 300 ml of coffee, decaffeinated coffee, tea, decaffeinated tea, and tap water. Regular coffee, but not decaffeinated coffee, induced significant gastroesophageal reflux compared to tap water and tea. Median pH during the three postprandial hours in the 16 subjects after intake of a standard breakfast with fluid intake was highest for regular coffee (pH 3.7, range 0-14.4), lower for decaffeinated coffee (pH 2.7, range 0-10.7), and lowest for water (pH 1.6, range 0 - 9.8). The researchers concluded that consumption of coffee increases gastroesophageal reflux, whereas consumption of water reduces gastroesophageal reflux. Wendl B, Pfeiffer A, Pehl C, Schmidt T, Kaess H, "Effect of decaffeination of coffee or tea on gastro-oesophageal reflux," *Aliment. Pharmacol. Ther.* 8(3):283-287.

f. Urological Conditions

Urological conditions include chronic kidney disease, urolithiasis, urinary tract infections, urinary incontinence, and lower urinary tract symptoms.

(1) Urolithiasis

Urolithiasis is the formation of calculi or stones in the urinary tract, usually in the kidneys or ureters, but also in the bladder and the urethra. Urolithiasis occurs in up to 10% of the population with a lifetime recurrence rate of up to 80%. de La Guéronnière V, Le Bellego L, Jimenez IB, Dohein O, Tack I, Daudon M, "Increasing water intake by 2 liters reduces crystallization risk indexes in healthy subjects," *Arch. Ital. Urol. Androl.* (2011) 83(1):43-50.

In 2014, Chinese researchers published a meta-analysis of coffee intake and the risk of urolithiasis. A total of 6 studies (2 cohort studies and 4 case-control studies) on coffee intake were included in the meta-analysis. The pooled odds ratio showed a significant reduction of the risk of urolithiasis for the highest consumption of coffee (OR 0.70, 95% CI 0.60 - 0.82). Wang S, Zhang Y, Mao Z, He X, Zhang Q, Zhang D, "A meta-analysis of coffee intake and risk of urolithiasis," *Urol. Int.* (2014) 93:220-228

(2) Lower Urinary Tract Symptoms

The term "lower urinary tract symptoms" or LUTS, has been used as a general term to refer to any combination of urinary symptoms or as a more specific term to refer to those symptoms primarily associated with overactive bladder (frequency, urgency, and nocturia). Consumption of caffeinated beverages has been reported to significantly increase risk of lower urinary tract symptoms.

In 2002 British researchers published a randomized controlled trial in which the experimental group received caffeine reduction education and the control group continued existing caffeine intake. The results were indicative of a trend for urgency, with a 37% reduction in symptoms among low users (101-200 mg caffeine), 1 5% reduction among medium users (201-300 mg), and a 4% increase in symptoms among the high users (> 301 mg). The investigators concluded that the decrease in caffeine intake in the experimental group established that an intervention that encourages caffeine reduction was successful in its aim. Outcome comparisons between the two groups showed a substantial beneficial effect among those who received the intervention. Significant improvements in occasions of urgency per day and number of voids per day were found and a beneficial non-significant trend was evidence in occasions of leakage a day. On the basis of this evidence, the investigators concluded that they could advise their patients that caffeine reduction to < 100 mg a day is likely to reduce their symptoms of urgency and frequency. Bryant CM, Dowell CJ, Fairbrother G, "Caffeine reduction education to improve urinary symptoms," *Br. J. Nursing* (2002) 11(8):560-565.

In 2010, Chinese researchers investigated risk factors for lower urinary tract symptoms in Chinese men without urinary tract infection or benign prostatic hyperplasia who satisfied criteria for painful bladder syndrome based on the O'Leary-Sant interstitial cystitis symptom and problem indices. The risk of lower urinary tract symptoms in men who met these criteria was increased more than four-fold for consumption of caffeinated beverages (OR 4.29, 95% CI 1.86 - 9.86). In the multivariate analysis, the risk among men decreased to slightly less than four-fold (OR 3.54, 95% CI 1.54 - 8.12, $p = 0.003$). Caffeinated beverage intake was the only modifiable association noted in the multivariate analysis in men. Li GZ, Zhang N, Du P, Yang Y, Wu SL, Xiao YX, Jin R, Liu L, Shen H, Dai Y, "Risk factors for interstitial cystitis/painful bladder syndrome in patients with lower urinary tract symptoms: a Chinese multi-center study," *Chinese Med. J.* (2010) 123(20):2842-2846.

In 2013, researchers from the New England Research Institute reported that consumption of more than two eight-ounce servings of caffeinated coffee per day doubled the risk of lower urinary tract symptoms in men (OR 2.09, 95% CI 1.29 - 3.40, $p < 0.01$). Maserejian NN, Wager CG, Giovannucci EL, Curto TM, McVary KT, McKinlay JB, "Intake of caffeinated, carbonated, or citrus beverage types and development of lower urinary tract symptoms in men and women," *Am. J. Epidemiol*. (2013) 177(12):1399-1410.

In 2014, British researchers published a double-blind randomized cross-over study of 14 community-dwelling women newly diagnosed with overactive bladder and a history of caffeine consumption. They were assigned to two groups - one which consumed caffeinated beverages for 14 days followed by decaffeinated beverages for 14 days, the other which consumed decaffeinated beverages for 14 days followed by caffeinated beverages. In the 11 women who completed the study, a significant reduction in urgency ($p < 0.01$) and frequency ($p < 0.05$) of urinary voids on day 3 of the diary, and total ICIQ-OAB score ($p < 0.01$) was found for the period of decaffeinated compared to caffeinated drink intake. Wells MJ, Jamieson K, Markham TC, Green SM, Fader MJ, "The effect of caffeinated versus decaffeinated drinks on overactive bladder: a double-blind, randomized, crossover study," *J. Wound Ostomy Continence Nurs.* (2014) 41(4):371-378.

In 2016 researchers from Michigan published a study that sought to determine whether lower urinary tract symptoms improves after elimination of potentially irritating beverages – coffee, tea, alcohol, and carbonated and/or artificially sweetened beverages. Thirty community-dwelling women were in three phases: (1) baseline, (2) eliminate the potentially irritating beverages, and (3) reintroduce the irritating beverages at 50% of baseline volume. Despite incomplete adherence to study protocols, the women reported reduction in symptoms of urge, inability to delay voiding, and bother during both phases ($p \leq 0.01$). The number of voids per day decreased on average by 1.3 and 0.9 voids during Phases 2 and 3 respectively ($p = 0.002$ and $p = 0.035$). The investigators concluded the findings of their study support instructing women to reduced intake of potentially irritating beverages to improve lower urinary tract symptoms. Miller JM, Garcia CE, Hortsch SB,

Guo Y, Schimpf MO, "Does Instruction to Eliminate Coffee, Tea, Alcohol, Carbonated, and Artificially Sweetened Beverages Improve Lower Urinary Tract Symptoms?: A Prospective Trial," *J. Wound Ostomy Continence Nursing* (2016) 43(1):69-79.

(3) Urinary Incontinence

There is consistent epidemiological evidence supported by consistent evidence from intervention studies implicating coffee/caffeine as a cause of urinary incontinence.

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 NJ, Vaughan CP, Johnson II TM, Goode PS, Burgio KL, Redden DT, Markland AD, "Caffeine intake and its association with urinary incontinence in United States men: results from National Health and Nutrition Examination Surveys 2005–2006 and 2007–2008," *J. Urology* (2013) 189(6):2170-2174) and women. Gleason JL, Richter HE, Redden DT, Goode PS, Burgio KL, Markland AD, "Caffeine and urinary incontinence in US women," *Int. Urogynecol. J.* (2013) 24(2):295-302. 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. Jura YH, Townsend MK, Curhan GC, Resnick NM, Grodstein F, "Caffeine intake, and the risk of stress, urgency and mixed urinary incontinence," *J. Urology* (2011) 185(5):1775-1780.

Intervention studies in which dietary caffeine was eliminated or reduced have reported decreased rates of urinary incontinence. Edelstein BA, Keaton-Brasted C, Burg MM, "Effects of caffeine withdrawal on nocturnal enuresis, insomnia, and behavior restraints," *J. Consult. Clin. Psychol.* (1984) 52(5):857-862;James JE, Sawczuk D, Merrett S, "The effect of chronic caffeine consumption on urinary incontinence in psychogeriatric inpatients," *Psychology Health* (1989) 3(4):297-305; Tomlinson BU, Doughterty MC, Pendergast JF, Boyington AR, Coffman MA, Pickens

SM, "Dietary caffeine, fluid intake and urinary incontinence in older rural women," *Int. Urogynecol. J.* (1999) 10(1):22-28.

The association between coffee/caffeine and urinary incontinence is consistent with the known diuretic effects of caffeine. [Report of Dr. Jack James - CERT's Submission No. 8).

In 2013 researchers from the Department of Veterans Affairs published two cross-sectional studies evaluating the caffeine intake and the risk of urinary incontinence - one in men (Davis NJ, Vaughan CP, Johnson TM 2nd, Goode PS, Burgio KL, Redden DT, Markland AD, "Caffeine Intake and Its Association With Urinary Incontinence in United States Men: Results from National Health and Nutritional Examination Surveys (NHANES) 2005-2006 and 2007-2008," *J. Urol.* (2013) 189(6):2170-2174), the other in women. Gleason JL, Richter HE, Redden DT, Goode PS, Burgio KL, Markland AD, "Caffeine and urinary incontinence in US women," *Int. Urogynecol. J.* (2013) 24(2):295-302. Both of the studies used data collected from the National Health and Nutrition Examination Surveys (NHANES).

In the study of U.S. men, urinary incontinence was defined using a standard questionnaire with Incontinence Severity Index scores 3 or greater categorized as moderate to severe. Structured dietary recall was used to determine caffeine consumption (mg per day), water intake (gm per day) and total dietary moisture (gm per day). Of the 5297 men, 3960 (75%) were 20 years old or older with complete data. Mean caffeine intake was 169 mg per day. Using stepwise multivariable logistic regression models, caffeine intake at the upper 75th percentile ($\geq$234 mg per day) significantly increased the risk of moderate to severe urinary incontinence (RR 1.72, 95% CI 1.18 - 2.49), and caffeine intake at the upper 90th percentile ($\geq$392 mg per day) doubled the risk of moderate to severe urinary incontinence (RR 2.08, 95% CI 1.15 - 3.77). In addition, after adjusting for prostate conditions, the effect size for the association between caffeine intake and moderate to severe urinary incontinence remained. The investigators concluded that caffeine consumption equivalent to approximately 2 cups of coffee per day is significantly associated with moderate to severe urinary incontinence in U.S. men. Davis NJ, Vaughan CP, Johnson TM 2nd, Goode PS, Burgio KL, Redden

DT, Markland AD, "Caffeine Intake and Its Association With Urinary Incontinence in United States Men: Results from National Health and Nutritional Examination Surveys (NHANES) 2005-2006 and 2007-2008," *J. Urol.* (2013) 189(6):2170-2174.

In the study of U.S. women, risk of urinary incontinence from caffeine consumption was assessed for 4309 non-pregnant women age 20 or older who had complete urinary incontinence and dietary data. After adjusting for multiple factors, caffeine intake in the highest quartile (≥204 mg/day) was associated with any urinary incontinence. The prevalence odds ratio was significantly increased for any urinary incontinence (POR 1.47, 95% CI 1.07 - 2.01), but the increased risk did not quite achieve statistical significance for moderate/severe urinary incontinence (POR 1.42, 95% CI 0.98 - 2.07). Gleason JL, Richter HE, Redden DT, Goode PS, Burgio KL, Markland AD, "Caffeine and urinary incontinence in US women," *Int. Urogynecol. J.* (2013) 24(2):295-302.

In 2011 researchers from Massachusetts published a study investigating urinary incontinence in 65,176 women without incontinence in the Nurses' Health Study. Incident incontinence was identified from questionnaires, during 4 years of follow-up. Caffeine intake was measured using food frequency questionnaires administered prior to incontinence development. They report a significantly increased risk of incontinence at least weekly among women with the highest versus lowest (>450 vs. <150 mg/day) intake of caffeine (RR 1.19, 95% CI 1.06 - 1.34) and a significant trend of increasing risk with increasing intake (p-for trend = 0.01). This risk was higher for incident urgency incontinence comparing highest versus lowest intake (RR 1.34, 95% CI 1.00 - 1.80, p-for trend = 0.05). Jura YH, Townsend MK, Curhan GC, Resnick NM, Grodstein F, "Caffeine intake, and the risk of stress, urgency and mixed urinary incontinence," *J. Urol.* (2011) 185(5):1775-1780.

In 2016 Chinese investigators published a meta-analysis of coffee and caffeine intake and risk of urinary incontinence based on 7 observational studies (1 case-control, 2 cohort, and 4 cross-sectional studies). The summary odds ratios for any versus non-consumption were 0.75 (95% CI 0.54 - 1.04) for coffee consumption and 1.29 (95% CI 0.94 - 1.76) for caffeine consumption. Compared with individuals who never drink coffee, the pooled odds ratio of urinary incontinence

was 0.99 (95% CI 0.83 - 1.18) for regular coffee/caffeine drinkers. The risk of moderate to severe urinary incontinence was nonsignificantly increased (OR 1.18, 95% CI 0.88 - 1.58). The investigators concluded that their meta-analysis found no evidence for an association between coffee/caffeine consumption and the risk of urinary incontinence. Sun S, Liu D, Jiao Z, "Coffee and caffeine intake and risk of urinary incontinence: a meta-analysis of observational studies," *BMC Urol.* (2016) 16(1):61. This meta-analysis should not be interpreted to negate the significant positive findings of the NHANES studies, because the exposure assessment of the two NHANES studies is superior to those of other studies included in the meta-analysis. [Report of Dr. Nachman Brautbar].

(4) Urinary Tract Infections

Urinary tract infections are the most common bacterial infection. According to the 1997 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, UTI accounted for nearly 7 million office visits and 1 million emergency department visits, resulting in 100,000 hospitalizations." Foxman B, "Epidemiology of urinary tract infections: incidence, morbidity, and economic costs," *Am. J. Med.* (2002) 113(1):5-13.

There is no evidence that consumption of coffee reduces the risk of urinary tract infections; the few published studies either report increased risks of urinary tract infections from consumption of coffee or caffeinated beverages (Vincent CR, Thomas TL, Reyes L, White CL, Canales BK, Brown MB, "Symptoms and risk factors associated with first urinary tract infection in college age women: a prospective cohort study," *J. Urol.* (2013) 189(3):904-910) or no significant effect. Kontiokari T, Laitinen J, Järvi L, Pokka T, Sundqvist K, Uhari M, "Dietary factors protecting women from urinary tract infection," *Am. J. Clin. Nutr.* (2003) 77(3):600-604.

g. Mortality

Some recent meta-analyses have reported decreased risks of total (all-cause) mortality in association with increased consumption of coffee. Malerba S, Turati F, Galeone C, Pelucchi C, Verga F, La Vecchia C, Tavani A, "A meta-analysis of prospective studies of coffee consumption and mortality for all causes, cancers and cardiovascular diseases," *Eur. J. Epidemiol*. (2013) 527-239; Je Y, Giovannucci E, "Coffee consumption and total mortality: a meta-analysis of twenty prospective cohort studies," *Br. J. Nutr.* (2014) 111(7):1162-1173; Crippa A, Discacciati A, Larsson SC, Wolk A, Orsini N, "Coffee consumption and mortality from all causes, cardiovascular disease, and cancer: a dose-response meta-analysis," *Am. J. Epidemiol.* (2014) 180(8):763-775; Zhao Y, Wu K, Zheng J, Zuo R, Li D, "Association of coffee drinking with all-cause mortality: a systematic review and meta-analysis," *Public Health Nutr.* (2015) 18(7):1282-1291; Grosso G, Micek A, Godos J, Sciacca S, Pajak A, Martínez-González MA, Giovannucci EL, Galvano F, "Coffee consumption and risk of all-cause, cardiovascular, and cancer mortality in smokers and non-smokers: a dose-response meta-analysis," *Eur. J. Epidemiol.* (2016) 31(12):1191-1205. However, the studies do not consistently report decreased mortality risks; some studies report significantly increased risks of all-cause mortality with increased coffee consumption. In a one-year follow-up study of 27,350 adult Seventh Day Adventists, increased risks of all-cause mortality were observed for consumption of 1-2 cups of coffee per day (RR 1.21, 95% CI 1.06 - 1.39) and ≥3 cups per day (RR 1.26, 95% CI 1.05 - 1.51), upon adjustment for age, history of cardiovascular disease, hypertension, diabetes, cancer, and smoking status. Kahn HA, Phillips RL, Snowdon DA, Choi W, "Association between reported diet and all-cause mortality. Twenty-one-year follow-up on 27,530 adult Seventh-Day Adventists." *Am. J. Epidemiol.* (1984) 119(5):775-787.

In a study of 60,000 Finnish men and women followed for over 23 years, a significant increase in all-cause mortality was found in men who drank 8 or more cups of coffee per day (HR 1.20, 95% CI 1.01 - 1.41), following adjustment for age, smoking status, alcohol intake, study year

and 4 pre-existing chronic diseases. Laaksonen M, Talala K, Martelin T, Rahkonen O, Roos E, Helakorpi S, Laatikainen T, Prättälä R, "Health behaviours as explanations for educational level differences in cardiovascular and all-cause mortality: a follow-up of 60 000 men and women over 23 years," *Eur. J. Public Health* (2007) 18(1):38-43.

In the Aerobics Center Longitudinal Study, all-cause mortality was investigated in 43,727 participants with a median of 17 years of follow-up. In multivariate analyses, coffee consumption was positively associated with all-cause mortality. Increased all-cause mortality for consumption of more than 28 cups of coffee per week was observed in men (RR 1.21, 95% CI 1.04 - 1.40) and women (RR 1.21, 95% CI 0.78 - 1.88) after adjusting for age, baseline examination year, decaffeinated coffee use, regular tea use, decaffeinated or herbal tea use, physical inactivity, BMI, smoking status, alcohol intake, diabetes, hypertension, hyper-cholesterolemia, family history of cardiovascular disease and fitness. Among participants less than 55 years of age who drank more than 28 cups of coffee per week, higher risks were found for both men (RR 1.56, 95% CI 1.30 - 1.87) and women (RR 2.13, 95% CI 1.26 - 3.59). Liu J, Sui X, Lavie CJ, Hebert JR, Earnest CP, Zhang J, Blair SN, "Association of Coffee Consumption With All-Cause and Cardiovascular Disease Mortality," *Mayo Clinic Proc.* (2013) 88(10):1066-1074.

5. Acute Cardiovascular Effects

"In the past two decades, experimental studies have shown that caffeine induces various acute cardiovascular effects, including effects on blood pressure, circulating catecholamines, arterial stiffness, and endothelium dependent vasodilation." Riksen NP, Rongen GA, Smits P, "Acute and long-term cardiovascular effects of coffee: implications for coronary heart disease," *Pharmacol. Ther*. (2009) 121(2):185-191.

"The large number and diversity of relevant studies provide unassailable evidence of adverse acute effects of caffeine on cardiovascular function, especially blood pressure." James JE, "Blood Pressure Effects of Dietary Caffeine Are a Risk for Cardiovascular Disease," *Caffeine and Activation Theory: Effects on Health and Behavior* (CRC Press 2007).

Experimental studies in healthy subjects have shown that drinking two cups of coffee acutely raises systolic and diastolic blood pressure and lowers heart rate. Nurminen ML, Niittynen L, Korpela R, Vapaatalo H, "Coffee, caffeine and blood pressure: a critical review," *Eur. J. Clin. Nutr.* (1999) 53(11):831-839. Caffeine appears to be responsible for this pressor effect, because the same response is observed after administration of caffeine (Robertson D, Frölich JC, Carr RK, Watson JT, Hollifield JW, Shand DG, Oates JA, "Effects of caffeine on plasma renin activity, catecholamines and blood pressure," *New Engl. J. Med.* (1978) 298(4):181-186; Smits P, Boekema P, De Abreu R, Thien T, van 't Laar A, "Evidence for an antagonism between caffeine and adenosine in the human cardiovascular system," *J. Cardiovasc. Pharmacol.* (1987) 10(2):136-143), but not of decaffeinated coffee. Smits P, Thien T, Van 't Laar A, "The cardiovascular effects of regular and decaffeinated coffee," *Br. J. Clin. Pharmacol.* (1985) 19(6):852-854.

At levels from coffee consumption, caffeine antagonizes the adenosine A_1 and A_{2A} receptor. (Fredholm BB, Lindström K, "Autoradiographic comparison of the potency of several structurally unrelated adenosine receptor antagonists at adenosine A1 and A(2A) receptors," *Eur. J. Pharmacol.* (1999) 380(2-3):197-202). Caffeine prevents systemic and local hemodynamic effects of adenosine,

which is compatible with effective adenosine receptor antagonism, especially for adenosine A_2 receptor-induced actions which are largely cAMP-dependent. (Smits P, Boekema P, De Abreu R, Thien T, van 't Laar A, "Evidence for an antagonism between caffeine and adenosine in the human cardiovascular system," *J. Cardiovasc. Pharmacol.* (1987) 10(2):136-143; Smits P, Lenders JW, Thien T, "Caffeine and theophylline attenuate adenosine-induced vasodilation in humans," *Clin. Pharmacol. Ther.* (1990) 48(4):410-418. Since adenosine receptor stimulation induces vasodilation in vascular beds (Rongen GA, Floras JS, Lenders JW, Thien T, Smits P, "Cardiovascular pharmacology of purines,"*Clin. Sci.* (1997) 92(1):13-24), caffeine may induce vasoconstriction. Riksen NP, Rongen GA, Smits P, "Acute and long-term cardiovascular effects of coffee: implications for coronary heart disease," *Pharmacol. Ther*. (2009) 121(2):185-191. Acute administration of caffeine increases systemic vascular resistance in healthy people. Pincomb GA, Lovallo WR, Passey RB, Whitsett TL, Silverstein SM, Wilson MF, "Effects of caffeine on vascular resistance, cardiac output and myocardial contractility in young men," *Am. J. Cardiol*. (1985) 56(1):119-122; Casiglia E, Bongiovi S, Paleari CD, Petucco S, Boni M, Colangeli G, Penzo M, Pessina AC, "Haemodynamic effects of coffee and caffeine in normal volunteers: a placebo-controlled clinical study," *J. Intern. Med.* (1991) 229(6):501-504; Farag NH, Vincent AS, McKey BS, Whitsett TL, Lovallo WR, "Hemodynamic mechanisms underlying the incomplete tolerance to caffeine's pressor effects," *Am. J. Cardiol.* (2005) 95(11):1389-1392.

Administering coffee or caffeine increases the circulating concentration of epinephrine and norepinephrine. Robertson D, Frölich JC, Carr RK, Watson JT, Hollifield JW, Shand DG, Oates JA, "Effects of caffeine on plasma renin activity, catecholamines and blood pressure," *New Engl. J. Med.* (1978) 298(4):181-186; Smits P, Thien T, Van 't Laar A, "The cardiovascular effects of regular and decaffeinated coffee," *Br. J. Clin. Pharmacol.* (1985) 19(6):852-854. The increase in epinephrine may contribute to the acute pressor effect of coffee. Smits P, Pieters G, Thien T, "The role of epinephrine in the circulatory effects of coffee," *Clin. Pharmacol. Ther.* (1986) 40(4):431-437.

Coffee also adversely affects arterial stiffness. Echeverri D, Pizano A, Montes FR, Forcada P, "Acute effect of coffee consumption on arterial stiffness, evaluated using an oscillometric method," *Artery Res.* (2017) 17:16-32; Karatzis E, Papaioannou TG, Aznaouridis K, Karatzi K, Stamatelopoulos K, Zampelas A, Papamichael C, Lekakis J, Mavrikakis M, "Acute effects of caffeine on blood pressure and wave reflections in healthy subjects: should we consider monitoring central blood pressure?" *Int. J. Cardiol*. (2005) 98(3):425-430; Vlachopoulos C, Hirata K, O'Rourke MF, "Effect of caffeine on aortic elastic properties and wave reflection," *J. Hypertension* (2003) 21(3):563-570; Mahmud A, Feely J, "Acute effect of caffeine on arterial stiffness and aortic pressure waveform," *Hypertension* (2001) 38(2):227-231, and endothelium dependent vasodilation. Papamichael CM, Aznaouridis KA, Karatzis EN, Karatzi KN, Stamatelopoulos KS, Vamvakou G, Lekakis JP, Mavrikakis ME, "Effect of coffee on endothelial function in healthy subjects: the role of caffeine," *Clin. Sci.* (2005) 109(1):55-60. Consumption of caffeinated coffee acutely increased pulse wave velocity in healthy subjects. Mahmud A, Feely J, "Acute effect of caffeine on arterial stiffness and aortic pressure waveform," *Hypertension* (2001) 38(2):227-231. Coffee drinking also resulted in an increased augmentation index of the aortic pressure waveform, indicating increased wave reflection. Karatzis E, Papaioannou TG, Aznaouridis K, Karatzi K, Stamatelopoulos K, Zampelas A, Papamichael C, Lekakis J, Mavrikakis M, "Acute effects of caffeine on blood pressure and wave reflections in healthy subjects: should we consider monitoring central blood pressure?" *Int. J. Cardiol*. (2005) 98(3):425-430; Mahmud A, Feely J, "Acute effect of caffeine on arterial stiffness and aortic pressure waveform," *Hypertension* (2001) 38(2):227-231.

Intake of 250 mg caffeine induces similar effects on arterial stiffness and augmentation index (Papamichael CM, Aznaouridis KA, Karatzis EN, Karatzi KN, Stamatelopoulos KS, Vamvakou G, Lekakis JP, Mavrikakis ME, "Effect of coffee on endothelial function in healthy subjects: the role of caffeine," *Clin. Sci.*(2005) 109(1):55-60), indicating that caffeine is responsible for the effects.

Lastly, consumption of one cup of coffee acutely impaired flow-mediated dilation in the brachial artery in healthy people without affecting nitroglycerin-induced vasodilation, indicating

impaired endothelium dependent vasodilation. Papamichael CM, Aznaouridis KA, Karatzis EN, Karatzi KN, Stamatelopoulos KS, Vamvakou G, Lekakis JP, Mavrikakis ME, "Effect of coffee on endothelial function in healthy subjects: the role of caffeine," *Clin. Sci.*(2005) 109(1):55-60.

Serious cardiovascular events have been reported to occur within 1 hour of drinking coffee in case-crossover studies, prompting some to refer to coffee as a "trigger" for acute cardiac death.

In one study, risk of acute cardiac death was increased in the hour after drinking coffee (RR 1.73, 95% CI 1.14 - 2.96). Selb Semerl J, Selb K, "Coffee and alcohol consumption as triggering factors for sudden cardiac death: case-crossover study," *Croat. Med. J.* (2004) 45(6):775-780.

In another study, the overall risk of myocardial infarction in the hour after drinking coffee was significantly increased by about half (RR 1.49, 95% CI 1.17 - 1.89), the risk being greatest among those drinking ≤1 cup of coffee per day (RR 4.14, 95% CI 2.03 -8.42) and decreasing with increasing coffee consumption. Baylin A, Hernandez-Diaz S, Kabagambe EK, Siles X, Campos H, "Transient exposure to coffee as a trigger of a first nonfatal myocardial infarction," *Epidemiology* (2006) 506-511.

In another study, the risk of stroke in the hour after drinking coffee was doubled (RR 2.0, 95% CI 1.4 - 2.8). Mostofsky E, Schlaug G, Mukamal KJ, Rosamond WD, Mittleman MA, "Coffee and acute ischemic stroke onset: the Stroke Onset Study," *Neurology* (2010) 75(18):1583-1588.

In yet another study, the population-attributable risk of coffee consumption for rupture of intracranical aneruysms was found to be 10.6%, which was the highest population-attributable risk for any factor. Vlak MH, Rinkel GJ, Greebe P, van der Bom JG, Algra A, "Trigger factors and their attributable risk for rupture of intracranial aneurysms: a case-crossover study," *Stroke* (2011) 42(7):1878-1882.

The association of coffee consumption in the hour preceding (near)-fatal cardiac emergencies has been attributed to the acute effects of caffeine on the cardiovascular system. Logroscino G, Kurth T, "Ischemic stroke Coffee may pull the trigger," *Neurology* (2010) 75(18):1576-1577; Siscovick DS, "Triggers of clinical coronary heart disease," *Epidemiology* (2006) 17(5):495-497.

X. OEHHA'S CLAIM THAT COFFEE IS UNIQUE

In the Initial Statement of Reasons, OEHHA writes: "Coffee is unique in that it shows reductions in certain human cancers, has not been shown to increase any cancers, and is particularly rich in cancer chemopreventive compounds." (ISOR at page 11). This statement is incorrect, because the same is true of tobacco.

A. Coffee and Smoking Are Associated with Reduced Risk of Certain Cancers

Coffee does not uniquely show reductions in human cancers in observational studies. While epidemiological studies regarding consumption of coffee have reported decreased risks of breast cancer, endometrial cancer, melanoma, and thyroid cancer, so too have epidemiological studies regarding cigarette smoking.

1. Endometrial Cancer

a. Coffee Studies

Several studies have demonstrated a significantly reduced risk of endometrial cancer in relation to coffee consumption. Koizumi T, Nakaya N, Okamura C, Sato Y, Shimazu T, Nagase S, Niikura H, Kuriyama S, Tase T, Ito K, Tsubono Y. "Case–control study of coffee consumption and the risk of endometrial endometrioid adenocarcinoma," *Eur. J. Cancer Prev.* (2008) 17(4):358-363; Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C, Tavani A. "Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies," *Am. J. Obstetr. and Gynecol.* (2009) 200(2):130-135; Je Y, Giovannucci E, "Coffee consumption and risk of endometrial cancer: Findings from a large up-to-date meta-analysis," *Int. J. Cancer* (2012) 131(7):1700-1710; Friberg

E, Orsini N, Mantzoros CS, Wolk A. "Coffee drinking and risk of endometrial cancer—A population-based cohort study," *Int. J. Cancer* (2009) 125(10):2413-2417; Gunter MJ, Schaub JA, Xue X, Freedman ND, Gaudet MM, Rohan TE, Hollenbeck AR, Sinha R. "A prospective investigation of coffee drinking and endometrial cancer incidence," *Int. J. Cancer* (2012) 131(4):E530-E536.

Koizumi reported a significant inverse trend for endometrial cancer and coffee consumption in postmenopausal women, but found a slight non-significant increase in endometrial cancer by the amount of coffee consumed among premenopausal women. The inverse relation for coffee consumption and endometrial cancer identified in the multivariate analysis for postmenopausal women, however, did not adjust for educational status, yet education was highly significantly correlated with endometrial cancer in the study. Therefore, the study results may have been confounded due to lack of control for educational status, but the amount of confounding cannot be determined as this necessary adjustment was not made. Koizumi T, Nakaya N, Okamura C, Sato Y, Shimazu T, Nagase S, Niikura H, Kuriyama S, Tase T, Ito K, Tsubono Y. "Case–control study of coffee consumption and the risk of endometrial endometrioid adenocarcinoma," *Eur. J. Cancer Prev.* (2008) 17(4):358-363;

A meta-analysis by Bravi showed a significant reduction in risk of endometrial cancer based on case-control studies, while the reduction in risk based on cohort studies was not significant. Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C, Tavani A. "Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies," *Am. J. Obstetr. and Gynecol.* (2009) 200(2):130-135; Je Y, Giovannucci E, "Coffee consumption and risk of endometrial cancer: Findings from a large up-to-date meta-analysis," *Int. J. Cancer* (2012) 131(7):1700-1710.

A prospective study by Je did not find an association with drinking fewer than 4 cups of coffee/day and endometrial cancer. However, those who consumed > 4 cups/day demonstrated a significant deficit, OR = 0.72 (95 CI = 0.55-0.95). Je Y, Giovannucci E, "Coffee consumption and

risk of endometrial cancer: Findings from a large up-to-date meta-analysis," *Int. J. Cancer* (2012) 131(7):1700-1710.

Friberg found a significant deficit of endometrial cancer among obese women only who drank > 4 cups of coffee/day as compared to those who drank< 1 cup/day, p-trend 0.007. It is noted, however, that women who drank > 4 cups/day were 10 years younger than those who drank < 1 cup/day (the comparison group). Since endometrial cancer risk is relatively greater among older aged women, those who drank > 4 cups/day would be expected to have a lower risk of endometrial cancer as compared to the controls who were 10 years older. Those who drank > 4 cups/day also had a 67% greater prevalence of cigarette smoking. Such a difference in cigarette smoking history would also favor the high coffee consumers to have a lower risk of endometrial cancer. Friberg E, Orsini N, Mantzoros CS, Wolk A. "Coffee drinking and risk of endometrial cancer—A population-based cohort study," *Int. J. Cancer* (2009) 125(10):2413-2417.

Even though the data were statistically adjusted for age, and cigarette smoking, the reduced risk among those who drank > 4 cups /day may still have been influenced by differences in both age and cigarette smoking. The differences of these parameters between those who drank > 4 cups/day versus the comparison group (< 1 cup/day) also suggests heterogeneity between the two populations that are being compared. Thus, the study has very disparate groups in smoking and age for the <1 vs. > 4 cups per day comparison groups. Friberg used a Cox proportional model that adjusted for smoking and age. However, a proper analysis requires examining for interaction effects between smoking and weight, smoking and coffee drinking, age and weight, then three way interaction effects (still using endometrial cancer as the independent variable). If there are any interaction effects, one cannot properly estimate the independent effects of coffee, smoking, age, or weight, since these can all potentially confound with each other. If one factors in the educational or caloric intake differences between the <1 and >4 cups/day groups, analyses by *adjusted* models become even more difficult. The results suggesting a lower risk of endometrial cancer among the highest coffee consumption group is therefore likely to have been influenced by differences other than coffee consumption.

Gunter reported an inverse relation between coffee consumption and endometrial cancer. The authors concluded that further research should be conducted to determine whether there is a true causal relationship between coffee drinking and endometrial cancer. Gunter MJ, Schaub JA, Xue X, Freedman ND, Gaudet MM, Rohan TE, Hollenbeck AR, Sinha R. "A prospective investigation of coffee drinking and endometrial cancer incidence," *Int. J. Cancer* (2012) 131(4):E530-E536.

The Wang 2016 meta-analysis reported a reduced risk for endometrial cancer (as well as many other cancer sites) in relation to coffee consumption. The study, however, does not provide the basis for selection of studies to be included, nor indicate the studies that were rejected and the basis for the rejection. The study results are difficult to interpret as the methodology is not clearly presented. Also, Figure 1 which indicates the potential number of articles identified for inclusion in the study along with the number of excluded studies do not add up and it is difficult to know from which group the "1,997" excluded studies were excluded. Further, "S" Table 3b titled "female genital organs" presents results for breast cancer only, which is not a cancer of female genital organs. Wang A, Sang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Niao R, He L, Sang X, Zhao H, "Coffee and cancer risk: A meta-analysis of prospective observational studies," *Sci. Rep.* (2016) 6:33711.

b. Smoking Studies

"[S]everal prospective investigations have reported inverse associations between cigarette smoking and endometrial cancer, a finding that has been attributed to possible anti-estrogenic effects of tobacco smoke." Gunter MJ, "Re: coffee drinking and risk of endometrial cancer – a population-based cohort study," *Int. J. Cancer* (2010) 126(7):1770.

A meta-analysis of cigarette smoking and endometrial cancer risk, based on 10 prospective cohort studies and 24 case-control studies, reported significant inverse associations. Ever smoking was associated with a reduced risk of endometrial cancer in prospective studies (RR 0.81, 95% CI

0.74 - 0.88) and case-control studies (OR 0.72, 95% CI 0.66 - 0.79). The inverse association was significant among current and former smokers. An increase in smoking of 20 cigarettes per day was significantly associated with 16% and 27% reduced risks of endometrial cancer in prospective and case-control studies, respectively. Zhou B, Yang L, Sun Q, Cong R, Gu H, Tang N, Zhu H, Wang B, "Cigarette smoking and the risk of endometrial cancer: a meta-analysis," *Am. J. Med.* (2008) 121(6):501-508.

"The inverse relationship between cigarette smoking and endometrial carcinoma risk is well established." Felix AS, Yang HP, Gierach GL, Park Y, Brinton LA, "Cigarette smoking and endometrial carcinoma risk: the role of effect modification and tumor heterogeneity," *Cancer Causes Control* (2014) 25(4):479-489.

"Endometrial cancer has been shown repeatedly to be inversely associated with cigarette smoking, with risk amongst heavy smokers up to half that of never smokers." Kuper H, Boffetta P, Adami H-O, "Tobacco use and cancer causation: association by tumour type," J. *Intern. Med*. (2002) 252:206-224.

In one study of cause-specific cancer mortality among never smokers (involving three large cohorts), the risk of endometrial cancer was doubled among those who drank the most coffee (more than 5 cups per day) in the multivariate analysis (RR 2.17, 95% CI 0.94 - 5.05). Ding M, Satija A, Bhupathiraju SN, Hu Y, Sun Q, Han J, Lopez-Garcia E, Willett W, van Dam RM, Hu FB, "Association of coffee consumption with total and cause-specific mortality in three large prospective cohorts," *Circulation* (2015) 132:2305-2315. This result suggests that the inverse association between coffee consumption and endometrial cancer observed in most studies is likely due to confounding by smoking. Even though some studies that have adjusted for smoking have found significantly decreased risks of endometrial cancer related to coffee consumption, a residual effect from cigarette smoking is still a likely confounder, just as increased risks of lung cancer in coffee drinkers are likely confounded by cigarette smoking, even though some studies that adjusted for cigarette smoking demonstrate elevated risks of lung cancer in relation to coffee consumption.

2. Breast cancer

a. Coffee Studies

Five meta-analyses regarding coffee consumption and breast cancer have been published to date, all by Chinese investigators.

In 2009 Chinese researchers from Shanghai published a meta-analysis of coffee consumption and breast cancer based on 9 cohort studies and 9 case-control studies. The combined RR showed a borderline significant decrease in breast cancer for the highest coffee consumption versus the lowest (RR 0.95, 95% CI 0.90 - 1.00). For an increment of 2 cups/day, the breast cancer risk was borderline significantly reduced with the data for Europe, the USA and Asia combined with the exclusion of 3 studies (RR 0.98, 95% CI 0.96 - 1.00), but results were not statistically significant with data for all 3 countries analyzed separately, e.g., USA (RR 0.99, 95% CI - 0.95 - 1.02). The investigators concluded that their findings suggest a possible influence of high coffee consumption or increased coffee consumption on the risk of breast cancer, but the risk of breast cancer from coffee consumption in the study is virtually 1.0. Tang N, Zhou B, Wang B, Yu R, "Coffee consumption and risk of breast cancer: a metaanalysis," *Am. J. Obstet. Gynecol.* (2009) 200(3):290.e1-9.

In 2011, Chinese researchers from Shanghai published a meta-analysis of prospective cohort studies regarding coffee consumption and risk of cancers. Based on 11 cohort studies, the risk of breast cancer was slightly decreased (RR 0.94, 95% CI 0.91 - 0.99). Yu X, Bao Z, Zou J, Dong J, "Coffee consumption and risk of cancers: a meta-analysis of cohort studies," *BMC Cancer* (2011) 11:96.

In 2013 Chinese researchers from Xuzhou published a meta-analysis of epidemiologic studies regarding coffee consumption and breast cancer. A total of 26 studies (16 cohort and 10 case-control studies) on coffee intake with 49497 breast cancer cases were included in the analysis. The pooled RR showed a borderline significant influence of highest coffee consumption (RR 0.96, 95% CI 0.93

-1.00). Low-to moderate coffee consumption showed no association with risk of breast cancer (RR 0.99, 95% CI 0.95 - 1.04); for an increment of 2 cups/day of coffee consumption the risk of breast cancer was (RR 0.98, 95% CI 0.97-1.00). In stratified analysis, a significant inverse association was observed in ER-negative subgroup. However, no significant association was noted in the others. The investigators concluded that increased coffee intake is not associated with a significantly reduced risk of breast cancer, but noted that an inverse association was observed in the ER-negative subgroup analysis. Li XJ, Ren ZJ, Qin JW, Zhao JH, Tang JH, Ji MH, Wu JZ, "Coffee consumption and risk of breast cancer: an up-to-date meta-analysis," *PLoS One* (2013) 8(1):e52681.

In 2013 Chinese researchers from Qingdao published a meta-analysis of 37 published studies regarding coffee consumption and breast cancer. This study included 966,263 participants and 59,018 breast cancer cases were included in the meta-analysis. No significant association was found between breast cancer risk and coffee (RR 0.97, $p = 0.09$), decaffeinated coffee (RR 0.98, $p = 0.55$) and caffeine (RR 0.99, $p = .73$), respectively. However, an inverse association of coffee/caffeine with breast cancer risk was found for postmenopausal women (RR 0.94, $p = 0.02$), and a strong and significant association of coffee with breast cancer risk was found for BRCA1 mutation carriers (RR 0.69, $p < 0.01$). A linear dose-response relationship was found for breast cancer risk with coffee consumption; the risk of breast cancer decreased by 2% ($p = 0.05$) for every 2 cups/day increment in coffee intake. The researchers concluded that the findings from their study suggested that coffee/caffeine might be weakly associated with breast cancer risk for postmenopausal women. Jiang W, Wu Y, Jiang X, "Coffee and caffeine intake and breast cancer risk: an updated dose–response meta-analysis of 37 published studies," *Gynecol. Oncol*. (2013) 129(3):620-629.

In 2016, researchers from Beijing and Tianjin published a meta-analysis of prospective cohort studies regarding coffee consumption and cancer risk. Seventeen cohort studies were included in the analysis of breast cancer. Comparing the highest versus lowest intake of coffee consumption, no association with risk of breast cancer risk was observed. (RR 0.99, 95% CI 0.94 - 1.04). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H,

"Coffee and cancer risk: A meta-analysis of prospective observational studies," *Sci. Rep.* (2016) 6:33711.

b. Smoking Studies

The inverse association of coffee consumption and breast cancer among postmenopausal women (and the absence of an association between coffee consumption and breast cancer generally) is likely, due, at least in part, to confounding by cigarette smoking.

"A review of 14 case-control studies and five cohort studies found that the RR for breast cancer among heavy smokers compared with never smokers generally ranged from 0.9 to 1.2." Kuper H, Boffetta P, Adami H-O, "Tobacco use and cancer causation: association by tumour type," J. *Intern. Med*. (2002) 252:206-224, citing Palmer JR, Rosenberg L, "Cigarette smoking and the risk of breast cancer," *Epidemiol. Rev.* (1993) 15(1):145-156.

"Although an association has rarely been found by epidemiological studies, a role of cigarette smoking in the aetiology of breast cancer is biologically plausible. Smoking has anti-oestrogenic effects and menopause occurs at an earlier age in smokers, supporting a protective effect on breast cancer risk." Kuper H, Boffetta P, Adami H-O, "Tobacco use and cancer causation: association by tumour type," J. *Intern. Med*. (2002) 252:206-224.

The investigators of an early case-control study of breast cancer and coffee consumption commented: "The recent paper by Vessey et al. reporting a statistically significant protective effect of smoking in BC patients is intriguing because smoking is known to be positively correlated with coffee consumption. Furthermore, in a review of the literature on smoking and estrogen-related disease, Baron found smoking to be a protective factor in several studies, even when weight and age at menopause were included as covariates. Inasmuch as our questionnaire did not include any data on smoking, we were unable to examine this possible confounding effect." Lubin F, Ron E, Wax

Y, Modan B, "Coffee and methylxanthines and breast cancer: a case-control study," *J. Natl. Cancer Inst.* (1985) 74(3):569-573.

In a cohort study of Swedish breast cancer patients, Swedish researchers commented that "coffee intake and smoking have been shown to be associated" and observed that "in the present study, current smoking was significantly associated with increasing coffee consumption." Simonsson M, Söderlind V, Henningson M, Hjertberg M, Rose C, Ingvar C, Jernström H, "Coffee prevents early events in tamoxifen-tgreated breast cancer patients and modulates hormone receptor status," *Cancer Causes Control* (2013) 24(5):929-940.

The inverse association of coffee/caffeine with breast cancer risk in postmenopausal women observed in the meta-analysis by Jiang 2013 may be due to confounding by the anti-estrogenic effect of cigarette smoking.

3. Melanoma

a. Coffee Studies

Five meta-analyses regarding coffee consumption and risk of melanoma have been published, all but one in the year 2016.

Researchers from Harvard identified nine observational studies with a total of 927,173 study participants, of whom 3,787 had melanoma. With random-effects modeling, the pooled relative risk for melanoma among regular coffee drinkers was reduced compared to controls (RR 0.75 (95 % CI 0.63 - 0.89, $p = 0.001$). However, the pooled relative risk for melanoma among decaffeinated coffee drinkers was not statistically significant (RR 0.92, 95 % CI 0.82 - 1.05). The investigators from Harvard concluded that their study showed some evidence for a beneficial effect of regular coffee consumption on the risk of melanoma, but that more prospective cohort studies with systematic quantification of coffee consumption would be necessary to further elucidate the association. Yew

YW, Lai YC, Schwartz RA, "Coffee Consumption and Melanoma: A Systematic Review and Meta-Analysis of Observational Studies" *Am. J. Clin. Dermatol.* (2016) 17(2):113-123.

Chinese researchers identified twelve studies involving 832,956 participants for total coffee consumption, 5 studies involving 717,151 participants for caffeinated coffee consumption, and 6 studies involving 718,231 participants for decaffeinated coffee consumption. Compared with the lowest level of consumption, the pooled RRs were 0.80 (95% CI 0.69 - 0.93), 0.85 (95 % CI 0.71 - 1.01) and 0.92 (95 % CI 0.81 - 1.05) for the consumption of total coffee, caffeinated coffee and decaffeinated coffee, respectively. In subgroup analysis by study design, the pooled RRs in cohort studies and case-control studies were 0.83 (95 % CI 0.72 - 0.97) and 0.74 (95 % CI 0.51 - 1.07) for total coffee consumption, respectively. They concluded that coffee consumption may reduce the risk of cutaneous melanoma. Wang J, Li X, Zhang D, "Coffee consumption and the risk of cutaneous melanoma: a meta-analysis," *Eur. J. Nutr.* (2016) 55(4):1317-1329.

Another meta-analysis by Chinese researchers was based on two case-control studies including 846 malignant melanoma patients and five cohort studies including 844,246 participants and 5,737 malignant melanoma cases. Risk of malignant melanoma was significantly reduced for highest versus lowest consumption of caffeinated coffee (RR 0.81, 95% CI 0.68 - 0.97), but not of decaffeinated coffee (RR 0.92, 95% CI 0.81 - 1.05). Analysis of data indicated a significant inverse relationship for women (pooled RR 0.76, 95% CI 0.61 - 0.95), but a slight increase in melanoma risk for men (pooled RR 1.11, 95% CI 0.91 - 1.36). The investigators concluded that their meta-analysis suggested that caffeinated, but not decaffeinated, coffee might have chemo-preventive effects against malignant melanoma, but that larger prospective studies and intervention studies were necessary to confirm their findings. Liu J, Shen B, Shi M, Cai J, "Higher Caffeinated Coffee Intake Is Associated with Reduced Malignant Melanoma Risk: A Meta-Analysis Study," *PLoS One* (2016) 11(1):e0147056.

In another meta-analysis based on six cohort studies that compared the highest versus the lowest intake of coffee, Chinese researchers calculated a reduced risk of melanoma (RR 0.89, 95%

CI 0.80 - 0.99, $p = 0.031$). Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, Sang X, Zhao H, "Coffee and cancer risk: A meta-analysis of prospective observational studies," *Sci. Rep.* (2016) 6:33711.

A recent meta-analysis of seven cohort studies, comprising 1,418,779 participants and 9,211 melanoma cases, showed a significant association between total coffee consumption and melanoma risk. An increase in coffee consumption of one cup per day was associated with a 3% reduction in melanoma risk (RR 0.97; 95% CI 0.95-0.99). The researchers concluded that their findings suggest that coffee intake may be inversely associated with incidence of melanoma, but that further studies exploring also the role of confounding factors are needed to explain the heterogeneity among studies. Micek A, Godos J, Lafranconi A, Marranzano M, Pajak A, "Caffeinated and decaffeinated coffee consumption and melanoma risk: a dose-response meta-analysis of prospective cohort studies," *Int. J. Food Sci. Nutr.* (2018) 69(4):417-426.

In the NIH-AARP study of coffee drinking and melanoma, "[e]vidence of a quantitative interaction between smoking status and coffee consumption was found for malignant melanoma (Pheterogeneity = .04); a statistically significant inverse trend was observed among ever (Ptrend = .006) but not never smokers (Ptrend = .67). A higher percentage of ever smokers reported caffeinated coffee intake (61% vs 50%), and risk estimates comparing those in the highest level of caffeinated coffee intake with nondrinkers were similar for ever smokers (HR=0.74, 95% CI 0.59 to 0.94) and never smokers (HR=0.78, 95% CI 0.59 to1.03)." Loftfield E, Freedman ND, Graubard BI, Hollenbeck AR, Shebl FM, Mayne ST, Sinha R, "Coffee drinking and cutaneous melanoma risk in the NIH-AARP diet and health study," *J. Natl. Cancer Inst.* (2015) 107(2) pii: dju421.

In a study of 167,720 participants in the Multiethnic Cohort in Hawaii and Los Angeles, coffee intake was inversely associated with melanoma (HR 0.72, 95% CI 0.52 - 0.99, p-trend = 0.002). Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW, "Prospective study of coffee consumption and cancer incidence in non-white populations," *Cancer*

Epidemiol. Biomarkers Prev. (May 18, 2018) pii: cebp.0093.2018, doi: 10.1158/1055-9965. EPI-18.0093 [Epub ahead of print].

b. Smoking Studies

In a review of smoking and different types of cancer, European researchers concluded that malignant melanoma is unlikely to be associated with smoking, noting that one case-control study conducted in Australia and Scotland had reported that current cigarette smoking was significantly inversely related to acral melanoma (RR 0.6, 95% CI 0.4 - 0.9). Kuper H, Boffetta P, Adami H-O, "Tobacco use and cancer causation: association by tumour type," *J. Intern. Med.* (2002) 252:206-224, citing Green A, McCredie M, MacKie R, Giles G, Young P, Morton C, Jackman L, Thursfield V, "A case-control study of melanomas of the soles and palms (Australia and Scotland)," *Cancer Causes Control* (1999) 10(1):21-25.

In its monograph on smoking and cancer, the International Agency for Research on Cancer noted that a number of case-control studies had found no difference in the prevalence of smoking between patients with malignant melanoma and controls, with an inverse association being found in one study, and that although smoking had been linked to the incidence of squamous-cell carcinoma in some studies, neither cohort studies nor case-control studies had found an effect of smoking on the incidence of basal-cell carcinoma. International Agency for Research on Cancer, "Tobacco Smoke and Involuntary Smoking," *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* Vol. 83 (IARC 2004).

In its most recent update of smoking and cancer, IARC noted that two cohort studies (Freedman DM, Sigurdson A, Doody MM, Rao RS, Linet MS. "Risk of melanoma in relation to smoking, alcohol intake, and other factors in a large occupational cohort," *Cancer Causes Control*. (2003) 14(9):847-857; Odenbro Å, Gillgren P, Bellocco R, Boffetta P, Håkansson N, Adami J, "The risk for cutaneous malignant melanoma, melanoma in situ and intraocular malignant melanoma in

relation to tobacco use and body mass index," *Br. J. Dermatol.* (2007) 156(1):99-105) reported inverse associations for smoking and melanoma, and that in the latter study the risk of melanoma was reduced in a dose-dependent manner; IARC concluded that smoking may reduce the risk of melanoma. International Agency for Research on Cancer, "Personal Habits and Indoor Combustions," *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* Vol. 100E (IARC 2012).

Three meta-analyses have reported that smoking is inversely associated with malignant melanoma. Leonardi-Bee J, Ellison T, Bath-Hextall F, "Lifestyle factors of smoking, BMI and alcohol on the risk of Non-Melanoma Skin Cancer in adults: a systematic review," *JBI Libr. Syst. Rev.* (2012) 10(6):352-398; Song F, Qureshi AA, Gao X, Li T, Han J, "Smoking and risk of skin cancer: a prospective analysis and a meta-analysis," *Int. J. Epidemiol.* (2012) 41(6):1694-1705; Li Z, Wang Z, Yu Y, Zhang H, Chen L, "Smoking is inversely related to cutaneous malignant melanoma: results of a meta-analysis," *Br. J. Dermatol.* (2015) 173(6):1540-1543.

In the most recent meta-analysis, the pooled relative risks of melanoma based on cohort studies, was 0.69 (95% CI 0.62 - 0.77) for current smokers, 0.88 (95% CI 0.77 - 1.01) for former smokers, and 0.92 (95% Ci 0.83 - 1.01) for ever smokers. A similar trend was noted in case-control studies. Li Z, Wang Z, Yu Y, Zhang H, Chen L, "Smoking is inversely related to cutaneous malignant melanoma: results of a meta-analysis," *Br. J. Dermatol.* (2015) 173(6):1540-1543.

4. Thyroid Cancer

a. Coffee Studies

About a half-dozen case-control studies have assessed the risk of thyroid cancer in relation to the consumption of coffee.

In a pooled analysis of four European case-control studies, the risk of thyroid cancer was decreased for high coffee consumption (OR 0.7). According to the authors of the study, an inverse association of borderline statistical significance was found for coffee intake. Franceschi S, Levi F, Negri E, Fassina A, La Vecchia C, "Diet and Thyroid Cancer: A Pooled Analysis of Four European Case-Control Studies," *Int. J. Cancer* (1991) 48(3):395-398.

In a hospital-based case-control study of thyroid cancer among Japanese women, the risk of thyroid cancer was decreased in relationship to consumption of coffee. (OR 0.6, 95% CI 0.3 - 1.04). Takezaki T, Hirose K, Inoue M, Hamajima N, Kuroishi T, Nakamura S, Koshikawa T, Matsuura H, Tajima K, "Risk factors of thyroid cancer among women in Tokai, Japan," *J. Epidemiol.* (1996) 6(3):140-147.

In a case-control study in Southwestern Germany, a known iodine-deficient area, on multivariate analysis, the risk of thyroid cancer was nonsigificantly decreased for the highest consumption of caffeinated coffee (OR 0.83, 95% CI 0.33 - 2.12). Frentzel-Beyme R, Helmert U, "Association between malignant tumors of the thyroid gland and exposure to environmental protective and risk factors," *Rev. Environ. Health.* (2000) 15(3):337-358.

In a population-based case-control study of thyroid cancer among women living in Los Angeles County, consumption of 6 or more cups of caffeinated coffee per day was slightly, but nonsignificantly, increased for all thyroid cancer (OR 1.3, 95% CI 0.5 - 3.1), as well as papillary thyroid cancer (OR 1.4, 95% CI 0.6 - 3.4). Mack WJ, Preston-Martin S, Bernstein L, Qian D, "Lifestyle and other risk factors for thyroid cancer in Los Angeles County females," *Ann. Epidemiol.* (2002) 12(6):395-401.

In a pooled analysis of 14 case-control studies conducted in the United States, Europe, and Asia, the risk of thyroid cancer, adjusted for current smoking, was slightly but nonsignificantly decreased among those drinking more than 30 cups of coffee per month (OR 0.9, 95% CI 0.6 - 1.2). Mack WJ, Preston-Martin S, Dal Maso L, Galanti R, Xiang M, Franceschi S, Hallquist A, Jin F, Kolonel L, La Vecchia C, Levi F, Linos A, Lund E, McTiernan A, Mabuchi K, Negri E, Wingren

G, Ron E, "A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea," *Cancer Causes Control* (2003) 14(8):773-785.

Three cohort studies regarding coffee consumption and thyroid cancer have been published.

In a population-based cohort study in Japan, on multi-variate analysis, the risk of thyroid cancer for consumption of 1 or more cups of coffee per day was increased among men (RR 1.18, 95% CI 0.48 - 2.91), but decreased among women (RR 0.96, 95% CI 0.62 - 1.48). Michikawa T, Inoue M, Shimazu T, Sasazuki S, Iwasaki M, Sawada N, Yamaji T, Tsugane S, "Green tea and coffee consumption and its association with thyroid cancer risk: a population-based cohort study in Japan," *Cancer Causes Control* (2011) 22(7):985-993.

In the Prostate, Lung, Colorectal and Ovarian cancer cohort, risk of thyroid cancer was not influenced by consumption of 2 or more cups of coffee per day (RR 1.00, 95% CI 0.85 - 1.53). Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang ZF, La Vecchia C, "Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort," *Br. J. Cancer* (2015) 113(5):809-816.

In a study of 167,720 participants in the Multiethnic Cohort in Hawaii and Los Angeles, coffee intake was inversely associated with thyroid cancer (HR 0.44, 95% CI 0.23 - 0.87, *p*-trend = 0.007). Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW, "Prospective study of coffee consumption and cancer incidence in non-white populations," *Cancer Epidemiol. Biomarkers Prev.* (May 18, 2018) pii: cebp.0093.2018, doi: 10.1158/1055-9965. EPI-18.0093 [Epub ahead of print].

One meta-analysis has been published regarding coffee consumption and thyroid cancer. Based on 5 case-control studies and 2 cohort studies, the summary risk for thyroid cancer comparing the highest with no or occasional coffee consumption was nonsignificantly decreased (RR 0.88, 95% CI 0.71 - 1.07). The authors noted that most of the studies adjusted for thyroid cancer risk factors such as age, sex, and thyroid disease, but several studies not not provide adjusted estimates. The investigators observed that they could not exclude some residual confounding variables, such as iodine intake, for which several original studies were not adjusted. Han MA, Kim JH, "Coffee

Consumption and the Risk of Thyroid Cancer: A Systematic Review and Meta-Analysis," *Int. J. Environ. Res. Public Health* (2017) 14(2). pii: E129.

b. Smoking Studies

A pooled analysis of 14 case-control studies showed that smoking was inversely associated with thyroid cancer. The sample consisted of 2,725 thyroid cancer cases and 4,775 controls. The inverse association was stronger among current smokers (RR 0.6, 95% CI 0.6 - 0.7) than former smokers (RR 0.9, 95% CI 0.8 - 1.1). Mack WJ, Preston-Martin S, Dal Maso L, Galanti R, Xiang M, Franceschi S, Hallquist A, Jin F, Kolonel L, La Vecchia C, Levi F, Linos A, Lund E, McTiernan A, Mabuchi K, Negri E, Wingren G, Ron E, "A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea," *Cancer Causes Control* (2003) 14(8):773-785.

In 2014 a meta-analysis reported a reduced risk of thyroid cancer in persons who had ever smoked compared with never-smokers (RR 0.79, 95% CI 0.70 - 0.88) . When the data were stratified by smoking status, an inverse association was observed among current smokers (RR 0.74, 95% CI 0.64 - 0.86), but not former smokers. An inverse association was also observed in the case-control studies (RR 0.75, 95% CI 0.66 - 0.85). Cho YA, Kim J, "Thyroid cancer risk and smoking status: a meta-analysis," *Cancer Causes Control* (2014) 25:1187- 1195.

5. Conclusion

Consumption of coffee and cigarette smoking have both been inversely associated with breast cancer, endometrial cancer, melanoma, and thyroid cancer. Thus, the assertion by OEHHA in its Initial Statement of Reasons that "[c]offee is unique in that it shows reductions in certain human cancers" is incorrect.

B. Coffee Has Been Shown to Increase the Risk of Certain Cancers

In the Initial Statement of Reasons, OEHHA writes: "Coffee is unique in that it . . . has not been shown to increase any cancers . . . .(ISOR at page 11). This statement is incorrect, because, as previously explained, consumption of coffee has been shown to increase the risk of bladder cancer, childhood brain cancer, childhood leukemia, esophageal cancer, gastric cancer, laryngeal cancer lung cancer, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, and total cancer. *See, supra.*

C. Coffee and Tobacco Both Contain "Cancer Chemopreventive Compounds"

In the Initial Statement of Reasons, OEHHA writes: "Coffee is unique in that it . . . is particularly rich in cancer chemopreventive compounds." (ISOR at page 11). This statement is erroneous, because the same is true of tobacco. Indeed, while coffee does contains polyphenolic chemicals and other chemicals that have antioxidant activity, so does tobacco/cigarette smoke.

"Tobacco, consumed by 20 to 50% of the worldwide population, contains significant concentrations of polyphenols and carotenoids, which are important naturally occurring antioxidants." Rodu B, Ou B, "The Antioxidant Properties of Tobacco," *Tobacco Sci.* (2000) 44:71-73.

"Major polyphenolics found in tobacco include chlorogenic acid, rutin, scopoletin and scopolen, along with materials such as quercetin and kaempferol. . . . The chlorogenic acids are primarily 3-O-caffeoyl-quinic acid with lesser amounts of the 5- and 6- linked isomers. Scopolin and scopoletin are the major coumarin compounds in tobacco." Leffingwell JC, "Basic Chemical Constituents of Tobacco Leaf and Differences among Tobacco Types," Chap. 8: Leaf Chemistry, in Davis DL and Nielson MT, eds., *Tobacco: Production, Chemistry, and Technology* (Blackwell Science, 1999).

"The amounts of polyphenols for Virgina NC 95 and Burley 21 [tobaccos] have been reported." *Id.*, citing Sheen SJ, De Jong DW, Chaplin JF, "Polyphenol accumulation in chlorophyll mutants of tobacco under two cultural practices," *Beitr. Z. Tabakforsch* (1979) 10(1):57-64. The content of these polyphenols in Virginia tobacco is as follows: Chlorogenic acids 34.71 mg/g, Rutin 7.95 mg/g, Scopoletin 0.13 mg/g, and Scopolin 0.94 mg/g. The concentration of these polyphenols in Burley tobacco is less: Chlorogenic acids 12.83 mg/g, Rutin 4.00 mg/g, Scopoletin 0.06 mg/g, and Scopolin 0.35 mg/g. *Id.*

"Many more phenolics are found in tobacco smoke than in leaf . . . ." Leffingwell JC, "Basic Chemical Constituents of Tobacco Leaf and Differences among Tobacco Types," Chap. 8: Leaf Chemistry, in Davis DL and Nielson MT, eds., *Tobacco: Production, Chemistry, and Technology* (Blackwell Science, 1999), citing Wilson RA, Mookherjee BC, Vinals JF, "A comparative analysis of gthe volatile componetns of Virginia, burley, Turkish and black tobaccos," paper presented at *18th Natl. ACS Meeting*, Kansas City, 1982). The major phenolics that are present in tobacco smoke are: phenol, *o*-Cresol, *m*-Cresol, *p*-Cresol, Guaiacol, Dimethylphenols, 4-Vinylphenol, 2-Acetyl-3-methylphenol, Trimethylphenols, 4-Ethylguaiacol, 4-*t*-Butylphenol, Eugenol, 4-Vinylguaiacol, 4-Allyl-2,y-dimethylphenol, and Vanillin. *Id.*

In a study published in 2000, the antioxidant properties and polyphenolic concentrations of 16 commercially available tobacco products were determined using the oxygen radical absorbance capacity (ORAC) assay. The tobacco products analyzed were ten moist snuff products, two chewing tobacco products, two pelletized leaf tobacco products and two cigarette brands that were purchased at a retail store in Birmingham, Alabama. "The antioxidant activity of the sixteen tobacco product, measured as ORAC, varied from 66 to 230 μmole TE g^{-1} on a dry weight basis, and there ws a strong correlation between ORAC level and total phenolic content ($R^2 = 0.96$). The range of ORAC activity in the tobacco products was similar to that reported for many fruits and vegetable." The highest ORAC values were found in the two cigarette products: Camel cigarette had the highest ORAC value (206 ± 6 μmole Trolox equivalent per gram), and also had the highest phenolic content (26.9

± 4.5 mg gallic acid equivalent per gram) of the 16 products tested. Marlboro Reds (the other cigarette product tested) had the second highest ORAC value 169 ± 1μmole Trolox equivalent per gram) and also had a high phenolic content (23.6 ± 0.5 mg gallic acid equivalent per gram). Rodu B, Ou B, "The Antioxidant Properties of Tobacco," *Tobacco Sci.* (2000) 44:71-73.

D. Coffee and Tobacco Have Been the Subject of Scientific Interest for Years

Towards the end of the Initial Statement of Reasons OEHHA writes: "Coffee is also unusual because it has been the subject of very high scientific interest for many years – IARC reviewed more than 1000 observational and experimental studies investigating the potential carcinogenicity of coffee in humans and animals, and in vitro and other experimental systems." (ISOR at pp. 11-12).

That coffee has been the subject of much scientific interest is hardly unusual for a chemical mixture that has long been the most widely consumed beverage in the world (other than water). Indeed, the large number of observational epidemiological studies and experimental studies in animals that have been published about coffee is not "unusual," but should be expected for a complex chemical mixture that is widely consumed worldwide because of its reinforcing properties. The large body of scientific literature regarding coffee and human health does not make coffee "unusual," but rather puts it in a small class of complex chemical mixtures of widespread use – along with tobacco. Indeed, among complex chemical mixtures, coffee is surpassed only by tobacco, for which even more observational and experimental studies have been published than have been regarding coffee. Of course, the most important analogy between coffee and tobacco is the addictive nature of these chemical mixtures, which arises from reinforcing properties of caffeine and nicotine.

In 2012, a commentary by Caroline Scott-Thomas was published in FoodNavigator.com. Titled "Acrylamide: A Scandal in the Making," Ms. Scott-Thomas reported:

> Acrylamide is a recognised carcinogen that we've known is in our food at dangerous levels for a decade. Today, the food industry has tools to mitigate it, but uptake is slow. Industry, beware. This is how scandals are made.
>
> Swedish researchers in 2002 were shocked to find acrylamide in many commonly consumed foods at levels up to 500 times the World Health Organization (WHO) maximum limit for drinking water.
>
> We now know that acrylamide is present at high levels in starchy foods when they are toasted, grilled or baked through a process called the Maillard reaction, in which sugars react with the amino acid asparagine to give foods like French fries, crisps, breakfast cereals, baked goods and coffee their brown colour and tasty flavour.
>
> For the past ten years, ingredient suppliers have been pulling out the stops to arm the food industry with tools to reduce acrylamide, and they have done a great job. There are now ingredients and processes to significantly cut the acrylamide content of a wide variety of foods. . . .
>
> Right now, acrylamide is off consumers' radar - and however cost-effective a solution may be, any reduction technique is still an expense. But acrylamide is not going anywhere, and the industry needs to do some damage control before it becomes a major PR disaster, even if public awareness of the problem is still relatively low... It may not be a big issue for consumers yet, who already have their plates full worrying about ingredients and processes that often have nowhere near as strong a link to cancer or genotoxicity. Surely it is just a matter of time.
>
> **'When you start talking about cancers, they don't want to hear.'**
>
> The food industry is getting it in the neck from all sides and, more and more often, Big Food is compared to Big Tobacco as the corporate bad guy sitting on a pile of cash while the world faces the dual food-related problems of overnourishment and undernourishment.
>
> Indeed, one supplier of acrylamide reduction technology speaking with FoodNavigator last week said: "*It's a bit like the tobacco industry. When you start talking about cancers they don't want to hear.*"
>
> Currently, unlike the tobacco industry, food companies have a window of opportunity to do the right thing for public health and to avoid tarnished reputations.
>
> There's a time for debate as evidence is gathered and there's a time for action. The evidence against acrylamide is clear. It's time for action.

IX. THE COFFEE INDUSTRY'S FALLACIOUS ARGUMENTS REGARDING SAFETY

A. The Dietary Guidelines Advisory Committee Report Doesn't Prove Safety

The coffee industry claims that the Scientific Report of the Dietary Guidelines Advisory Committee ("DGAC"), published in 2015, establishes that coffee consumption confers multiple health benefits. However, that report does not address any concerns regarding acrylamide in foods nor does it recommend an acceptable risk level for this carcinogen in coffee. The claim of multiple health benefits by the coffee industry is both inaccurate and misleading. Most notably, the FDA has never authorized any health claim for coffee.

In its report the DGAC wrote that "moderate coffee consumption can be incorporated into a healthy dietary pattern, along with other healthful behaviors." However, this statement does not indicate recognition of any health benefits of coffee. Rather, the DGAC recommends healthy diets and concluded that *moderate* consumption of coffee by *healthy* individuals who are *not susceptible individuals* (e,g, pregnant women and children) "can be incorporated" into healthy dietary patterns.

For example, the following statement appears on page 23 of Part D (Chapter 5) of the DGAC report: "Consistent observational evidence indicates that moderate coffee consumption is associated with reduced risk of type 2 diabetes and cardiovascular disease in healthy adults."

The word "observational" is an important limitation on the quality of the epidemiologic evidence supporting an association of coffee consumption with a statistical reduction in the risk of type 2 diabetes and cardiovascular disease. The word "observational" refers to epidemiologic studies such as cohort studies and case-control studies that are "observational" in nature and distinguishes such studies from controlled studies such as randomized controlled trials and other types of interventional studies. The distinction between observational and interventional studies is critically important, because "[i]n contrast to intervention studies, even the best-designed observational studies cannot establish cause and effect between an intervention and an outcome." U.S. Food and Drug

Agency, *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims-Final* (US FDA 2009).

The word "moderate" is an important limitation on "coffee consumption," because it suggests that the statistical reductions in risk (which are by no means causal) were observed only at lower levels of coffee consumption, suggesting that consumption of coffee at higher levels may well be detrimental to human health. Indeed, a recent industry-sponsored review of numerous health effects of coffee consumption concluded that coffee may have beneficial effects, but only for "moderate coffee consumption in adult consumers." Pourshahidi, LK, Navarini L, Petracco M, Strain JJ, "A Comprehensive Overview of the Risks and Benefits of Coffee Consumption," (2016) *Comp. Rev. Food Sci. Food Safety* 15:671-684.

The word "healthy" is an important limitation on "adults" (i.e., adult coffee drinkers, because it indicates that the statistical reductions in risk for coffee consumption have been found only in healthy adults and not in others, such as children, fetuses, and unhealthy adults (who comprise a large percentage of the adult population). Indeed, Dr. David Kessler, former Commissioner of the federal Food and Drug Administration, who was retained on behalf of the coffee industry for the *CERT v. Starbucks* Phase 2 trial, testified that he himself recommends abstinence or limitation of caffeine intake (from coffee and other caffeine sources) among pregnant women, infants, children, and "sensitive individuals."

The conclusion of the Advisory Committee that coffee can be part of a healthy diet if consumed in moderation by individuals who are not susceptible to its adverse effects is not unique to coffee; the Committee also reached the conclusion that other unhealthy beverages can be part of a healthy diet if consumed in moderation, such as alcohol (a known cause of human liver cancer) and sugar-sweetened carbonated and other beverages (a recognized causes of obesity and heart disease, which likely contribute to diabetes, metabolic syndrome, and other chronic human diseases as well).

Finally, the DGAC report cannot be interpreted as concluding that consumption of coffee confers health benefits, because the report itself states that "individuals who do not consume caffeinated coffee should not start to consume it for health benefits alone."

B. Coffee's Long Use by Hundreds of Millions of People Does Not Prove Safety

The coffee industry claims that because coffee has been consumed by many millions of peope for centuries, it must be safe and cannot cause cancer. This assertion is as absurd as the equally unscientific assertion that because many millions of people who drink coffee get cancer and other chronic diseases, coffee must cause these diseases.

The fallacy that a long history of use without apparent ill effects establishes safety is readily demonstrated by the common food flavoring diacetyl, which, coincidentally occurs naturally in coffee and has also been used as a flavoring in coffee.

In 2002 – the very year that acrylamide was discovered in food – medical researchers discovered that the butter flavoring, diacetyl, was responsible for an epidemic of a rare lung disease called bronchiolitis obliterans at a popcorn manufacturing plant. Kreiss, K., et al., "Clinical Bronchiolitis Obliterans in Workers at a Microwave-Popcorn Plant," *New Engl. J. Med.* (2002) 347(5):330-338.

Like acrylamide, diacetyl was shocking news to the food industry, because diacetyl was classified by the FDA as Generally Recognized as Safe (GRAS) and, as an ingredient in many foods for many decades, had been consumed by hundreds of millions of people worldwide. In the years following this discovery, studies conducted by the National Institute for Occupational Safety and Health showed that diacetyl was causing this rare lung disease not only among chemical workers who produced diacetyl, van Rooy FG, Rooyackers JM, Prokop M, Houba R, Smit LA, Heederik DJ, "Bronchiolitis Obliterans Syndrome in Chemical Workers Producing Diacetyl for Food Flavorings," *Am. J. Respir. Crit. Care Med.* (2007) 176:498-504, but also among flavoring plant workers exposed

to diacetyl among many other food flavorings. Kanwal R, "Bronchiolitis Obliterans in Workers Exposed to Flavoring Chemicals," *Curr. Opin. Pulm. Med.* (2008) 14(2):141-146.

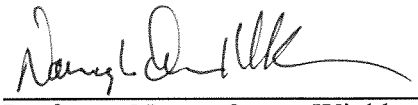
Subsequently, cases of the rare disease were even reported among consumers of microwave popcorn. Egilman DS, Schilling JH, "Bronchiolitis Obliterans and Consumer Exposure to Butter-flavored Microwave Popcorn: A Case Series," *Int. J. Occup. Environ. Health* (2012) 18(1):29-42, and, most recently, among coffee roasting plant workers exposed to diacetyl in coffee. Bailey RL, Cox-Ganser JM, Duling MG, LeBouf RF, Martin SB Jr, Bledsoe TA, Green BJ, Kreiss K, "Respiratory Morbidity in a Coffee Processing Workplace with Sentinel Obliterative Bronchiolitis Cases," *Am. J. Ind. Med.* (2015) 58(12): 1235-1245.

Thus, the contemporaneous discovery of diacetyl – an extremely toxic food flavoring that had been generally recognized as safe by the FDA and had been consumed by millions of people – with the discovery of acrylamide in cooked foods, belies the unscientific assertion that because coffee has been used by many millions of people for many years it must be safe.

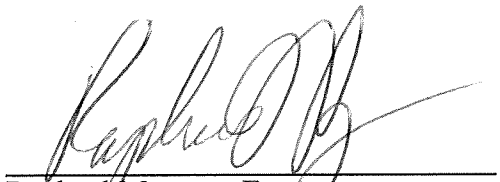
XII. CONCLUSION

The proposed regulation is unfounded, is not supported by sound science and is, in fact, contrary to good science. The proposed regulation is also contrary to provisions of the Safe Drinking Water and Toxic Enforcement Act ("Proposition 65") and contradicts and contravenes that Act rather than implement its provisions. The proposed regulation also thwarts the intent of the Electorate in adopting Proposition 65. The proposed regulation should therefore be withdrawn and abandoned.

Respectfully submitted by the Council for Education and Research on Toxics (CERT).



Professor Nancy Quam-Wickham
Secretary and Director of the
Council for Education and Research
on Toxics, a public benefit corporation



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