Comment Submissions - Proposed Adoption of Exposures to Listed Chemicals in Coffee Posing No Significant Risk

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CERT’s Submission No. 6 regarding the Opinions of Dr. Peter F. Infante Regarding Epidemiologic Studies Regarding Coffee and Cancer.

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August 15, 2018

Via electronic submission to
https://oehha.ca.gov/comments
Monet Vela
Office of Environmental Health Hazard Assessment
P.O. Box 4010
Sacramento, California 95812-4010

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

CERT'S SUBMISSION NO. 6

Dear Ms. Vela:

Enclosed herewith are the following documents that are being submitted on behalf of our client, the Council for Education and Research on Toxics (CERT) regarding the Opinions of Dr. Peter F. Infante Regarding Epidemiologic Studies Regarding Coffee and Cancer.

1. Exhibit A - Opinions of Dr. Peter F. Infante Regarding the Cancer Epidemiology of Coffee (2014).

2. Exhibit B - Opinions of Dr. Peter F. Infante Regarding the Cancer Epidemiology of Coffee (2017).

3. Exhibit C - Testimony of Dr. Peter Infante in *CERT v. Starbucks* trial, October 20, 2014 a.m.

4. Exhibit D - Testimony of Dr. Peter Infante in *CERT v. Starbucks* trial, October 20, 2014 p.m.

5. Exhibit E - Testimony of Dr. Peter Infante in *CERT v. Starbucks* trial, October 21, 2014 a.m.

6. Exhibit F - Testimony of Dr. Peter Infante in *CERT v. Starbucks* trial, September 25, 2017 a.m.

7. Exhibit G - Testimony of Dr. Peter Infante in *CERT v. Starbucks* trial, September 25, 2017 p.m.

8.. Exhibit H - Curriculum Vitae of Dr. Peter Infante.

Kindly include these materials of Dr. Peter F. Infante in the record for this rulemaking proceeding.

Very truly yours,

Raphael Metzger

RM:ip
encls: as specified

EXHIBIT “A”

Opinions of Dr. Peter F. Infante Regarding the Carcinogenicity of Coffee to Humans

[These opinions were formed by Dr. Infante in 2014 before the Phase 1 *CERT v Starbucks* trial; these opinions were updated and supplemented by Dr. Infante in 2017 for Phase 2 of the trial].

Authoritative Body Determinations Regarding Coffee Carcinogenicity

Based upon limited evidence of carcinogenicity to the human bladder and other evidence, the International Agency for Research on Cancer concluded that coffee is possibly carcinogenic to humans. (IARC 1991)

Epidemiologic Studies of Coffee Consumption and Bladder Cancer

Numerous case-control studies report statistically significant increases in bladder cancer in relation to coffee consumption. Dunham 1968 (in black females), Cole 1971 (in females and female nonsmokers), Fraumeni 1971 (in blacks), Simon 1975 (in females), Wynder 1977 (in men), Marrett 1983 (in males and nonsmokers), Rebakalos 1985, Bravo 1986, Piper 1986, Claude 1986 (in men), Iscovich 1987, Kantor 1988, Rische 1988 (in females), La Vecchia 1988, Howe 1988 (in men), Clavel 1991, Kunze 1992, D'Avanzo 1992, McGeehin 1993, Vena 1993, Momas 1994, Donato 1997, Geoffray-Perez 2001, Radosavljevic 2003, De Stefani 2007, Covollo 2008, Porru 2014. One cohort study also reports a statistically significant increase in bladder cancer in relation to coffee consumption in men. Zeegers 2001.

A number of these epidemiologic studies demonstrate statistically significant dose-response relationships. Wynder 1977 (in men), Piper 1986, Kantor 1988, Clavel 1991 (in smokers and nonsmokers), Kunze 1992 (in both sexes), D'Avanzo 1992, Vena 1993, Momas 1994, Donato 1997, Geoffray-Perez 2001 (in nonsmokers), De Stefani 2007, Porru 2014.

Three meta-analyses based on case-control studies demonstrate significant associations between coffee consumption and bladder cancer. Sala 2000 (pooled analysis of 10 case-control studies of nonsmokers), Zeegers (meta-analysis of 34 case-control studies 2001 (in men), Zhou 2012 (meta-analysis of 23 case-control studies). Three meta-analyses based on cohort studies do not report increased risks of bladder cancer. Ross 2010 Yu 2011, Zhou 2012.

Significant increased risks with dose-response relationships have also been reported among nonsmokers, which suggests that the elevated risks of bladder cancer among coffee consumers are not due to confounding by smoking. Sala 2000, Clavel 1991, Geoffray-Perez 2001, Zhou 2012. One possible explanation for this observation is that smokers eliminate caffeine more rapidly than nonsmokers. (Zhou 2012, citing Zevin & Benowitz 1991)

In conclusion, twenty-seven case-control studies demonstrate significant increased risks of bladder cancer in relation to coffee consumption. Eleven of these studies also demonstrate dose-response relationships between coffee consumption and bladder cancer. In its 1991 review, IARC concluded that there was limited evidence of bladder cancer for consumption of coffee. However, since IARC published its review, twelve additional case-control studies have reported significant increases in bladder and eight of these studies demonstrate a dose-response relationship. The case-control studies published since IARC's review provide additional evidence for a carcinogenic effect of coffee on the human bladder. This conclusion is supported by four studies of bladder cancer among nonsmokers, three meta-analyses, and one cohort study. These studies provide strong evidence of an association between coffee consumption and bladder cancer.

Coffee Consumption and Pancreatic Cancer

A number of case-control studies demonstrate significantly elevated risks of pancreatic cancer in relation to consumption of coffee. MacMahon 1981, Wynder 1986 (decaffeinated coffee in females), Gold 1985, Mack 1986, Gorham 1988, Clavel 1989, Ghadirian 1991 (decaffeinated coffee), Lyon 1992, Gullo 1995, Nishi 1996, Silverman 1998 (in blacks), Morales 2007 (with *k-ras* mutations), Turati 2011, Porta 2011 (with *k-ras* mutations).

Several of these studies also report dose-response relationships between coffee consumption and risk of pancreatic cancer. MacMahon 1981, Gold 1985 (in females), Gorham 1988, Clavel 1989, Ghadirian 1991 (decaffeinated coffee), Lyon 1992, Gullo 1995, Nishi 1996, Morales 2007 (with *k-ras* mutations), Turati 2011 (in females and nonsmokers), Porta 2011 (with *k-ras* mutations)

A few case-control studies also report significant increased risks of pancreatic cancer in relation to consumption of coffee among non-smoking populations. Lyon 1992, Gullo 1995, Nishi 1996, Turati 2011.

Two cohort studies also report significant increased risks of pancreatic cancer in relation to coffee consumption and both demonstrate dose-response relationships. Harnack 1997 (post-menopausal females), Nilsson 2010 (boiled coffee).

In conclusion, fourteen case-control studies demonstrate significant increased risks of pancreatic cancer in relation to coffee consumption. Eleven of these studies also demonstrate dose-response relationships between coffee consumption and pancreatic cancer. In addition, two cohort studies report significant increased risks of pancreatic cancer in relation to coffee consumption, both of which demonstrate dose-response relationships. These studies provide strong evidence of an association between coffee consumption and pancreatic cancer.

Epidemiologic Studies of Maternal Coffee Consumption and Childhood Acute Leukemia

A number of epidemiologic studies have evaluated the risk of childhood acute leukemia from maternal consumption of coffee during pregnancy. (Ross 1996, Petridou 1997, Clavel 2005, Menegaux 2005, Menegaux 2007, Milne 2011, Bonaventure 2013)

All of these studies except Petridou 1997 report increased risks of childhood acute leukemias in association with maternal consumption of coffee during pregnancy. Ross 1996 (OR 2.5, 95% CI 1.0 - 6.2); Clavel 2005 (OR 4.1 for consumption of ≥3 cups per day, 95% CI 1.6 - 10.1); Menegaux 2005 (OR 1.9 for consumption by nonsmokers of ≥3 cups per day, 95% CI 1.0 - 3.5); Menegaux 2007 (OR 2.1 for consumption of 4-8 cups per day, 95% CI 1.2 - 3.8); Milne 2010 (OR 2.55 for consumption of > 2 cups per day among nonsmoking mothers whose children had acute lymphocytic leukemia with chromosomal translocations, 95% CI 1.04 - 6.22); Bonaventure 2013 (OR 1.6 for consumption of >2 cups per day, 95% CI 1.2 - 2.1).

Petridou 1997 was the smallest study that evaluated childhood leukemia to age 14 of all the studies. It evaluated only 153 cases of childhood leukemia and reported a small decrease in leukemia risk which was not statistically significant (OR 0.89, 95% CI 0.55 - 1.46). It is the outlier among the studies, as all the other studies reported increased risks of childhood leukemia that were statistically significant.

In summary, the epidemiologic data for maternal consumption of coffee during pregnancy show a consistent significant association with an elevated risk of childhood leukemia. Six studies report a significant association, while one does not. The six studies represent five separate populations. The association is strengthened by several studies demonstrating statistically significant dose-response relationships. All four studies that evaluated cigarette smoking demonstrated the highest risk of childhood leukemia among nonsmoking mothers.

Meta-Analyses of Maternal Coffee Consumption and Childhood Acute Leukemia

The two meta-analyses of maternal coffee consumption and childhood leukemia conducted to date both demonstrate elevated risks of childhood leukemia.

The first meta-analysis of maternal coffee consumption and childhood leukemia was published by Milne in 2011. They showed an increased risk of childhood acute leukemia among mothers who consumed more than 3 cups of coffee per day (OR 1.67, 95% CI 1.2 - 2.33). When the studies were analyzed by smoking status for mothers who drank 3 or more cups of coffee per day, risk was not increased among mothers who smoked (OR 1.09, 95% CI 0.54 - 2.22), but was significantly increased among nonsmokers (OR 3.22, 95% CI 1.51 - 3.57).

A recent meta-analysis reported that combined odds ratios for maternal consumption of coffee during pregnancy and childhood acute leukemia were 1.22 (95% CI 1.04 - 1.43) for ever drinkers, 1.16 (95% CI 1.00 - 1.34) for low to moderate drinkers, and 1.72 (95% CI 1.37 - 2.16 for heavy drinkers. Risks were also significantly increase for childhood acute lymphocytic leukemia (1.65, 95% CI 1.28 - 2.12) and childhood acute myelogenous leukemia (1.58, 95% CI 1.20 - 2.08). Dose-response relationships were also statistically significant. (Cheng 2014).

The Cheng meta-analysis is a well-designed and well-conducted meta-analysis. It included data from all the published studies. The study was conducted using modern statistical techniques, including a 2-stage random effects dose-response analysis which took heterogeneity among studies into account. The authors calculated the log OR for various levels of coffee consumption and estimated a restricted cubic spline model with 4 knots at percentiles of levels of coffee consumption using generalized least square regression. The authors also assessed publication bias using the Egger regression asymmetry test. The authors made efforts to avoid double-counting of cases, as they did not double-count the cases of Clavel 2005 and Menegaux 2005, which provide different analyses of the same cases. Although the authors do not state that there was no overlap of cases among Menegaux 2005 and Menegaux 2007, the French investigators confirmed that there was no overlap of cases between these studies. (J. Rudant personal communication of April 28, 2014 with P. Infante in response to Infante inquiry of April 25, 2014 to F. Menegaux).

The epidemiologic studies of maternal coffee consumption and the development childhood acute leukemia, along with the Milne and Cheng meta-analyses, provide strong epidemiologic evidence for the development of childhood acute leukemia as the result of maternal coffee consumption during pregnancy.

Mechanism for Maternal Coffee Consumption and Childhood Acute Leukemia

A mechanism for the development of childhood acute leukemia from maternal consumption of coffee during pregnancy has been described. (Ross 1996, Milne 2011)

The mechanism involves chromosomal breakage by clastogenic constituents of coffee, inhibition of functionality of the Topoisomerase II DNA repair enzyme, consequent alteration of critical genes that regulate blood cell differentiation and proliferation, with resultant development of specific types of forms of acute leukemia. (Ross 1996, Milne 2011, Martyn Smith 2014).

Several constituents of brewed coffee are clastogenic. (Deposition of Martyn Smith 2014)

Brewed coffee and instant coffee both induced chromosomal aberrations in cultured human lymphocytes, and the urine of coffee drinkers induced chromosomal aberrations in cultured mammalian cells." (IARC 1991)

After its discovery in food, acrylamide was found to cross the human placenta. (Sorgel 2002). Concentrations of N-2-carbamoylethylvaline (a hemoglobin adduct of acrylamide) in umbilical cord blood were found to be about half that in mothers' blood; higher levels were detected in the blood of a smoking mother and her child's cord blood. (Schettgen 2004). In placental perfusion studies, acrylamide and glycidamide, its mutagenic metabolite, were found to cross the placenta from maternal to fetal circulation with similar kinetics to antipyrine. (Annola 2008). Concentrations of acrylamide hemoglobin adducts in cord blood have also been shown to increase with gestational age. (Von Stedingk 2011).

The published epidemiologic studies and mechanistic studies provide strong evidence to support a carcinogenic effect of maternal coffee consumption during pregnancy on the developing fetus, with the resultant development of childhood acute leukemia.

Criticisms of Dr. Boffetta's Opinions

Dr. Boffetta did not conduct thorough literature searches to identify all types of human cancer that have been associated with coffee consumption.

Although Dr. Boffetta relies primarily on cancer meta-analyses and although he favors recent meta-analyses, he failed to identify important recent meta-analyses regarding maternal coffee consumption and childhood leukemia. (Milne 2011, Cheng 2014)

The Milne and Cheng meta-analyses refute Dr. Boffetta's opinion that meta-analyses regarding coffee consumption do not report a significantly increased risk of any type of human cancer.

Dr. Boffetta also failed to consider other meta-analyses reporting increased meta-risks for coffee consumption and cancer. Sala 2000 (bladder cancer), Zeegers 2001 (urinary tract cancer), Botelho 2006 (gastric cancer), Steevens 2007 (ovarian cancer), Park 2010 (prostate cancer), Tang 2010 (lung cancer), Genkinger 2012 (pancreatic cancer), Turati 2012 (pancreatic cancer), Zhou 2012 (bladder cancer).

Dr. Boffetta improperly discounted much of the epidemiologic literature regarding coffee consumption and cancer based on his perception that confounding by cigarette smoking was responsible for the reported associations. However, studies of nonsmokers demonstrate significantly elevated risks and dose-response relationships for various cancers in relation to coffee consumption.

As best I can ascertain, Dr. Boffetta's methodology was to consider only meta-analyses of cohort studies of specific cancers. He only considered meta-analyses of case-control studies in the absence of a meta-analysis of cohort studies providing a result for a particular cancer. In so doing, Dr. Boffetta failed to consider several positive meta-analyses of case-control studies. He also failed to consider many studies reporting significantly increased risks of cancer and dose

response relationships. In fact, the only dose-response evaluation that Dr. Boffetta did was for those meta-analyses of cohort studies which did not report increased risks.
He thereby missed the large body of literature reporting significant dose-response relationships for consumption of coffee and various cancers. Thus, Dr. Boffetta's analysis did not reveal the strong dose-response relationships for coffee consumption and bladder cancer, pancreatic cancer, and childhood acute leukemia.

EXHIBIT “B”

OPINIONS OF DR. PETER F. INFANTE

I. COFFEE

A. Epidemiologic Studies Regarding Coffee and Cancer

1. The epidemiologic studies that have investigated risks of cancer from coffee consumption are mostly observational studies (case-control studies and cohort studies).

2. Unlike intervention studies, observational epidemiologic studies are subject to multiple types of bias and confounding.

3. "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).

4. Published, peer-reviewed articles by esteemed scientists have also stated the scientific opinion that observational studies are an insufficient basis for establishing causal effects. Thus, the authors of a meta-analysis of 37 epidemiologic studies regarding coffee consumption and breast cancer risk stated: "Observational studies cannot prove causality." (Jiang 2013). Likewise, the authors of a recent meta-analysis regarding consumption of nuts and risk of cancers and other diseases wrote that "results from observational studies alone cannot be used to draw conclusions with regards to whether the observed associations are causal." (Aune 2016).

5. Dietary epidemiology studies are inherently unreliable for determining causal effects because of multiple biases (especially measurement error) and innumerable confounding dietary factors, as well as other problems. Defendant's epidemiology expert, Dr. Paolo Boffetta, acknowledged this when he testified during the Phase I trial that "diet is remarkably difficult to measure, and separation of the effects of individual components is extremely complicated, given the multiple correlations which exist between the elements." (Boffetta Testimony 9/12/2014 p.m. at 181:4-15).

6. "Measurement error in exposure leads to seriously biased relative risks of cancer for dietary intakes and substantially reduces the statistical power to detect existing relationships.... When the exposure, but none of the confounders, is measured with error, this error attenuates the relative risk, i.e., biases the relative risk toward no effect. Although statistical tests for

the association remain valid, that is, they preserve the nominal statistical significance level, the measurement error reduces the statistical power to detect the association.... Moreover, although adjustment for measurement error can remove existing bias in estimated relative risks, it cannot compensate for the loss of statistical power.... The effects of measurement error increase in complexity when confounders are also measured imprecisely. Although estimated relative risks are still attenuated by error in the main exposure, they are further 'contaminated' by errors in the confounders (i.e., residual confounding). As a consequence, estimated relative risks can be attenuated or inflated by any magnitude. Moreover, unadjusted statistical tests no longer preserve the nominal statistical significance level, so that the observed diet-disease association cannot be reliably interpreted.... In summary, continued caution is required when interpreting associations, or the lack thereof, between dietary factors and disease.... Given the current limitations of available self-report instruments used for measuring diet or as references and the paucity of recovery biomarkers, it will be rare when we will be able to regard the results of individual nutritional epidemiology studies, even after correction for measurement error, as definitive. Only when multiple studies with different designs in diverse populations produce consistent, robust results, can the evidence regarding an association be sufficiently persuasive." (Kipnis 2008). For example, coffee consumption is usually determined at the time of enrollment only, or within the past year, and this does not account for consumption habits prior to the survey, nor for any change in consumption of coffee subsequent to the time of the initial interview. The same can be said for all of the confounders as well. In addition, many studies did not provide information on the characteristics of the coffee, such as cup size, type of coffee powder (Robusta or Arabica) and brewing methods, which are responsible for different concentrations of caffeine and other chemicals in the coffee. These procedures results in measurement error, e.g., exposure misclassification.

7. "Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease." (International Agency for Research on Cancer, Preamble, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (1996)). "Confounding is a special form of bias, due to exposure to risk factors other than those under study." (Boffetta, P., "Molecular Epidemiology," *J. Intern. Med.* 248:447-454 (2000)). "Confounding is one of the most common and important biases in primary care research." (Sonis, J., "A Closer Look at Confounding," *Fam. Med.* 30(8):584-588 (1998)).

8. Confounding is a major problem in epidemiologic studies regarding coffee consumption and risk of cancers and chronic diseases not only because of innumerable confounding effects of other dietary constituents, but also because consumption of coffee has been shown to be highly correlated

with cigarette smoking (Marshall 1980, Emurian 1982, Shirlow 1983, Carmody 1985, Brown 1989, Zavela 1990, Klesges 1994, Lane 1996, Talcott 1998, Brice 2002, Hewlett 2006, de Castrol 2008, Loftfield 2016, Treur 2016, Treur 2016), especially among those who either have been or are currently addicted to alcohol. (Aubin 1995, Aubin 1999, Junghanns 2005, Reich 2008, Reich 2011, Loftfield 2016). The consistent and rather strong correlation between cigarette smoking and coffee consumption has resulted in substantial confounding in epidemiologic studies of coffee consumption and cancer (Heyden 1979, Savitz 1989), as well as chronic disease. (Heyden 1979, Schreiber 1988, Brown 1989, Klatsky 2008). For example, cigarette smoking which is a confounder for a large number of specific types of cancer even when adjusted for in the study is often based on current or former smoking status, but with no quantitative information on the amount smoked. Smoking habits may change subsequent to the interview used to record smoking habit and such changes are usually not accounted for in prospective studies. This limitation to the studies is pointed out by a number of investigators.

B. Overview of Epidemiology Coffee Consumption and Cancer

1. There is a large body of published epidemiological studies regarding coffee and cancer. The studies are observational studies -- mostly case-control studies and cohort studies. Additionally, a rather large number of meta-analyses have been published for several types of human cancer.

2. The quality of the studies is variable, as are the results of the studies. Several studies report increased risks of several human cancers; several studies report decreased risks of human cancers; and numerous studies report neither increased nor decreased risks of human cancers.

3. The epidemiological studies regarding coffee and cancer are perhaps best generally described as being "mixed," i.e., showing both increased and decreased risks of human cancers.

C. International Agency for Research on Cancer (IARC)

1. The International Agency for Research on Cancer (IARC) is generally considered to be the foremost authority in the world for classifying the carcinogenicity of chemicals.

2. IARC's assessments are published in a series of Monographs called "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans." Although these monographs include the word "risks" in their title, they do not quantitatively determine the risk that populations or individuals will develop cancer from agents (chemicals and biological or physical agents) that IARC evaluates. Rather, IARC makes qualitative determinations as to whether an "agent" causes human cancer or is to likely to do so.

3. IARC has devised a system for classifying chemicals as carcinogens. The classification system is generally described as follows: Group 1 - known human carcinogens, Group 2A - probable human carcinogens, Group 2B - possible human carcinogens, Group 3 - Unclassifiable as to human carcinogenicity, and Group 4 - Probably not carcinogenic to humans. Each of these classifications has precise definitions and criteria that are specified in the Preamble to the Monographs.

4. Most of the chemicals that IARC has evaluated to date have received a Group 3 classification, i.e., they have been deemed "unclassifiable" as to human carcinogenicity. "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." (International Agency for Research on Cancer, "Preamble," IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (1996)).

5. IARC recently reevaluated the carcinogenicity of coffee. Although IARC has not yet published its new monograph regarding coffee, IARC has announced the overall result of its recent evaluation. IARC concluded that coffee drinking is "unclassifiable as to its carcinogenicity to humans (Group 3)." (Loomis 2016). IARC explained: "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." (IARC "Q & A on Monographs Volume 116: Coffee, maté, and very hot beverages," 2016, available online at http://www.iarc.fr/en/media-centre/pr/2016/pdfs/pr244_E.pdf). Thus, IARC's classification does not mean that coffee is "safe" or that it does not cause human cancer. Rather, "the existing scientific data do not enable a conclusion to be made about whether it causes cancer."

6. I believe that IARC reached the conclusion that "the existing scientific data do not enable a conclusion to be made about whether [coffee] causes cancer" for at least two reasons. First, although they are numerous, the epidemiological studies regarding coffee consumption and human cancer are mixed, with many studies reporting increased risks of human cancers, many studies reporting decreased risks of human cancers, and many studies reporting neither increased nor decreased risks of human cancers. Second, the epidemiology of coffee consumption and cancer all suffer from multiple types of bias, primarily confounding and exposure misclassification.

7. The authors of the IARC summary concluded that positive associations reported in some studies [of bladder cancer] could have been due to inadequate control for tobacco smoking, which can be strongly associated with heavy coffee drinking." While it is possible that the positive associations, including dose-response relationships, reported in some studies of coffee consumption and bladder cancer "could have been due to

inadequate control for tobacco smoking," this is unlikely the case, because several of the studies, including one meta-analysis (Wu 2015) reported significantly increased risks of bladder cancer among nonsmokers.

8. The authors of the IARC summary also observed that inverse relationships had been observed for two cancers in particular: endometrial cancer and liver cancer: "[F]or endometrial cancer, the five largest cohort studies showed mostly inverse associations with coffee drinking. These results were supported by the findings of several case-control studies and a meta-analysis. Inverse associations with coffee drinking were also observed in cohort and case-control studies of liver cancer in Asia, Europe, and North America. A meta-analysis of prospective cohort studies estimated that the risk of liver cancer decreases 15% for each 1 cup per day increment." Despite the inverse associations that IARC observed for coffee and endometrial and liver cancers, IARC did not conclude that the inverse associations were causal. Rather, as to all cancer sites, "coffee drinking was evaluated as unclassifiable as to its carcinogenicity to humans." There are many reasons why the inverse associations between coffee consumption and endometrial and liver cancers are unlikely causal, which I will explain in my discussion of the studies regarding these cancers.

9. The authors of the summary published in *Lancet Oncology* also observed: "More than 40 cohort and case-control studies and a meta-analysis including nearly 1 million women consistently indicated either no association or a modest inverse association for cancer of the female breast and coffee drinking. Similarly, numerous cohort and case-control studies of cancers of the pancreas and prostate consistently indicated no association between these cancers and coffee drinking." I disagree with the statement that the epidemiology studies for these cancers "consistently show no association between these cancers and coffee drinking," because numerous case-control studies and cohort studies have, in fact, reported statistically significantly increased risks of these cancers in association with consumption of coffee, and some of the studies have even reported dose-response relationships for coffee consumption and these cancers.

10. The authors of the summary also observed: "Data were also available for more than 20 other cancers, including lung, colorectal, stomach, oesophageal, oral cavity, ovarian, and brain cancers, and childhood leukaemia. Although the volume of data for some of these cancers was substantial, the Working Group judged the evidence to be inadequate for all of the other cancers reviewed for reasons including inconsistency of findings across studies, inadequate control for potential confounding, potential for measurement error, selection bias or recall bias, or insufficient numbers of studies." Thus, for these sites, "coffee drinking was evaluated as unclassifiable as to its carcinogenicity to humans."

D. Coffee Consumption and Specific Human Cancers

1. Overview.

a. Epidemiologic studies of coffee consumption have reported increased risks for the following cancers: bladder cancer, childhood acute leukemia, childhood brain cancer, colorectal cancer, gastric cancer, kidney cancer, laryngeal cancer, lung cancer, non-Hodgkin lymphoma, ovarian cancer, pancreatic cancer, and prostate cancer. However, studies of coffee consumption have inverse associations for a endometrial cancer, liver cancer, and skin cancer. For other cancer sites, there is little evidence of an association.

b. Numerous epidemiologic studies report statistically significant increases in human cancers, with statistically significant dose-response trends.

c. Meta-analyses of coffee-cancer epidemiology studies have reported increased risks of the following cancers: bladder cancer, childhood leukemia, gastric cancer, laryngeal cancer, lung cancer, non-Hodgkin lymphoma, ovarian cancer, pancreatic cancer, and prostate cancer.

d. The case-control studies generally tend to report increased risks of cancer more frequently than do the cohort studies. However, some cohort studies report increased risks of cancer that were not reported in case-control studies. As observational studies, both case-control and cohort studies have important limitations.

e. Some of the studies are confounded by smoking. However, significantly increased risks of cancers have been reported in studies that adjusted for smoking and some large studies among non-smokers reported significantly increased risks of cancer, indicating that smoking does not explain all of the increased risks of cancer among coffee drinkers who develop cancers whose risk is increased by smoking. Likewise, decreased risks of cancer among coffee drinkers for cancers whose risk is decreased by smoking should also be assessed for confounding by smoking.

f. Some studies may be confounded by obesity. There is sufficient evidence in humans for the cancer-preventive affect of the absence of excess body fatness. The absence of excess body fatness reduces the risk of cancers of the colon and rectum, pancreas, gall bladder, oesophagus (adenocarcinoma), gastric cardia, liver (hepatocellular carcinoma), kidney (renal cell carcinoma), ovary, endometrium of the uterus, breast in postmenopausal women, and thyroid, and meningioma and multiple myeloma." Thus, an

evaluation of coffee consumption in relation to these cancers needs to consider confounding from obesity. [IARC Handbooks, Vol. 16 – Questions and Answers (2017)]

2. Bladder Cancer

a. Numerous case-control studies report statistically significant increases in bladder cancer in relation to coffee consumption. (Dunham 1968 (in black females), Cole 1971 (in females and female nonsmokers), Fraumeni 1971 (in blacks), Schmauz 1974 (in males, the only sex evaluated), Simon 1975 (in females), Wynder 1977 (in men), Marrett 1983 (in males and nonsmokers), Rebakalos 1985, Bravo 1986, Piper 1986, Claude 1986 (in men), Iscovich 1987, Kantor 1988, Rische 1988 (in females), La Vecchia 1988, Howe 1988 (in men), Clavel 1991, Kunze 1992, D'Avanzo 1992, McGeehin 1993, Vena 1993, Momas 1994, Donato 1997, Geoffroy-Perez 2001, Radosavljevic 2003, De Stefani 2007, Covollo 2008, Porru 2014).

b. A number of these epidemiologic studies demonstrate statistically significant dose-response relationships. (Wynder 1977 (in men), Piper 1986, Kantor 1988, Clavel 1991 (in smokers and nonsmokers), Kunze 1992 (in both sexes), D'Avanzo 1992, Vena 1993, Momas 1994, Donato 1997, Geoffroy-Perez 2001 (in nonsmokers), De Stefani 2007, Porru 2014).

c. At least 12 cohort studies regarding coffee consumption and bladder cancer have been published. (Snowdon 1984; Jacobsen 1986, Nomura 1986, Mills 1991, Chyou 1993, Stensvold 1994, Michaud 1999, Nagano 2000, Zeegers 2001, Tripathi 2002, Kurahashi 2009, Gunter 2017). One cohort study reported a statistically significant trend in relation to coffee consumption in men and increased risk of bladder cancer (Zeegers 2001), while three additional studies show a positive trend that did not achieve statistical significance (Snowdon 1984; Nomura 1986; Kurahashi 2009).

d. Eight meta-analyses have been published regarding coffee consumption and bladder cancer. (Sala 2000, Zeegers 2001, Yu 2011, Zhou 2012, Bai 2014, Huang 2014, Wu 2015, Wang 2016). <u>Five</u> meta-analyses based on case-control studies demonstrate significantly increased risks of bladder cancer. Sala 2000 (pooled analysis of 10 case-control studies of nonsmokers), Zeegers (meta-analysis of 34 case-control studies in men and women), Zhou 2012 (meta-analysis of 23 case-control studies), Bai 2014 (meta-analysis of 17 case-control studies and 4 cohort studies), Wu 2015 (meta-analysis of 34 case-control studies). The Zhou 2012 meta-analysis also demonstrates a monotonic dose response for coffee

consumption and increased risk of bladder cancer among non-smokers. Three meta-analyses based on cohort studies do not report significantly increased risks of bladder cancer. (Yu 2011, Huang 2014, Wu 2015).

e. A recent meta-analysis based on 12 studies, however, reported a rather high increased risk of bladder cancer among coffee consumers who were nonsmokers as compared to smokers (RR 1.72, 95% CI 1.25 - 2.35) (Wu 2015).

f. Significantly increased risks with dose-response relationships had previously been reported for coffee consumers who were nonsmokers, which suggests that the elevated risks of bladder cancer among coffee consumers are not due to confounding by smoking. (Sala 2000, Clavel 1991, Geoffroy-Perez 2001, Zhou 2012, Wu 2015). One possible explanation for this observation is that smokers eliminate caffeine more rapidly than nonsmokers. (Zhou 2012, citing Zevin 1991).

3. Brain Cancer

a. Few epidemiologic studies have been published regarding coffee consumption and adult brain cancer.

b. Two case-control studies have reported risks of brain cancer for coffee consumption.

(1) In a population-based case-control study in Southern Ontario of 215 cases, risk of brain tumors was increased for high coffee consumption (≥38,000 6-ounce cups): OR 1.40, 95% CI 0.76 - 2.58 (Burch 1987).

(2) In a hospital-based case-control study in Boston, Providence and Baltimore of 160 cases of glioblastoma in adults, risk of glioblastoma was nonsignificantly increased among those drinking 1 to 3 cups of coffee per day (OR 1.3, 95% CI 0.6 - 2.5), and nonsignificantly decreased among those drinking 4 or more cups of coffee per day (OR 0.9, 95% CI 0.5 - 1.8). (Hochberg 1990).

c. Five cohort studies have reported risks of brain cancer for coffee consumption.

(1) In a cohort study of 133,811 Kaiser Permanente Medical Care Program subscribers in Northern California, on multivariate analysis, subscribers who drank 7 or more cups of coffee per day had a 70% increased risk of malignant primary adult-onset glioma on multivariate

analysis (RR 1.7, 95% CI 0.8 - 3.6), and a dose-response relationship was observed for increasing coffee consumption (*p*-trend = 0.05). (Efird 2004).

(2) In a study using data pooled from three U.S. cohorts (the Nurses' Health Study I and II and the Health Professionals Follow-Up Study), risk of glioma was nonsignificantly reduced for those with the highest consumption of coffee (RR 0.80, 95% CI 0.54 - 1.17); p-trend = 0.51 for 5 coffee consumption groups. For caffeinated coffee only, the risk of brain cancer in highest consumption group was the same RR 0.80, 95% CI 0.55 - 1.15). For decaffeinated coffee, the risk of brain cancer was nonsignificantly elevated, RR 1.06, 95% CI 0.71 - 1.58). (Holick 2010).

(3) In the European Investigation into Cancer and Nutrition (EPIC) cohort study, those in the highest quintile of coffee consumption had nonsignificantly decreased risks of glioma (RR 0.98, 95% CI 0.67 - 1.41) and meningioma (RR 0.71, 95% CI 0.46 - 1.08). (Michaud 2010).

(4) In the NIH-AARP Diet and Health Study, risk of glioma was nonsignificantly increased in the full multivariate analysis among those consuming 6 or more cups of coffee per day (RR 1.04, 95% CI 0.70 - 1.55). (Dubrow 2012).

(5) In the Japan Public Health Center-Based Prospective (JPHC) Study, a borderline significant reduction in risk, RR 0.48, 95% CI 0.23 - 1.00; N = 8 cases, was observed for the highest coffee consumption group (> 3 cups/day), but the trend for an increase in risk with coffee consumption was not significant, p-trend = 0.13. (Ogawa 2016).

d. One meta-analysis regarding coffee consumption and risk of glioma, based on 2 case-control studies and 4 cohort studies, was published in 2013 by Italian investigators. Comparing coffee drinkers versus non drinkers/occasional drinkers, the risk of glioma was nonsignificantly reduced (RR 0.96, 95 % CI 0.81 - 1.13). Comparing the highest and lowest categories of coffee consumption, the risk of glioma was just above unity (RR 1.01, 95 % CI 0.83 - 1.22). (Malerba 2013).

e. In conclusion, the studies regarding coffee consumption and brain cancer yield mixed results and are too few in number to allow causal assessment. Furthermore, none of the studies controlled for cell phone use which is likely to be the major confounder when assessing brain cancer risk. (Momoli 2017, Bann 2011).

4. Breast Cancer

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

(1) In a case-control study that was 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 2009).

(2) 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 1992).

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

(1) 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 2008).

(2) 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 who drank boiled coffee, the risk was reduced, but not significantly. (Nilsson 2010).

(3) 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 2010).

(4) In a study of 96 women treated for breast cancer, consumption of coffee was also 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 of coffee per day, and 42.9% among women who drank 3 or more cups of coffee per day. The effect of coffee consumption on survival was highly significant (p = 0.006, log rank test). (Lehrer 2013).

(5) 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). (Zhu 2013). The authors concluded that a higher BMI may influence the adverse effect of coffee on advanced breast cancer development.

(6) In a prospective study of 14,593 Norwegian women, for those consuming $\geq$ 5 cups/day, the authors found a positive association between coffee consumption and breast cancer among obese women (BMI > 24) IRR 2.1, 95% CI 0.8 - 5.2) and a negative association between coffee consumption and breast cancer among lean women (BMI < 24) 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 1990).

(7) In the EPIC cohort, no association between coffee consumption and breast cancer was observed. (Gunter 2017).

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

(1) 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. (Tang 2009). However, the risk of breast cancer from coffee consumption in the study is virtually 1.0.

(2) 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 2011).

(3) 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 2013).

(4) 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 2013).

(5) 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 2016).

d. In its recent evaluation of the carcinogenicity of coffee, a Working Group of the International Agency for Research on Cancer (IARC) commented: "More than 40 cohort and case-control studies and a meta-analysis including nearly 1 million women consistently indicated either no association or a modest inverse association for cancer of the breast and coffee drinking." (Loomis 2016).

e. 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.

(1) "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 1993).

(2) "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 2002).

(3) 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 1985).

(4) 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 2013).

(5) 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.

f. Exposure Misclassification.

(1) Several epidemiologic studies regarding coffee consumption and breast cancer have acknowledged problems with exposure misclassification. Oh 2015 ("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 2015 ("[C]offee . . . intakes were measured only at baseline."); Harris 2012 ("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 2010 ("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 2008 ("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 2008 ("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.")

(2) Some studies have acknowledged that exposure misclassification is inevitable from use of food frequency questionnaires and from self-reporting of consumption. Larsson 2009 ("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 2013 ("The coffee variable and other potential risk factors were self-reported and may thus constitute an error in measurement."); Oh 2015 ("Misclassification of coffee . . . consumption due to measurement error associated with the FFQ certainly occurred in our study.").

g. Confounding Other Than Smoking.

(1) Effect of Multiple Confounders. 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 2010).

(2) Known and Unknown Confounders. 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 1990). The authors stated that they had no information on variables like age at menarche and age at first full term pregnancy.

(3) Menopausal Status. 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 2012). Some studies regarding coffee consumption and breast cancer have acknowledged confounding by menopausal status. Bhoo Pathy 2015 ("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 2015 ("Misclassification of menopausal status due to imputation for women without information on age at menopause may also have occurred in our study.").

(4) Energy intake. At least one study has commented on potential confounding by energy intake. Nkondjock 2006 ("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.* 18:2842-2850.

(5) Brewing Methods. Brewing methods affect the chemical composition of coffee beverages and are therefore another potential source of confounding (Nilsson 2010). Brewing method has been recognized as a source of confounding in a few studies of coffee consumption and breast cancer. Bhoo Pathy 2015 ("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 2012 "[W]e did not collect information on the coffee brewing method")

(6) Other Factors Shown to Reduce the Risk of Breast Cancer. Epidemiology studies regarding coffee consumption and breast cancer have neither controlled nor adjusted for several factors that have been shown to <u>reduce</u> the risk of breast cancer in epidemiologic studies or meta-analyses: dietary factors: calcium (Hidayat 2016, Wulaningsih 2016), carotenoids (Nagel 2010, Eliassen 2012), dietary fiber

(Aune 2012), fatty acids (Saadatian-Elahi 2004, Kim 2009; Zheng 2013), fish (Kim 2009; Zheng 2013, Haraldsdottir 2016), flavan-3-ols (Lei 2016), folate (Li 2015), fruit (Howe 1990, Jung 2013, Song 2013), Mediterranean diet (Schwingshackl 2015), soy (Key 1999, Trock 2006, Dong 2011), vegetables (Howe 1990, Jung 2013); vitamins: Vitamin B (Wu 2013), Vitamin C (Howe 1990, Nagel 2010), Vitamin D (Yin 2010, Bauer 2013, Wang 2013, Jamshidinaeini 2016, Sofi 2016); physical activity (Mathew 2009, Wu 2013); breastfeeding (Gajalakshmi 2009, Islami 2015). 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."

5. Childhood Acute Leukemia

a. At least eight epidemiologic studies have evaluated the risk of childhood acute leukemia from maternal consumption of coffee during pregnancy. (Ross 1996, Petridou 1997, Clavel 2005, Menegaux 2005, Menegaux 2007, Milne 2011, Bonaventure 2013, Orsi 2015)

b. All of these studies except Petridou 1997 report increased risks of childhood acute leukemias in association with maternal consumption of coffee during pregnancy. Ross 1996 (OR 2.5, 95% CI 1.0 - 6.2); Clavel 2005 (OR 4.1 for consumption of ≥3 cups per day, 95% CI 1.6 - 10.1); Menegaux 2005 (OR 1.9 for consumption by nonsmokers of ≥3 cups per day, 95% CI 1.0 - 3.5); Menegaux 2007 (OR 2.1 for consumption of 4-8 cups per day, 95% CI 1.2 - 3.8); Milne 2011 (OR 2.55 for consumption of > 2 cups per day among nonsmoking mothers whose children had acute lymphocytic leukemia with chromosomal translocations, 95% CI 1.04 - 6.22).

c. Bonaventure 2013 (OR 1.6 for consumption of >2 cups per day, 95% CI 1.2 - 2.1); OR 1.3 for childhood acute lymphocytic leukemia for >2 cups per day, 95% CI 1.0 - 1.8). Several aspects of the study design, participation rate and results would tend to minimize several aspects of potential bias: 1) participation rate was high (91% cases and 71% controls); 2) controls were comparable to the French population in terms of region, birth order and maternal education (would tend to minimize <u>selection bias</u>); 3) the study used identical questionnaire and interview conditions which would tend to reduce differential <u>recall bias</u>; 4) there was no modifying effect when data were adjusted for birth order, breast feeding, maternal education, socio-professional category of household; 5) additional adjustments for factors that have found "some" association in previous studies that did not affect the

association with coffee consumption observed in the study included, a) type of housing, b) rural/urban living, c) density of heavy traffic roads close to residence, d) pesticide exposure, e) repeated early common infections, f) family history of cancer, g) CYP2E1 x EPHX1 x NQO1 gene-gene interactions. Items "4" and "5" would tend to rule out potential confounding from these specific variables.

d. A further question can be raised related to Bonaventure 2013 about whether the mothers of children with CAL over-report coffee consumption out of "guilt" because it may be considered a "risky behavior" and that such over-reporting resulted in a spurious association between coffee consumption and CAL (differential recall bias). Although this could be hypothesized, study results for other foods or behavior known to have some risk to the developing fetus that were evaluated in the study make such a hypothesis seem less likely. For example, no association was observed between alcohol consumption, nor with cigarette smoking and CAL, both of which are recognized to have adverse consequences to the developing fetus and much more so than coffee consumption. Further, there is unlikely any general awareness that coffee consumption may be related to CAL. While selection bias and differential recall bias cannot be entirely ruled out in case-control studies, the specific findings in the Bonaventure et al. (2013) study as indicated above in my opinion make it unlikely that such bias occurred. In addition, the observation of a dose-response for both ALL and AML separately adds strength to the association.

e. Orsi 2015 identified cases of childhood leukemia diagnosed in France between 2010-2011. Thus, there is no overlap with data from previous case-control studies conducted in France. Mothers who drank > 2 cups/day demonstrated a significantly elevated risk of ALL, OR 1.3, 95% CI 1.0 - 1.8, based on 111 cases. The risk for childhood AML was not elevated (OR 0.60, 95% CI 0.3 - 1.2).

f. Petridou 1997 was the smallest study that evaluated childhood leukemia to age 14 of all the studies. It evaluated only 153 cases of childhood leukemia and reported a small decrease in leukemia risk which was not statistically significant (OR 0.89, 95% CI 0.55 - 1.46). It is the outlier among the studies, as all the other studies reported increased risks of childhood leukemia that were statistically significant. Several of the studies demonstrate statistically significant dose-response relationships. All four studies that evaluated cigarette smoking demonstrated the highest risk of childhood leukemia among nonsmoking mothers, so the studies do not appear to be confounded by cigarette smoking.

g. Four meta-analyses of these studies have been published. (Milne

2011, Cheng 2014, Thomopoulos 2015, and Yan 2015, Yan 2016).

(1) The first meta-analysis of maternal coffee consumption and childhood leukemia was published by Milne in 2011. They showed an increased risk of childhood acute leukemia among mothers who consumed more than 3 cups of coffee per day (OR 1.67, 95% CI 1.2 - 2.33). When the studies were analyzed by smoking status for mothers who drank 3 or more cups of coffee per day, risk was not increased among mothers who smoked (OR 1.09, 95% CI 0.54 - 2.22), but was significantly increased among nonsmoking mothers (OR 3.22, 95% CI 1.51 - 3.57). (Milne 2011).

(2) Cheng (2014) reported that combined odds ratios for maternal consumption of coffee during pregnancy and childhood acute leukemia were 1.22 (95% CI 1.04 - 1.43) for ever drinkers, 1.16 (95% CI 1.00 - 1.34) for low to moderate drinkers, and 1.72 (95% CI 1.37 - 2.16 for heavy drinkers. Risks were also significantly increase for childhood acute lymphocytic leukemia (1.65, 95% CI 1.28 - 2.12) and childhood acute myelogenous leukemia (1.58, 95% CI 1.20 - 2.08). Dose-response relationships were also statistically significant. The Cheng meta-analysis is a well-designed and well-conducted meta-analysis. It included data from all the published studies. The study was conducted using modern statistical techniques, including a 2-stage random effects dose-response analysis which took heterogeneity among studies into account. The authors calculated the log OR for various levels of coffee consumption and estimated a restricted cubic spline model with 4 knots at percentiles of levels of coffee consumption using generalized least square regression. The authors also assessed publication bias using the Egger regression asymmetry test. The authors made efforts to avoid double-counting of cases, as they did not double-count the cases of Clavel 2005 and Menegaux 2005, which provide different analyses of the same cases. Although the authors do not state that there was no overlap of cases among Menegaux 2005 and Menegaux 2007, the French investigators confirmed that there was no overlap of cases between these studies. (J. Rudant personal communication of April 28, 2014 with P. Infante in response to Infante inquiry of April 25, 2014 to F. Menegaux).

(3) Thomopoulous reported a significantly increased risk when comparing highest versus never-lowest consumption (OR 1.57, 95% CI 1.16 - 2.11). The increased risk was higher for acute myelogenous leukemia (OR 1.81, 95% CI 0.93 -

3.53) than for acute lymphocytic leukemia (OR 1.43, 95% CI 1.22 - 1.68). (Thomopoulos 2015).

(4) Yan (2015) reported a borderline significant excess of childhood acute lymphatic leukemia (ALL) in relation to maternal coffee consumption during pregnancy (ever vs never), meta-OR 1.15 95% CI 0.99 - 1.32). Because of what the authors indicated were erroneous applications of multiple publications, corrected results were published in 2016. These results report a significantly increased risk of childhood ALL from maternal consumption during pregnancy ALL OR 1.44, 95% CI 1.07-1.92). (Yan 2016).

h. The epidemiologic studies of maternal coffee consumption and the development childhood leukemia provide strong epidemiologic evidence for the development of childhood acute leukemia from maternal coffee consumption during pregnancy.

i. A mechanism for the development of childhood acute leukemia from maternal consumption of coffee during pregnancy has been described. (Ross 1996, Milne 2011) The mechanism involves chromosomal breakage by clastogenic constituents of coffee, inhibition of functionality of the Topoisomerase II DNA repair enzyme, consequent alteration of critical genes that regulate blood cell differentiation and proliferation, with resultant development of specific types of forms of acute leukemia. (Ross 1996, Milne 2011, Smith 2014). Several constituents of brewed coffee are clastogenic (Testimony of Martyn Smith). Brewed coffee and instant coffee both induced chromosomal aberrations in cultured human lymphocytes, and the urine of coffee drinkers induced chromosomal aberrations in cultured mammalian cells" (IARC 1991). After its discovery in food, acrylamide was found to cross the human placenta. (Sorgel 2002). Concentrations of N-2-carbamoylethylvaline (a hemoglobin adduct of acrylamide) in umbilical cord blood were found to be about half that in mothers' blood; higher levels were detected in the blood of a smoking mother and her child's cord blood. (Schettgen 2004). In placental perfusion studies, acrylamide and glycidamide, its mutagenic metabolite, were found to cross the placenta from maternal to fetal circulation with similar kinetics to antipyrine. (Annola 2008). Concentrations of acrylamide hemoglobin adducts in cord blood have also been shown to increase with gestational age. (Von Stedingk 2011).

j. The published epidemiologic studies and mechanistic studies provide strong evidence to support a carcinogenic effect of maternal coffee consumption during pregnancy on the developing fetus, with the resultant development of childhood acute leukemia.

6. Childhood Brain Cancer

a. Four studies have evaluated childhood central nervous system tumors in relation to maternal consumption of coffee during pregnancy. (Cordier 1994, Plichart 2008, Greenop 2014; Bailey 2017).

b. Cordier reported a 90% increase in the risk of any childhood brain tumor. (OR 1.9, 95% CI 0.9 - 3.9). (Cordier 1994).

c. Plichart reported increased risks from maternal consumption of more than 3 cups of coffee per day for central nervous system tumors (OR 1.4, 95% CI 0.8 - 2.4) and ependymomas (OR 2.7, 95% CI 0.9 - 8.1). They also reported significant increased risks for consumption of more than 3 cups of coffee and more than one cup of tea per day for all central nervous system tumors combined (OR 4.4, 95% CI 1.5 - 13) and ependymomas (OR 23.1, 95% CI 4.4 - 120). (Plichart 2008)

d. Greenop reported increased risks of childhood brain tumors from maternal consumption of coffee during the last 6 months of pregnancy. For any coffee consumption, the childhood brain tumor OR 1.76, 95% CI 1.09 - 2.84 for diagnosis made between 0-4 years of age. For consumption of $\geq$ 2 cups/day, OR 2.52, 95% CI 1.26 - 5.04) for children diagnosed between 0-4 years of age. (Greenop 2014).

e. Bailey pooled data from two French population-based case-control studies. Overall, any coffee consumption (>1 cup/week) did not show a statistically significant increase in childhood brain tumors (CBT) (OR 1.15, 95% CI 0.94 - 1.40). However, any maternal consumption during the first trimester showed a significantly elevated risk of CBT (OR 1.29, 95% CI 1.00 - 1.67), data only available for the ESTELLE study population). (Bailey 2017).

7. Colorectal Cancer

a. **Case-Control Studies.** Some case-control studies report increased risks of colorectal cancer in association with coffee consumption.

(1) 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 1989).

(2) 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 (Olsen 1993). 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.

(3) 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 1999).

(4) 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 2002).

(5) 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 2003).

(6) 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 2012).

(7) 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 2014).

(8) A recent meta-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 HS, et al., (2017) "Coffee consumption and the risk of colorectal cancer by anatomical subsite in Japan: Results from the HERPACC studies," *Int. J Cancer* (in press).

b. **Cohort Studies.** Some of the cohort studies regarding coffee consumption and colorectal cancer report increased risks.

(1) 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 1985).

(2) 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 1987).

(3) 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 2006).

(4) In a Japanese 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 2007).

(5) 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 2010).

(6) 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 2010).

(7) 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 investigators found that the risk of colorectal cancer was nonsignificantly increased for coffee consumption of 2-3 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). The authors concluded that "the findings of this study do not provide evidence to suggest that drinking coffee . . . is beneficial in protecting against colorectal cancer." (Dominianni 2013).

(8) In the European Investigation into Cancer and Nutrition (EPIC) cohort study, involving 477,071 participants, 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, risk of colorectal cancer was nonsignificantly increased (HR 1.06, 95% CI 0.95 - 1.18). (Dik 2014).

(9) The most recent evaluation of data rom the EPIC cohort based on 521,330 participants indicates 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 2017).

(10) 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 2014).

c. At least 8 meta-analyses have been published regarding coffee consumption and the risk of colorectal cancer.

(1) 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 1998).

(2) 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 2009).

(3) 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 2010).

(4) 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 2011).

(5) 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 2012).

(6) 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 2013).

(7) In a meta-analysis of prospective cohort studies by Chinese researchers, the risk of colorectal cancer from consumption of coffee was slightly and nonsignificantly decreased (OR 0.98, 95% CI 0.90 - 1.06). (Gan 2016).

(8) 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 2016).

d. The inverse relationship between coffee consumption and colorectal cancer 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 protective factors.

(1) Dietary factors. Mediterranean diet (Schwingshackl 2015), Cruciferous vegetables (Johnson 2013, Wu 2013), dietary fibre (Aune 2011, Ben 2014) including cereal fiber and whole grain (Aune 2011), total dairy products and milk (Aune 2012), fish (Wu 2012), garlic (Hu 2014, Chiavarini 2015), flavonoids (Lee 2013), nuts (Wu 2015), omega-3 polyunsaturated fatty acids (Li 2015), soy and isoflavones (Tse 2016, Yu 2016)

(2) Physical activity (Je 2013, Johnson 2013, Robsahm 2013, Liu 2016)

(3) Vitamins. Multivitamins (Heine-Bröring 2015), Vitamin B2 (Liu 2015), Vitamin D (May 2011, Touvier 2011) , 25-

Hydroxyvitamin D Status (Touvier 2011), Vitamin D Receptor Polymorphisms (Touvier 2011, Serrano 2015), calcium (Heine-Bröring 2015), folate (Chuang 2013) , magnesium (Wark 2012, Ko 2014), zinc (Qiao 2013, Li 2014).

(4) Pharmaceuticals: Aspirin (Algra 2012), Bisphosphonates (Oh, Bonovas 2013), Statins (Lytras 2014).

(5) Reproductive factors: Menopausal hormone therapy (Green 2012), Oral contraceptive use (Luan 2015).

e. Some studies have reported inverse associations between coffee consumption and colorectal cancer. However, in its summary, the IARC Working Group judged the evidence to be inadequate for colorectal cancer 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 2016).

f. Colon Cancer

(1) Case-Control Studies

(a) 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." Numerical data not shown in report. (Graham 1978).

(b) 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 1987).

(c) 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 1990).

(d) 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 1996).

(e) In a case-control study of 352 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 2003).

(f) A recent meta-analysis using data from two case-control studies in Japan (HERPACC-1 AND -2), compared to 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, 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 2017).

(2) Cohort Studies

(a) 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 1984).

(b) 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 1985).

(c) 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 1994).

(d) 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 2001).

(e) In a pooled analysis of primary data from 13 cohort studies, researchers from Harvard, 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 2010).

(f) 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 he tr4end was not statisitcally 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 2014).

(g) 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 2016).

g. Rectal Cancer

(1) Case-Control Studies

(a) 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 1989).

(b) 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 2003).

(c) 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. The results suggested an inverse relationship, but the trend was not statistically significant, $p = 0.07$. The authors concluded that

inherent limitations of the study warranted verification using prospective cohort studies (Nakagawa 2017).

(2) Cohort Studies

(a) 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 2001).

(b) 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 2005).

(c) 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 highest consumption of coffee (> 6 cups/day, HR 1.41, 95% CI 0.75 - 2.63) although the trend was not statistically significant (Simons 2010).

(d) 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 2014).

8. Endometrial Cancer

a. Endometrial cancer is one of the cancers that has been reported to be inversely associated with coffee consumption (Loomis 2016). It is therefore important to evaluate whether the inverse association

between coffee consumption and endometrial cancer is causal or whether it is more likely due to confounding or bias.

b. Preliminarily, the results of epidemiologic studies of coffee consumption and endometrial cancer are not entirely consistent.

(1) In a study of coffee consumption and cause-specific mortality in three cohorts (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 2015).

(2) Some studies reported risks of endometrial cancer in association with consumption of coffee that generally showed no association (McCann 2009, Levi 1993; Stensvold 1994; Jacobsen 1986). McCann 2009 report 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. The study, however, did not control for cigarette smoking–a known risk factor for endometrial cancer. Thus, confounding cannot be evaluated in the study. Levi 1993, reported an increase in the OR for endometrial cancer in relation to moderate and high coffee consumption, OR = 1.18 and 1.22, respectively, but the trend was not statistically significant. Stensvold 1994 reported a slight increase in the risk of uterine cancer in relation to coffee consumption, ORs for 3-4, 5-6 and >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 (Levi 1993) and factors related to endogenous estrogen exposure (McCann 2009). Another study showed no association between coffee consumption and endometrial cancer (Jacobsen 1986).

(3) Some studies did not identify significantly decreased risks of endometrial cancer for coffee consumption though risk was somewhat reduced (Bandera 2010, Giri 2011, Gunter 2017). The Bandera 2010 study showed a slight reduction in endometrial cancer risk at the highest level of coffee consumption (> 2 cups/day), p-trend = 0.11. In the Giri 2011 study, eight results are available and a significant

decrease for ≥2 cups/day of caffeinated coffee among the obese only was observed, OR = 0.66 (95% CI = 0.45-0.97). In the Gunter 2017 study the inverse trend was not statistically significant, p-trend = 0.28. In the highest quartile of consumption, RR 0.69, 95% CI 0.40 - 1.16).

(4) On the other hand, some studies did demonstrate a significantly reduced risk of endometrial cancer in relation to coffee consumption (Koizume 2008; Bravi 2009; Je 2011; Friberg 2009; Gunter 2009). For example, Koizume 2008, 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. A meta-analysis by Bravi 2009 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. A prospective study by Je 2011 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). Friberg 2009 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. 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 2011 recently 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. The Wong 2016 meta-analysis reports 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.

c. Epidemiologic studies of coffee consumption and risk of endometrial cancer are subject to multiple confounding factors.

(1) Cigarette Smoking

(a) "[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 2010).

(b) 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 2008).

(c) "The inverse relationship between cigarette smoking and endometrial carcinoma risk is well established." (Felix 2014).

(d) "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 2002).

(e) 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 2015). 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) Oral Contraceptives.

(a) 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 1997).

(b) 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 Endometrial Cancer, 2015).

(3) Intrauterine Devices (IUDs).

(a) An early meta-analysis of endometrial cancer and use of intrauterine devices, based on 10 studies, reported a significant reduction in risk of endometrial cancer with intrauterine device use (OR 0.54, 95% CI 0.47 - 0.63). (Beining 2008)

(b) 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 2014).

(4) Obesity and Diabetes. In a recent study, 2015, obesity was associated with a significant 3-fold increase and diabetes was associated with 30-40% increase in risk of endometrial cancer. (Cote 2015)

(5) Bisphosphonates. A recent 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 2016).

(6) Aspirin.

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

(b) 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 2013).

(c) 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 2016).

(d) 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 2016).

(7) Breastfeeding. Three meta-analyses of breastfeeding and the risk of endometrial cancer were published in 2015. They all reported significantly reduced risks ranging from 23% to 26% of endometrial cancer in association with

breastfeeding. (Wang 2015, Ma 2015, Zhan 2015).

(8) Reproductive Factors.

(a) 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 2015)

(b) 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 Consttortium 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 2012).

(c) Parity has been shown to be inversely related with the risk of endometrial cancer in 2 meta-analyses.

i) 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 2015).

ii) 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 2015).

(9) Physical activity has been shown to be inversely related with the risk of endometrial cancer in 2 meta-analyses.

(a) 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), occupational activity (RR 0.81, 95% CI 0.75 - 0.87), household activity (RR 0.79, 95% CI 0.47 - 1.02) and walking (RR 0.82, 95% CI 0.69 - 0.97). (Schmid 2015).

(b) 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 2013).

(10) Dietary Factors.

(a) 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 2016).

(b) 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 2015).

(c) 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 2007).

(d) 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 2007).

(e) 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 2015).

(f) 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 2015).

(g) 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 2009). 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 2008).

d. 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.

(1) "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 2009).

(2) "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 2012).

(3) Thus, the inverse relation between coffee consumption and endometrial cancer as reported in the epidemiological literature, may be the result of the lack of control for numerous factors related to endometrial cancer.

9. Esophageal Cancer

a. Three case-control studies have reported increased risks of esophageal cancer for consumption of coffee: Brown 1995 (OR 1.50, 95% CI 0.62 - 3.62) for adenocarcinoma; Garidou 1996 (OR 1.15, 95% CI 0.84 - 1.58 for squamous cell carcinoma, OR 1.11, 95% CI 0.86 - 1.43) for adenocarcinoma; Castellsagué 2000 (OR 1.86, 95% CI 0.72 - 3.93) for women, (OR 1.19, 95% CI 0.80 - 1.78) for men.

b. One cohort study reported an elevated risk of squamous cell carcinoma (RR 1.53, 95% CI 0.83 - 2.82) and a decreased risk of adenocarcinoma (RR 0.81, 95% CI 0.57 - 1.16) in relation to consumption of coffee. (Ren 2010).

c. Three meta-analyses of coffee consumption have been published.

(1) One meta-analysis reported an increased risk of adenocarcinoma (RR 1.18, 95% CI 0.81 - 1.71) based on 6 case-control studies and one 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 2011).

(2) A second meta-analysis based on cohort studies reported an inverse association for esophageal cancer (RR 0.55, 95% CI 0.37 - 0.74), but this study does not indicate which studies were included in the analysis, so it is therefore impossible to assess the selection criteria or the individual study results upon which risk was based. (Yu 2011).

(3) A third meta-analysis based on 10 case-control studies and 4 cohort studies showed a borderline significant deficit for esophageal cancer (OR 0.88, 95% CI 0.76 - 1.01). However, there was no inverse association, for every 2 cup/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 2013).

d. Subsequent to these meta-analysis studies have been published.

(1) A cohort study indicates no association between adenocarcinoma in men, but an increases risk in women who consumed more than 477 ml/day (HR 2.26, 95% CI 0.54 - 9.45). Squamous cell carcinoma showed a

significant inverse relation in men who drank more than 477 ml/day (HR 0.42, 95% CI 0.20 - 0.88), but no association was observed in women. (Zamora-Ros 2014).

(2) A study in Japan indicated a non-significant decreased risk of esophageal cancer for consumption of 3 or more cups of coffee per day (OR 0.82, 95% CI 0.53 - 1.27). (Oze 2014).

(3) A study conducted in the U.S. demonstrated a significantly elevated risk of adenocarcinoma of the esophagus in relation to daily intake of iosflavones, for which coffee was the main source (OR 1.65, 95% CI 1.02 - 2.65), for those with an intake of more than 60 mg/day. Adenocarcinoma of the gastric cardia, which abuts the esophagus, also was elevated (OR 1.56 95% CI 0.93 - 2.60). (Petrick 2015).

(4) Other epidemiological findings 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 2017).

10. Gastric Cancer

a. At least 16 hospital-based case-control studies regarding coffee consumption and risk of gastric cancer have been published (Higginson 1966, Haenszel 1972, Correa 1985, Trichopoulos 1985, Jarebinski 1989, LaVecchia 1989, Lee 1990, Agudo 1990, Memik 1992, Inoue 1994, Inoue 1998, Komoto 1998, Rao 2002, De Stefani 2004, Gallus 2009, Incli 2011). Of these, about half of the studies reported nonsignificantly elevated risks. (Higginson 1966, Haenszel 1972, Correa 1985 (increased risk in Whites but not in Blacks), Trichopoulos 1985, Jarebinski 1989, Lee 1990, Inoue 1994, Komoto 1998 (increased risk of diffuse cancer but not intestinal type gastric cancer), Rao 2002, Gallus 2009.

b. At least 8 population-based case-control studies regarding coffee consumption and gastric cancer have been published. (Hoshiyama 1992, Hansson 1993, Ji 1996, Chow 1999, Terry 2000, Munoz 2001, Gallus 2009, Petrick 2015). About half of these reported nonsignificantly elevated risks. (Hansson 1993, Chow 1999, Terry 2000 (increased risk for gastric cardia but not esophageal adenocarcinoma), Gallus 2009, Petrick 2015).

c. The most important of the population-based case-control studies is the recent study by Petrick which estimated daily intake of isoflavones, for which coffee was the main dietary source, and calculated risks for gastric cardia, other gastric adenocarcinomas and esophageal adenocarcinomas. Risk of gastric cardia cancer was increased for consumption of 0.42 - 0.59 mg isoflavones per day (OR 1.62, 95% CI 1.00 - 2.63) and 60 or more mg isoflavones per day (OR 1.56, 95% CI 0.93 - 2.60). Risk of other gastric adenocarcinomas was increased for consumption of 0.42 - 0.59 mg isoflavones per day (OR 1.68, 95% CI 1.10 - 2.56) and 60 or more mg isoflavones per day (OR 1.50, 95% CI 0.96 - 2.37). Risk of esophageal adenocarcinomas was increased for consumption of 0.42 - 0.59 mg isoflavones per day (OR 1.51, 95% CI 0.97 - 2.37) and 60 or more mg isoflavones per day (OR 1.65, 95% CI 1.02 - 2.65). (Petrick 2015).

d. At least 16 cohort studies have been published regarding coffee consumption and risk of gastric cancer. (Jacobsen 1986, Nomura 1986, Stensvold 1994, van Loon 1998, Galanis 1998, Tsubono 2001, Nagata 2002, Khan 2004, Tlkui 2005, Larsson 2006, Nilsson 2010, Ren 2010, Bidel 2012, Ainslee-Waldman 2014, Sanikini 2015, Gunter 2017). In about half of these studies risk of gastric cancer was increased. Jacobsen 1986, Nomura 1986, van Loon 1998, Galanis 1998, Nagata 2002, Larsson 2006, Ren 2010, Sanikini 2015. Four of the studies observed significantly increased risks of gastric cancer: Galanis 1998 (OR estimated with data for sexes combined by Xie 2014: 1.80, 95% CI 1.00 - 3.30 for consumption of 2 or more cups of coffee per day versus none), Larsson 2006 (OR 1.86, 95% CI 1.07 - 3.25 for consumption among women of 4 or more cups of coffee per day compared to less than or equal to 1 cup of coffee per day), Ren 2010 (OR 1.57, 95 % CI 1.03 - 2.39 for risk of gastric cardia cancer for consumption of more than 3 cups of coffee per day versus less than 1 cup of coffee per day), Sanikini (2015) for gastric cardia for quartile 1 versus 3 of coffee consumption (or 1.98, 95% CI 1.16 - 3.36). A recent study that indicated no association between stomach cancer and coffee consumption did not evaluate data for gastric cardia separately (Gunter 2017).

e. Ten meta-analyses have been published regarding coffee consumption and the risk of gastric cancer. (Botelho 2006, Fant 2014, Xie 2014, Li 2015, Liu 2015, Shen 2015, Zeng 2015, Deng 2016, Xie 2016, Wang 2016). All of these meta-analyses except one report increased risks of gastric cancer, including statistically significant increases in risk. Unlike most of the coffee-cancer epidemiology literature, meta-analyses of cohort studies report greater gastric cancer risks than those of the case-control studies.

(1) The earliest meta-analysis was based on 16 case-control studies and 7 cohort studies, and calculated risks comparing highest and lowest exposure groups. Risks were close to unity except that a significantly increased risk was noted for those studies conducted in the United States (RR 1.26, 9% CI 1.02 - 1.57). (Botelho 2006).

(2) A 2014 meta-analysis, based on 8 cohort studies, found a non-significant slight increase in risk comparing consumption versus non-consumption (RR 1.02, 95% CI 0.79 - 1.31). (Fang 2014).

(3) Another meta-analysis published the same year, based on 12 cohort studies assessed risk comparing the highest and lowest exposure groups. They reported a nonsignificantly increased risk of gastric cancer based on all the cohort studies (RR 1.12, 95% CI 0.93 - 1.36) and significantly increased risks based on 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 2014)

(4) A meta-analysis published the following year, based on 13 cohort studies (Li 2015) reported increased risks similar to those of Xie 2014, e.g., for "all cohort studies" (RR = 1.13) and for American cohorts only (RR = 1.36)

(5) A meta-analysis of 9 cohort studies published in 2015 reported a significantly increased risk of gastric cardia cancer (RR 1.23, 95% CI 1.04 - 1.45). (Liu 2015).

(6) Another meta-analysis published in 2015, 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 2015)

(7) Another meta-analysis published in 2015 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 2015).

(8) A meta-analysis published in 2016, 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 2016).

(9) Another meta-analysis published in 2016, 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 case-control studies (OR 0.85, 95% CI 0.77 - 0.95). (Xie 2016).

(10) Thus, a majority of meta-analyses demonstrate a significantly elevated risk for gastric cardia cancer in relation to coffee consumption. Further, there seems to be a secular rise in cancer of the gastric cardia since 1976 , more rapidly than for any other type of cancer in the USA and Sweden (where analyses have been done). Devesa and Fraumeni, "The rising incidence of gastric cardia cancer," *J. Natl. Cancer Inst.* 91:747-749 (2009).

11. Kidney Cancer (Renal Cell Carcinoma)

a. Some case-control studies have reported significantly increased risks of kidney cancer related to coffee consumption. Wynder 1974, Armstrong 1976, McLaughlin 1984, Goodman 1986 (decaffeinated coffee only),Yu 1986 (doubling of risk in women but not men), Asal 1988, Ross 1989, Wolk 1996 (doubling of risk in women but not men), Hu 2009. Other case-control studies have reported increased risks of kidney cancer for coffee consumption that did not achieve statistical significance. (Maclure 1990, Talamini 1990, Benhamou 1993, Montella 2009).

b. Most cohort studies investigating the risk of kidney cancer from consumption of coffee, have not reported increased risks. However, in a cohort study of 779,369 women in the UK of whom 588 developed kidney cancer after an average of 5.2 years of followup, on multivariate analysis, the risk of kidney cancer was nonsignificantly increased in women who drank 8 to 9 cups of coffee per day (RR 1.13, 95% CI 0.29 - 1.38) and 12 or more cups of coffee per day (RR 1.05, 95% CI 0.78 - 1.42) but not those who drank 10 to 11 cups per day (RR 0.78, 95% CI 0.60 - 1.02). (Allen 2011). The recent EPIC study of 521,330 participants indicated a monotonic increase in risk of kidney cancer in both men and women. With data for the sexes combined, as compared to nonconsumers and low coffee consumption, the RRs for coffee consumption quartiles 2-4 were:0.89, 1.18, and 1.23, respectively, p-trend = 0.15. (Gunter 2017).

c. Dose-response relationships were observed in some of the studies.

(1) In an early case-control study of cancer of the renal pelvis and ureter a 15-fold increased risk of cancer was found among men who drank more than 7 cups of coffee per day compared to those who drank 1 cup of coffee per day (RR 14.9, 95% CI 2.4 - 94.3). A dose-response relationship is apparent from the data as those who consumed 4-7 cups demonstrated a 2.5-fold risk. (Schmauz 1974).

(2) In an American case-control study, the risk of death from renal cell cancer was almost doubled among those who drank decaffeinated coffee (OR 1.93, 95% CI 1.04 - 3.61), with a significant dose-response trend being observed for consumption of decaffeinated coffee ($p = 0.04$). (Goodman 1986).

(3) In a case-control study of cancer of the renal pelvis and ureter in Los Angeles County, the risk of cancer of the renal pelvis and ureter increased 80% among those drinking 7 or more cups of coffee per day, and there was a monotonic increase in cancer risk with increasing levels of coffee consumption ($p = 0.11$). Coffee consumption combined with aspirin taken on 30 consecutive days also demonstrated an elevated risk, RR 2.2, 95% CI 1.1 - 4.2. (Ross 1989).

(4) In a Japanese cohort study, risk of death from kidney cancer increased with coffee consumption. Compared to no consumption, risk of death from kidney cancer increased for consumption of up to 2 cups of coffee per day (HR 1.25, 95% CI 0.67- 2.33) and was higher for consumption of 3 or more cups of coffee per day (HR 2.69, 95% CI 0.89 - 8.10). The dose-response *p*-trend = 0.082). (Washio 2005).

(5) In a large Canadian case-control study of 1,138 histologically confirmed renal cell carcinoma cases, a highly significant difference in coffee consumption was observed between cases and controls, $p < 0.0001$. For those who drank > 2.5 cups/day, OR = 1.36, 95% CI 1.07 - 1.66 for sexes combined with a slightly higher risk among men than women. Dose response analysis indicated a significant association between coffee consumption and kidney cancer, *p*-trend = 0.006). (Hu 2009).

(6) In a case-control study of renal cell carcinoma cases identified at 2 Mayo clinics in the US, the investigators

concluded that they observed an inverse association with caffeinated coffee, OR 0.74, 95% CI 0.57 - 0.99 and an increased risk with decaffeinated coffee, OR 1.47, 95% CI 0.98 - 2.19 and particularly with the more aggressive subtype ccRCC, OR = 1.80, 95% CI 1.01 - 3.22. Among those who never drank alcoholic beverages, a significant deficit of RCC was observed for those who drank caffeinated coffee and a significant excess was observed for those who drank decaffeinated coffee. (Antwi 2017).

(7) The EPIC cohort study as mentioned in section "b" above also indicates a monotonic positive dose-response (Gunter 2017).

d. Meta-analyses of the risk of kidney cancer from consumption of coffee have not reported significantly increased or decreased risks of kidney cancer. Lee 2007 (RR 0.84, 95% CI 0.67 - 1.05), Yu 2011 (RR 0.74, 95% CI 0.46 - 1.03), Huang 2014 (RR 0.99, 95% CI 0.52 - 1.89), Wang 2016 (RR 0.79, 95% CI 0.54 - 1.16), WCRF 2007 (RR 0.99, 95% CI 0.96 - 1.01).

e. Protective factors related to risk of kidney cancer have been reported in meta-analyses for several risk factors, including alcohol consumption (Song 2012, Xu 2015, Hu 2009), physical activity (Behrens 2013) consumption of cruciferous vegetables (Liu 2013, Zhao 2013), consumption of dietary fiber (Huang 2014), Vitamin B2, B6, and B12 intake (Mao 2015), Vitamin E intake (Shang 2015, Shen 2015), folic acid intake (Mao 2015), and oral contraceptive use (Liu 2014).

f. Increased risks of kidney cancer have been reported in meta-analyses for cigarette smoking (Hunt 2005), obesity (Wang 2014) in both men (Idaphonse 2009) and women (Mathew 2009), height (Liang 2015), diabetes mellitus (Larsson 2011), use of analgesics (Choueiri 2014), aristolochic acid (Wu 2013), parity (Guan 2013), hysterectomy (Karami 2014), occupational exposure to tricholoroethylene (Kelsh 2010, Karami 2012) and to pentachlorophenol (Zheng 2008), prior kidney stones (Cheungpasitporn 2015), and family history of kidney cancer (Hung 2007).

g. The relatively small number of epidemiologic studies of coffee consumption and kidney cancer have neither controlled nor adjusted for many of the risk factors established in meta-analyses, especially protective factors. It would therefore be scientifically improper to attribute any protective or null associations of kidney cancer to consumption of coffee.

12. Laryngeal Cancer

a. At least 13 case-control studies have been published regarding coffee consumption and laryngeal cancer. (Restrepo 1989, Franceschi 1990, La Vecchia 1990, Pintos 1994, Sokić 1994, Levi 1998, Franceschi 1999, Bosetti 2003, Benhamou 2004, Peters 2005, Cui 2006, Zvrko 2008, and Vassileiou 2012). Nine of these studies reported increased risks of laryngeal cancer. Statistically significant increased risks were reported in three studies. (Sokić 1994, Zvrko 2008, and Vassileiou 2012). Three studies reported risks below 1.00, but none indicated a significant deficit in laryngeal cancer risk. The study from Yugoslavia (Sokić 1994) reported an overall significant risk, OR = 13.0, 95% CI = 4.30 - 12.94) for laryngeal cancer among regular and long term coffee drinkers. The overall risk was slightly reduced in the conditional logistic regression analysis that adjusted for smoking, alcohol and 23 other variables considered risk factors for laryngeal cancer, OR 9.87, 95% CI 0.82 - 119.0. For those who consumed coffee for > 10 years, OR = 2.7, 95% CI 1.35-5.38 (Sokić 1994). A hospital-based case-control study of 108 cases of laryngeal cancer from Montenegro demonstrated significant risks of laryngeal cancer for coffee consumption overall, OR = 3.32, 95% CI = 1.16 - 9.49 and a dose response by coffee consumption: > 2 cups/day OR 2.48, 95% CI 1.39 - 4.39, and > 5 cups/day OR = 5.72, 95% CI 2.09 - 15.61. Multiple logistic regression analysis for those who drank > 5 cups/day also was highly significant, OR = 4.52, 95% CI 1.01 - 20.12. (Zvrko 2008). A clinic-based case-control study conducted in Greece demonstrated a highly significant association between coffee consumption and laryngeal cancer, p = 0.001. Logistic regression analysis also indicated a highly significant result, OR = 1.77, 95% CI 1.24 - 2.52, p = 0.002 (Vassileiou 2012).

b. Apparently only one cohort study has investigated coffee consumption and laryngeal cancer, which reported a risk close to unity for consumption of more than 3 cups per day. (Ren 2010).

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

(1) 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 2010).

(2) 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 2011).

(3) 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 2014).

(4) 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), the seven case-control studies (RR 1.28, 95% CI 0.91 - 1.80) and the 6 hospital-based case-control studies (RR 1.32, 95% CI 0.91 - 1.90). (Ouyang 2014).

13. Liver Cancer (Hepatocellular Carcinoma)

a. Hepatocellular carcinoma (HCC) is one of the cancers that has been reported to be inversely associated with coffee consumption. (Loomis 2016). It is therefore important to consider whether the inverse association between coffee consumption and liver cancer is likely causal or whether it is likely due to confounding or bias.

b. Preliminarily, the epidemiologic studies of coffee consumption and liver cancer are not entirely consistent; some of the studies do not report significantly decreased risks of liver cancer, while others do.

(1) The most recent meta-analysis of data indicates an inverse relationship between coffee consumption and HCC. The

authors nevertheless concluded that causation could not be inferred from observational studies and that randomized clinical trials are needed (Kennedy 2017). It also is noteworthy that most of the studies included in the meta-analysis did not adjust for HBV, HCV, BMI and T2DM–all known risk factors for HCC.

(2) In a case-control study of risk factors for hepatocellular carcinoma conducted in Belgrade, the risk of hepatocellular carcinoma was not decreased by coffee consumption (OR 1.0, 95% CI 0.4 - 2.7). (Kanazir 2010).

(3) In a study of atomic bomb survivors using sera stored before hepatocellular cancer diagnosis, daily consumption of coffee significantly reduced the risk of hepatocellular carcinoma without adjustment for other risk factors, but in the multivariate adjusted analysis, the reduction in risk was not statistically significant, OR 0.40, 95% CI 0.04 - 1.02) (Ohishi 2008).

(4) In a hospital-based case-control study of 185 histologically confirmed cases of hepatocellular carcinoma in Italy, risk of hepatocellular carcinoma was not significantly decreased among those who drank > 28 cups/week, OR 0.43, 95% CI 0.16 - 1.13, but the overall p-trend 0.02 was significant. No association was found for those who had evidence of Hepatitis B & C infection, but a significant trend in reduction in HCC risk was observed for those without evidence of hepatitis infection. (Montella 2007).

(5) In a cohort study of 110,688 adults aged 40 to 79, Japanese researchers found an inverse relationship between coffee consumption (>1 cup/day) and HCC (Kurozawa 2005)

(6) A pooled analysis of two prospective cohort studies in Japan shows findings opposite to those reported by Montella 2007 above; "among the subjects without a history of liver disease, the inverse association between coffee consumption and the risk of liver cancer was not significant, but the RR of liver cancer was below unity, RR 0.75, 95% CI 0.37 - 1.50, p-trend 0.33. Among the subjects with a history of liver disease, the inverse trend for coffee consumption and "primary liver cancer" was significant, p = 0.05. The authors could not conclude from their data whether the failure to detect a significant inverse association between coffee consumption and the risk of liver cancer among non-liver disease individuals was due to insufficient statistical power or whether there might be no

association." (Shimazu 2005). The multivariate analysis, however, did not adjust for BMI, nor for type-2 diabetes.

(7) In a case-control study conducted by Harvard researchers in Greece, the risk of liver cancer in all subjects was not decreased on multivariate analysis for either those who drank less than 20 cups of coffee per week (OR 1.1, 95% CI 0.5 - 2.6) or more than 20 cups of coffee per week (OR 0.9, 95% CI 0.4 - 2.5). However, in those subjects who were serologically confirmed not to have Hepatitis B Virus or Hepatitis C Virus, the risk of liver cancer was increased by consumption of less than 20 cups of coffee per week (OR 1.9, 95% CI 0.6 - 5.9) and more than 20 cups of coffee per week (OR 1.7, 95% CI 0.5 - 5.9). (Kuper 2000).

(8) In the EPIC cohort study that included participants from 10 European countries, a significant inverse dose-response was reported for both men and women (p-trend < 0.001). (Gunter 2017).

c. Many of the studies did not control for hepatitis infections. Petrick 2015 stated "While 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." In the Setiawan 2015 study, "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." Lai 2013 stated "We possessed information on HBV and HCV for only a subset of our cohort." Gao 2012 stated "All of the cohort studies were from Japan where coffee consumption was less frequent and did not control for HBV/HCV infections." Johnson 2011 ("Potential limitations of this study include the lack of HBV and HCV status for all cohort participants"), Leung 2011 ("The lack of control on viral load, platelet count, alanine aminotransferase level and other possible factors for HCC is another limitation"); Ui 2009 ("The most substantial limitation of our study was that we had no information about history of HBV or HCV infection"); Ioannou 2009 ("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."); Hu 2008 ("We had no data on history of either HBV or HCV infections at baseline"); Inoue 2005 ("there are 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"); Shimazu 2005 ("We had no information about history of HBV or HCV infection").

d. Many of the studies did not control for liver disease or other chronic diseases that have been associated with liver cancer. Setiawan 2015 ("Another limitation is the lack of information on liver disease other than HCC at baseline."); Lai 2013 ("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 2005 ("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 2002 ("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.").

e. The inverse association between coffee consumption and liver cancer may also be due to exposure misclassification and/or other types of misclassification. Petrick 2015 ("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 2015 ("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 2013 ("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 2010 ("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 2009 ("[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 2008 ("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 2007 ("the major limitation of the present study was a possible decrease of coffee use among HCC cases due to their advanced liver disease."); Wakai 2007 ("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 2007 ("Physicians' recommendation about restriction of coffee drinking in patients with liver diseases could have influenced the results"); Inoue 2005 ("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 2005 ("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.")

f. The inverse association between coffee consumption and liver cancer may also be due to reverse causation, i.e., that it 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. Petrick 2015 ("there are a number of reasons, particularly due to health concerns, that may lead individuals to alter their coffee consumption, specifically caffeinated coffee"); Jenab 2010 ("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 2005 ("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 2005 ("persons might reduce coffee intake because of symptoms related to impaired caffeine clearance (hawegawa *et al,* 1989) of poor liver function or nonspecific medical advice") . 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.

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

(1) 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 2007).

(2) 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 2007).

(3) 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 2009).

(4) 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 2007).

(5) "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 2015).

(6) "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 2007).

h. The inverse association between coffee consumption and liver cancer may also be due to confounding by uncontrolled and/or unknown factors. Lai 2013 ("it is possible that our observations, despite our consideration of a number of known and potential confounders, may be due to uncontrolled confounding"); Sang 2013 ("Because liver cancer is a multifactorial disease, it is uncertain whether other factors may have influenced the results."); Jenab 2010 ("In any study, whether case-control or prospective, additional bias can arise from missed or uncontrolled confounding."); Tanaka 2007 ("Although potential confounding effects by known risk factors were taken into account in the data analyses, other possible confounders such as dietary factors (e.g. vegetable consumption) could be relevant. We did not ascertain information on other food items and thus could not address this issue.").

(1) None of the epidemiology studies regarding coffee consumption and liver cancer either control or adjust for fluid intake generally or water intake specifically. Thus, none of the studies provide evidence that the reduced risk of liver cancer from increased coffee consumption is due to any constituents of coffee as opposed to increased water intake from coffee beverages, which contain 98-99% water. Water intake is an important confounder of the studies, not only because increased water intake has been associated with reduced risk of cancer, but because uncontaminated

drinking water has been shown to reduce liver cancer risk.

(2) In a review of risk factors of liver cancer, Chinese researchers identified contaminated drinking water as a risk factor for liver cancer. (Gao 2012). They noted that the hypothesis of some types of drinking water as a risk factor for hepatocellular carcinoma was first raised in 1972 by Su De-long, who observed that in epidemic areas such as Qidong, Haimen, Fusui, and Taixing, the increased incidence of hepatocellular carcinoma could not be totally explained by Hepatitis B Virus and Aflatoxin. (Su 1979) Subsequent epidemiological studies in Qidong, Haimen and Nanhui counties indicated that people who drank surface water (pond, ditch, river versus well or deep water) had increased risks of hepatocellular carcinoma. In the Qidong-Haimen area, people who drank pond-ditch water had a HCC mortality of 100/100,000, while those who drank water from the Yangtze River or deep well water had a HCC mortality of about 20/100,000 and 10/100,000 respectively. (Yu 1989) A meta-analysis of 6 case-control studies in China showed an increased risk of HCC from drinking pond-ditch water (OR 2.46, 955 CI 1.69 - 2.59) (Yu 2001). Changing from pond-ditch water to deep well (at least 200 m) water led to a subsequent decrease in the mortality rate from HCC. (Yu 1986; Huang 1992). The increased risk of hepatocellular carcinoma from pond ditch water was attributed to contamination with microcystins, a type of cyanotoxin that induces severe intrahepatic hemorrhage and liver necrosis, and may have synergistic effects with aflatoxins. (Ueno 1996, Yu 2001, Clark 2008).

(3) Cyanotoxins are produced by bacteria and are ubiquitous in nature. Consumption of cyanotoxin-contaminated drinking water is therefore a risk factor for human liver cancer, as was shown in China where changing the drinking water supply from pond-ditch to deep well water resulted in decreased liver cancer mortality. (Huang 1992).

(4) None of the epidemiologic studies of coffee consumption and liver cancer assessed water, drinking water sources (pond or shallow surface water versus well or deep well), or types of drinking water (tap water versus bottled water). As will be discussed in detail below, increased water intake has been shown to reduce risk of some human cancers (Bar David 2004) and in one study drinking bottled water reduced the risk of kidney cancer. (Hu 2009) The inverse association between coffee consumption and liver cancer may therefore be due to increased water intake among

coffee drinkers (coffee beverages being comprised of 98-99% water), or may be due to uncontaminated sources of drinking water, rather than any effect of coffee itself. Since none of the epidemiologic studies regarding consumption of coffee and liver cancer have assessed fluid or water intake, have assessed source of drinking water or drinking water quality, none of the studies has controlled for confounding by water intake or water quality. Especially because increased consumption of uncontaminated water has been reported to decrease risk of human cancer, water remains an uncontrolled confounder of the coffee-liver cancer association and it is scientifically improper to attribute the inverse association between coffee drinking and liver cancer to a protective effect of coffee itself, as opposed to the water content of coffee beverages.

(5) Another source of confounding of the inverse association between coffee consumption and liver cancer, which relates to water, concerns different methods of brewing coffee.

(a) Boiled coffee reduces the risk of microbial contamination, because water boils at a temperature of 212°F, which is sufficiently high to destroy most types of water-borne pathogens (Backer 2002). However, unlike filtered coffee, boiled coffee contains diterpenes which increase cholesterol (Urgert 1997) and therefore increase the risk of cardiovascular disease (Godos 2014, Ranheim 2005) and potentially cancer as well.

(b) According to the National Coffee Association, the optimal temperature for brewing coffee is 195-205°F. Brewing coffee also reduces the risk of microbial contamination, although to a lesser degree than boiling coffee. (NCA webpage on brewing coffee).

(c) Many people brew coffee using drip coffee makers, which filter coffee brew through paper filters. Paper filters remove diterpenes from coffee brew (Urgert 1997), but are not effective in removing microbial and chemical contaminants. Bleached paper filters also introduce chlorinated compounds into brewed coffee. (Wiberg 1989).

(d) In recent years, single-serving coffee brewing machines that use pods have become quite popular.

14. Lung Cancer

a. At least thirteen case-control studies regarding coffee consumption and lung cancer have been published. (Mettlin 1989, Chen 1990, Axelson 1996, Mendilaharsu 1998, Nyberg 1998, Takezaki 2001, Hu 2002, Baker 2005, Chiu 2010, Ganesh 2011, Luqman 2014, Sanikini 2015, Pasquet 2016). Most of these studies report increased risks of lung cancer in association with coffee consumption. At least a third of the studies report increased risks that are statistically significant. (Axelson 1996, Takezaki 2001, Baker 2005, Ganesh 2011, Luqman 2014). Three of the case-control studies indicate dose-response relationships. (Axelson 1996, Takezaki 2001, Baker 2005).

b. At least eleven cohort studies regarding coffee consumption and lung cancer have been published. (Jakobson 1986, Nomura 1986, Chow 1992, Stensvold 1994, Fu 1997, Khan 2004, Nilsson 2010, Hashibe 2015, Guertin 2016, Lukic 2016, Gunter 2017). Most of these report increased risks of lung cancer; at least nine reporting some significantly increased risks. (Jakobson 1986, Chow 1992, Stensvold 1994, Fu 1997, Khan 2004, Nilsson 2010, Hashibe 2015, Guertin 2016, Lukic 2016, Gunter 2017). Three studies report significant dose-response relationships. (Nomura 1986, Lukic 2016, Gunter 2017). When adjustment was made for cigarette smoking, the risk of lung cancer remained statistically significant in the Lukic (2016) study but not in the Nomura study. The Gunter 2017 study adjusted for cigarette smoking and demonstrated a significant positive monotonic dose response for lung cancer related to coffee consumption in both men and women, p-trend < 0.001.

c. Five meta-analyses of coffee consumption and lung cancer have been published. (Tang 2010, Yu 2011, Xie 2016, Galarraga 2016, Wang 2016). Except for Yu (2011), all of these reported some significantly increased lung cancer risks.

(1) 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 2010).

(2) The next meta-analysis, 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 2011).

(3) 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). (Xie 2016). 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. For coffee drinkers vs non-drinkers, RR 1.15 (95% CI 1.01-1.32); for the highest category versus the lowest category of coffee drinkers, RR 1.29, 95% CI 1.08-1.54.

(4) 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 also 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 2016).

(5) 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 2016).

(6) In summary, 5 case-control studies demonstrate

significantly increased risks of lung cancer. Three indicate a dose-response. Most cohort studies indicate elevated risk of lung cancer and 9 report significantly increased risks, with 3 indicating a dose response. Four out of 5 meta-analyses related to coffee consumption and lung cancer demonstrate significantly elevated risks. In some studies adjustment for cigarette smoking lowered the risk to a non-statistically significant excess or no excess at all, while in other studies, adjustment for cigarette smoking resulted in the elevated risk remaining statistically significant.

15. Non-Hodgkin Lymphoma

a. At least a dozen case-control studies regarding coffee consumption and non-Hodgkin lymphoma have been published. (Franceschi 1989, Tavani 1994, Ward 1994, Tavani 1997, Matsuo 2001, Chang 2005, Chiu 2008, Gong 2010, Balasubramanian 2013, Cocco 2015, Parodi 2016, Cerliani 2016). Five of these studies reported significantly increased risks of lymphoma for coffee consumption (Tavani 1994, Gong 2010, Cocco 2015 (NAT1 acetylator fast vs slow), Parodi 2016 (B-cell lymphomas), Cerliani 2016).

b. Further analyses of data from the Parodi 2016 study indicated that the overall excess of NHL was related to subtypes, follicular (OR 2.0, 95% CI 1.2 - 3.4), DLBC (OR 1.7, 95% CI 1.2 - 2.5) and MALT (OR 2.1, 95% CI 1.2 - 3.8) for those who consumed > 4 cups/day. A highly significant dose-response (ranging from p = 0.027 to 0.001) was observed for follicular lymphoma depending upon the number of years of coffee consumption. (Parodi 2016).

c. Another case-control study has also demonstrated a significant dose-response. A Master's degree student at Queen's University in Ontario investigated whether exposure to chemical emissions from proximity to pulp and paper mills is associated with an increased risk of non-Hodgkin lymphoma in Western Canada. She observed a 46% increased risk of non-Hodgkin lymphoma for consumption of > 14 cups of coffee per week (OR 1.46, 95% CI 1.13 -1.88), with a highly significant trend (*p*-trend = 0.002). (Gong 2010).

d. At least 3 cohort studies regarding coffee consumption and non-Hodgkin lymphoma have been published. (Jacobsen 1986, Stensvold 1994, Nilsson 2010). Increased risks of lymphoma were reported in the two Norwegian studies (Jacobsen 1986, Stensvold 1994). In the later of these studies, the risk of lymphoma was more than tripled for consumption of 3 to 4 cups of coffee per day (OR 3.19, 95% CI 1.12 - 9.05) and was nonsignificantly increased for higher consumption. (Stensvold 1994). Lymphoma risk was not significantly increased in the Swedish study. (Nilsson 2010)

e. Two meta-analyses regarding coffee consumption and non-Hodgkin lymphoma have recently been published by Chinese researchers. (Han 2016, Wang 2016).

(1) 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 2016). Three case-control studies that demonstrate significantly risks of NHL, however, were published after the literature search was conducted by Han 2016 and therefore were included in the meta-analysis (Cocco 2015, Parodi 2016, Cerliani 2016) and a fourth was not identified (Gong 2000). Therefore, the meta-analysis bases 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.

(2) The other meta-analysis, based on three cohort studies, e.g., the same three used by Han 2016, reported a higher increased risk comparing highest intake versus lowest intake (RR 1.23, 95% CI 0.75 - 2.03). (Wang 2016). Thus, the results are virtually identical.

f. In summary, the risk of NHL was statistically significantly elevated in 5 out of 12 case-control studies identified. Two of these demonstrated a significant dose-response, e.g., increase in NHL risk with increased coffee consumption. The meta-analysis by Han 2016 fails to include 4 case-control studies that demonstrated significantly elevated risks. Two meta-analysis based on the same three cohort studies indicate elevated risks of NHL ranging between 1.23 and 1.29 that were not statistically significant. Overall, the data on NHL suggest an elevated risk in association with consumption of coffee. However, too few studies have been published to determine causality.

16. Oropharyngeal Cancer

a. Case Control Studies.

(1) Some of the case-control studies of coffee consumption and oropharyngeal cancer have reported significantly reduced risks of such cancers. Franceschi 1992 (mouth cancer only), Tavani 2003, Biazevic 2011, Hsu 2012, Oze 2013.

(2) Some of the case-control studies of coffee consumption and oropharyngeal cancer have reported nonsignificantly reduced risks of such cancers. La Vecchia 1989, Franceschi 1992 (tongue cancer), Mashberg 1993, Pintos 1994, Takezaki 1996, Radoi 2013).

(3) A few case-control studies of coffee consumption and oropharyngeal cancer have reported nonsignificantly increased risks of cancer. Bundgaard 1995, Lagiou 2009.

b. Cohort Studies.

(1) In the Miyagi Cohort Study in Japan, among 38,679 participants, 157 cases of oral, pharyngeal, and esophageal cancers were identified during 13.6 years of followup. The multivariate-adjusted hazard ratio of these cancers for consumption of 1 or more cups of coffee per day versus none was 0.51 (95% CI 0.33 - 0.77). (Naganuma 2008).

(2) In the Cancer Prevention Study II cohort, of 968,432 participants, 868 deaths due to oropharyngeal cancer occurred during 26 years of followup. Compared to less than 1 cup of coffee per day, the risk of death from oropharyngeal cancer was decreased for consumption of more than 4 cups of caffeinated coffee per day (RR 0.58, 95% CI 0.37 - 0.92) and for consumption of more than 2 cups of decaffeinated coffee per day (RR 0.61, 95% CI 0.37 - 1.01). (Hildebrand 2013).

c. Meta-Analyses.

(1) In a 2011 meta-analysis based on 3 cohort studies, Chinese investigators reported a significantly reduced risk of oropharyngeal cancer for consumption of (RR 0.49, 95% CI 0.29 - 0.70), with a lower risk for high consumption of coffee (RR 0.40, 95% CI 0.12 - 0.68). (Yu 2011).

(2) In a 2016 meta-analysis of 6 cohort studies by Chinese investigators, the summary relative risk was 0.69 (95% CI 0.48 - 0.99). The subgroup analysis indicated that the inverse association was observed in Asia and with followup of more than 10 years. (Wang 2016).

d. Anthropometric, dietary, oral hygiene, and physical activity factors have been reported in meta-analyses to significantly reduce the risk of oropharyngeal cancer.

(1) Anthropometric factors: Height (INHANCE 2014).

(2) Dietary Factors: antioxidant vitamins and fiber (Edefonti 2011), calcium supplements (Li 2012), carotenoid intake (Leoncini 2016), egg consumption among never-smokers (Butler 2016), "fats" dietary pattern (Edefonti 2011), flavan-3-ols (Lei 2016), folate (Galeone 2015a), fruit (Chuang 2012), garlic (Galeone 2015b), vegetables (Chuang 2012, (Butler 2016 in smokers only), Vitamin C (Li 2012, Edefonti 2015a), Vitamin E (Edefonti 2015b),

(3) Oral Hygiene Factors: less than 5 missing teeth (Hashim 2016), annual dentist visits (Hashim 2016), daily tooth brushing (Zeng 2015, Hashim 2016), no gum disease (Hashim 2016).

(4) Physical Activity Factors: Moderate recreational physical activity (Nicolotti 2011), High recreational physical activity among persons 45 years or older (Nicolotti 2011).

e. The epidemiologic studies of coffee consumption and oropharyngeal cancer have neither controlled nor adjusted for all of the factors that have been shown to significantly reduce the risk of oropharyngeal cancer in meta-analyses and critical reviews. Since established risk factors for oropharyngeal cancer have not been adequately addressed in the epidemiologic studies of coffee consumption and oropharyngeal cancer, it would be scientifically improper to conclude that decreased risks of oropharyngeal cancer are causally related to consumption of coffee.

17. Ovarian Cancer

a. Most of the case-control studies of coffee consumption and ovarian cancer reported increased risks for the highest level of consumption. Trichopoulos 1981: ≥3 cups/day (OR 2.2); Hartge 1982: ≥4 cups/day (OR 1.4, 95% CI 0.6 - 3.0); Byers 1983: ≥3 cups/day (OR 0.97); Cramer 1984: ≥5 cups/day (OR 1.50); La Vecchia 1984: ≥4 cups/day (OR 2.2, 95% CI 1.2 - 1.4); Tzonou 1984: ≥3.5 cups/day (OR 1.5); Miller 1987: ≥5 cups/day (OR 1.1, 95% CI 0.6 - 2.0); Whittemore 1988: ≥4 cups/day (OR 2.07, 95% CI 0.97 - 4.38); Polychronopoulou 1993: ≥2 cups/day (OR 1.09, 95% CI 0.52 - 2.27); Kuper 2000: ≥4 cups/day (OR 1.88, 95% CI 1.14 - 3.09); Tavani 2001: ≥4 cups/day (OR 0.93, 95% CI 0.69 - 1.27); Goodman 2003: regular drinkers (OR 1.8, 95% CI 1.1 - 2.8); Jordan 2004: ≥4 cups/day (OR 0.51, 95% CI 0.32 - 0.80); Riman 2004: ≥4 cups/day (OR 0.68, 95% CI 0.42 - 1.10); Baker 2007: ≥4 cups/day (OR 1.05, 95% CI 0.73 - 1.52); Hirose 2007: ≥3 cups/day (OR 1.33, 95% CI 0.68 - 2.60); Song 2008: ≥3 cups/day (OR 0.87, 95% CI 0.64 - 1.19); Kotsopoulos 2009: ≥2.5 cups/day (OR 1.08, 95% CI 0.90 - 1.30, premenopausal (OR 1.35, 95% CI 1.03 - 1.78).

b. Most of the cohort studies regarding coffee consumption and ovarian cancer reported nonsignificantly increased risks for the highest level of consumption. Snowdon 1984: ≥2 cups/day (RR 1.2, 95% CI 0.6 - 2.5); Jacobsen 1986: ≥7 cups/day (RR 1.25); Stensvold 1994: ≥7 cups/day (RR 2.0); Larson 2005: ≥4 cups/day (RR 1.02, 95% CI 0.62 - 1.69); Silvera 2007: ≥4 cups/day (RR 1.62, 95% CI 0.95 - 2.75); Steevens 2007: ≥5 cups/day (RR 1.07, 95% CI 0.75 - 1.53); Lueth 2008: ≥5 cups/day (RR 1.81, 95% CI 1.11 - 2.95); Tworoger 2008: ≥3 cups/day (RR 0.75, 95% CI 0.55 - 1.02); Nilsson 2010: ≥4 occasions/day (RR 1.41, 95% CI 0.53 - 3.74); Braem 2012: 5th quintile (RR 1.05, 95% CI 0.75 - 1.46); Hashibe 2015: ≥2 cups/day (RR 1.17, 95% CI 0.82 - 1.67).

c. The recently published EPIC cohort study of participants from 10 European countries, demonstrates a statistically significant positive dose response by amount of coffee consumption and risk of ovarian cancer (*p*-trend = 0.02). For those consuming coffee in the highest quartile, risk of ovarian cancer mortality was significantly increased (RR 1.31, 95% CI 1.07 - 1.61). (Gunter 2017).

d. Three meta-analyses have been published regarding coffee consumption and ovarian cancer. (Steevens 2007, Braem 2012, Wang 2016).

(1) 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 2007).

(2) In 2012 European researchers published a meta-analysis of all prospective cohort studies until April 2011, including 3 studies published after the meta-analysis by Steevens and EPIC data. They observed a non-significant positive association between consumption of coffee (highest compared with lowest categories) and risk of ovarian

cancer (HR 1.13, 95% CI 0.89 - 1.43). They also did a dose-response, random-effects, meta-regression analysis, which did not include the EPIC data, calculating the risk of ovarian cancer for an increment of one cup of coffee per day: HR 1.02, 95% CI 0.99 - 1.05. (Braehm 2012).

(3) 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 increased (RR 1.04, 95% CI 0.90 - 1.20). (Wang 2016).

18. Pancreatic Cancer

a. A number of case-control studies demonstrate significantly elevated risks of pancreatic cancer in relation to consumption of coffee: MacMahon 1981, Wynder 1986 (decaffeinated coffee in females), Mack 1986, Gorham 1988, Clavel 1989, Ghadirian 1991 (decaffeinated coffee), Lyon 1992, Gullo 1995, Silverman 1998 (in blacks), Morales 2007 (with *k-ras* mutations), Turati 2011, Porta 2011 (with *k-ras* mutations).

b. Several of these studies also report dose-response relationships between coffee consumption and risk of pancreatic cancer. MacMahon 1981, Gold 1985 (in females), Gorham 1988, Clavel 1989, Ghadirian 1991 (decaffeinated coffee), Lyon 1992, Gullo 1995, Nishi 1996, Morales 2007 (with *k-ras* mutations), Turati 2011 (in females and nonsmokers), Porta 2011 (with *k-ras* mutations)

c. A few case-control studies also report significant increased risks of pancreatic cancer in relation to consumption of coffee among non-smoking populations. Lyon 1992, Gullo 1995, Nishi 1996, Turati 2011.

d. More than 20 cohort studies regarding coffee consumption and pancreatic cancer have been published including (Nomura 1981, Whittemore 1983, Jacobsen 1986, Nomura 1986, Hiatt 1988, Stensvold 1994, Shibata 1994, Harnack 1997, Michaud 2001, Isaksson 20012, Stolzenberg-Solomon 2002, Khan 2004, Luo 2007, Bidel 2013, Bhoo-Pathy 2013, Gunter 2017). Two of the cohort studies that report significant increased risks of pancreatic cancer in relation to coffee consumption also demonstrate dose-response relationships. Harnack 1997 (post-menopausal females), Nilsson 2010 (boiled coffee). Eight additional cohort studies indicate risks of pancreatic cancer above unity (Whittemore 1983, Snowdon 1984, Nomura 1986, Mills 1988, Hirayama 1989,

Stensvold 1994, Lin 2002, Porta 1999), with five cohort studies overall presenting evidence of statistically significant elevated risks of pancreatic cancer (Hirayama 1989, Harnack 1997, Lin 2002, Nilsson 2010, Porta 1999). Overall, fewer cohort studies indicate significantly elevated risks of pancreatic cancer as compared to case-control studies.

e. Six meta-analyses regarding coffee consumption and pancreatic cancer have been published. (Dong 2011, Yu 2011, Turati 2012, Nie 2016, Ran 2016, Wang 2016).

f. The studies published by Dong and Yu in 2011 were both based on 14 cohort studies and reported 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 2011, Yu 2011).

g. A study 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). (Turate 2012).

h. A meta-analysis published in 2016, based on 20 cohort studies that compared highest versus lowest exposure, found a risk for all 20 cohort studies near unity (RR 0.99, 95% CI 0.81 - 1.21), which increased slightly when one heterogenous study was excluded (RR 1.06, 95% CI 0.94 - 1.20). (Nie 2016).

i. Another meta-analysis published in 2016, also based on 20 cohort studies that compared highest versus lowest exposure, reported 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 2016).

j. The most recent meta-analysis, based on 15 cohort studies, found a risk of pancreatic cancer close to unity comparing highest and lowest exposures (RR 1.02, 95% CI 0.87 - 1.18). (Wang 2016).

19. Prostate Cancer

a. At least 14 case-control studies regarding coffee consumption and prostate cancer have been published. (Slattery 1993, Gronberg 1996, Jain 1998, Villleneuve 1999, Hsieh 1999, Sharpe 2002,

Chen 2005, Gallus 2007, Ganesh 2011, De Stefani 2011, Polesel 2012, Geybels 2013, Wilson 2013, Russnes 2016). Most of these studies report increased risks. Four studies report significantly increased risks. (Villeneuve 1999, Chen 2005, Gallus 2007, De Stefani 2011). However, 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 2016).

b. At least 15 cohort studies regarding coffee consumption and prostate cancer have been published. (Jacobsen 1986, Nomura 1986, Severson 1989, Hsing 1990, Le Marchand 1994, Stensvold 1994, Ellison 2000, Allen 2004, Nilsson 2010, Wilson 2012, Shafique 2012, Bosire 2013, Discacciati 2013, Li 2013, Russnes 2014, Tverdal 2015, Gunter 2017). These studies report both increased and decreased risks of prostate cancer. The more recent studies report decreased risks of prostate cancer (Discacciati 2013, Li 2013, Russnes 2014, Tverdal 2015), that are statistically significant in the two most recent studies (Russnes 2014, Tverdal 2015 for boiled coffee only). The EPIC cohort indicates a risk around unity with RRs by three increasing categories of coffee consumption being 1.04, 1.01 and 1.03, respectively. (Gunter 2017).

c. Nine meta-analyses regarding coffee consumption and prostate cancer have been published. (Park 2010, Yu 2011, Discacciati 2014, Zhong 2014, Cao 2014, Lu 2014, Huang 2014, Liu 2015, Wang 2016). As would be expected meta-analyses based on case-control studies indicate higher risks for prostate cancer, while those based on cohort studies indicate risks that are relatively lower and sometimes statistically significant.

d. 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 2010).

e. A meta-analysis published in 2011, 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 2011).

f. A meta-analysis published in 2014, 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), 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 2014)

g. 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 2014).

h. 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).

i. 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 2014).

j. 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 2014)

k. 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 2015).

l. The most recent meta-analysis, 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 2016).

20. Skin Cancer

a. Only a few case-control studies have been published regarding coffee consumption and skin cancer. Of these, one study reported increased risks of basal cell carcinoma of the skin in men and in women (Milán 2003), and another study reported increased risks of cutaneous malignant melanoma (Naldi 2004).

b. Only a handful of prospective cohort studies have been published regarding coffee consumption and skin cancer. An early study reported a 3½-fold increased risk of melanoma in association with coffee consumption, with a statistically significant linear trend. (Jacobsen 1986). Other studies reported increased risks in men, but not women (Veierod 1997) and for decaffeinated. but not caffeinated coffee, in cohorts of men and women (Wu 2015).

c. Six meta-analyses of coffee consumption and risk of skin cancer have been published, all in the year 2016.

(1) 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 2016).

(2) 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, 2015).

(3) 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 2016).

(4) In a meta-analysis of cohort studies and case-control studies regarding coffee consumption and non-melanoma skin cancer risk, Iranian researchers observed a dose-response relationship between coffee consumption and non-melanoma skin cancer risk. The summary relative risks for non-melanoma skin cancer were 0.96 (95% CI 0.92 - 0.99) for one cup of coffee, 0.92 (95% CI 0.88 -0.97) for one to two cups of coffee, 0.89 (95% CI 0.86 -0.93) for two to three cups of coffee, and 0.81 (95% CI 0.77 - 0.85) for more than three cups of coffee per day, respectively. The investigators concluded that caffeinated coffee might have chemopreventive effects against basal cell carcinoma, but that additional prospective studies should be conducted to confirm these effects. (Vaseghi 2016).

(5) Italian researchers identified 37,627 non-melanoma skin cancer cases from 13 studies. Comparing those in the highest and lowest categories of intake, caffeinated coffee was inversely associated with non-melanoma skin cancer risk (RR 0.82, 95 % CI 0.75 - 0.89). In subgroup analysis, the association was limited to the basal cell cancer histotype. There was no association between intake of decaffeinated coffee and non-melanoma skin cancer risk (RR 1.01, 95 % CI 0.85 - 1.21). The researchers concluded that coffee intake appears to exert a moderate protective effect against basal cell cancer development, but noted that the observational nature of studies included were subject to bias and confounding, and recommended that the results be

verified in randomized clinical trials. (Caini 2016).

(6) 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 2015).

d. Epidemiologic studies of coffee consumption and risk of skin cancer are subject to multiple confounding factors.

(1) Cigarette Smoking

(a) 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 2002, citing Green 1999).

(b) 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. (IARC 2004).

(c) In its most recent update of smoking and cancer, IARC noted that two cohort studies (Freedman 2003, Odenbro 2007) reported inverse associations for smoking and melanoma, and that in the latter study the risk of melanoma was reduced in a dose-dependant manner; IARC concluded that smoking may reduce the risk of melanoma. (IARC 2012).

(d) Three meta-analyses have reported that smoking is inversely associated with malignant melanoma. (Song 2012, Leonardi-Bee 2012, Li 2015). 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 2015).

(e) Few of the case-control studies and cohort studies regarding coffee consumption and melanoma either controlled or adjusted for smoking.

(f) 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 ($P_{heterogeneity}$ = .04); a statistically significant inverse trend was observed among ever (P_{trend} = .006) but not never smokers (P_{trend} = .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 to 1.03)." (Loftfield 2015).

(g) The investigators of the NIH-AARP study noted that "studies have suggested that smoking is inversely associated with melanoma risk" and that "in our cohort, heavy coffee drinkers were more likely than non-coffee drinkers to be current or former smokers." Even though they adjusted for smoking, they acknowledged the possibility that the inverse association between coffee consumption and melanoma risk could be due to residual confounding by smoking. (Loftfield 2015).

(h) Just as increased risks of lung cancer in coffee drinkers are confounded by cigarette smoking, decreased risks of melanoma in coffee drinkers are confounded by cigarette smoking. Indeed, most of the studies regarding coffee consumption and melanoma failed to control or adjust for smoking. The decreased risks of melanoma and other skin cancers in these studies could be due to a protective effect of smoking on melanoma risk rather than any protective effect of any constituents of coffee.

(2) Recognized Confounding Factors Not Measured.

(a) The investigators of the NIH-AARP study noted that "known risk factors for melanoma, including individual UVR exposure, nevi, fair skin, freckling,

light hair, and a family history of melanoma, were not measured in this cohort." They also acknowledged that "inability to assess potential confounding by these known risk factors is an important limitation of this study." (Loftfield 2015)

(3) Reported Confounding Factors Not Considered.

(a) Dietary factors that have been reported to reduce the risk of melanoma include weekly consumption of fish and shellfish (Fortes 2008), daily tea drinking (Fortes 2008), high consumption of vegetables, in particular carrots, cruciferous and leafy vegetables and fruits (Fortes 2008).

(b) Other factors that have been reported to reduce the risk of melanoma in some, but not all studies, include α and β-carotene (Millen 2004), aspirin (Muranushi 2015, Zhu 2015), crytoxanthin (Millen 2004), lutein (Millen 2004), lycopene (Millen 2004), nonsteroidal anti-inflammatory drugs (Muranushi 2015), omega-3 fatty acids (Noel 2014), retinol (Feskanich 2003, Asgari 2012, Zhang 2014), soluble carbohydrates (Vinceti 2005), Vitamin A (Naldi 2004), Vitamin B (Zhang 2016), Vitamin C (Malavolti 2013), Vitamin D (Millen 2004, Vinceti 2011).

(c) These factors that have been reported to be protective for melanoma risk have neither been controlled nor adjusted for in most epidemiologic studies regarding coffee drinking and melanoma.

21. Thyroid Cancer

a. About a half-dozen case-control studies have assessed the risk of thyroid cancer in relation to the consumption of coffee.

(1) In a pooled analysis of four European case-control studies, the risk of thyroid cancer was slightly increased (OR 1.1) for medium coffee consumption and 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 1991)

(2) In a hospital-based case-control study of thyroid cancer among Japanese women, the risk of thyroid cancer was nonsignificantly decreased in relationship to consumption

of coffee. (OR 0.6, 95% CI 0.3 - 1.04). (Takezaki 1996).

(3) In a case-control study in Southwestern Germany, a known iodine-deficient area, on multivariate analysis, the risk of thyroid cancer was nonsignificantly decreased for the highest consumption of caffeinated coffee (OR 0.83, 95% CI 0.33 - 2.12), but nonsignificangtly increased for the highest consumption of decaffeinated coffee (OR 2.70, 95% CI 0.72 - 10.2). (Frentzel-Beyme 2000).

(4) 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 associated with a nonsignificant increase of 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 2002).

(5) 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 nonsignificantly decreased among those drinking more than 30 cups of coffee per month (OR 0.9, 95% CI 0.6 - 1.2). (Mack 2003).

b. Only two cohort studies regarding coffee consumption and thyroid cancer have been published.

(1) 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 2011).

(2) 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 2015).

c. 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 2017).

d. In summary, the few epidemiological studies available for review indicate thyroid cancer risks close to unity. The data upon which to make a determination of risk are too sparse.

22. Total Cancer

a. At least fourteen cohort studies have evaluated the risk of total cancer in relation to coffee consumption.

b. In a Norwegian cohort study among men, 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 1986).

c. A Norwegian cohort study of men and women found no association between coffee consumption and total cancer incidence. (Stensvold 1994).

d. In a Finnish cohort study of the elderly, no association was observed between coffee consumption and total cancer mortality. (Happonen 2008)

e. A Swedish cohort study also found no association between coffee consumption and total cancer incidence (HR 0.92, 95% CI 0.80 - 1.05). (Nilsson 2010).

f. 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). These data reflect a monotonic dose response that did not achieve statistical significance. Among women risk of total cancer mortality was not increased. (Sugiyama 2010).

g. In the NIH-AARP Diet and Health Survey, a significant positive dose-response in relation to coffee consumption and mortality from all cancers was observed (*p*-trend = 0.002). (Freedman 2012).

h. In a cohort study of a rural Japanese population followed for ten years no association was observed between coffee consumption

and total cancer mortality. (Iwai 2012).

i. In the Northern Manhattan Cohort Study, an inverse relationship for all coffee consumption as well as regular coffee consumption was observed for total cancer mortality. (Gardener 2013).

j. In the Women's Health 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 2015).

k. In a cohort study of Swedish women, the most adjusted model for coffee consumption demonstrated a positive association for total cancer mortality. For those who drank 2 to 5 cups of coffee per day or greater than 5 cups of coffee per day, the relative risks of total cancer mortality were 1.06 (95% CI 0.86 - 1.13) and 1.53 (95% CI 1.21 - 1.93) respectively. (Löf 2015).

l. In the PLCO Cohort Study, among those in the highest quartile of coffee consumption, risk of total cancer mortality was increased, but did not quite reach statistical significance. (RR 1.05, 95% CI 0.99 - 1.11). (Hashibe 2015).

m. In another publication regarding the PLCO Cohort Study, in the most adjusted model, no association was observed between total coffee consumption and total cancer mortality. (Loftfield 2015).

n. In a cohort study conducted in three Eastern European countries, multivariate analysis indicated no association between coffee consumption and total cancer mortality among the entire population and also among non-smokers (Grosso 2016).

o. The recently published EPIC prospective cohort study that included 521,330 participants from 10 European countries demonstrates a significant increase in total cancer 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). Women who were in the highest quartile of coffee consumption (compared to nonconsumers) had increased total cancer mortality (RR 1.12, 95% CI 1.02 - 1.23). (Gunter 2017) As coffee drinking habits was assessed only one time in this prospective study, dose-response analyses would be biased toward the null.

p. Thus, of the 14 cohort studies evaluated, 4 studies demonstrated a significant positive association, 3 studies indicated non-significant elevated risks, 6 studies showed no association, and 1 study showed an inverse association with total cancer mortality.

II. SUMMARY

A. Bladder Cancer

1. Numerous case-control studies report statistically significant increases in bladder cancer in relation to coffee consumption. A number of these demonstrate statistically significant dose-response relationships.

2. One cohort study reported a statistically significant trend in relation to coffee consumption in men and increased risk of bladder cancer (Zeegers 2001), while three additional studies show a positive trend that did not achieve statistical significance (Snowdon 1984; Nomura 1986; Kurahashi 2009). The EPIC cohort (Gunter 2017) indicates little association between bladder cancer and coffee consumption, however, among men the RRs for 3 categories of coffee consumption ranged between 1.52 and 1.15.

3. Eight meta-analyses have been published. Five based on a large number of case-control studies demonstrate significantly increased risks of bladder cancer. Three based on cohort studies do not report significantly increased risks. The Zhou 2012 meta-analysis demonstrates a monotonic dose response for coffee consumption and increased risk of bladder cancer among non-smokers. Significant dose-response relationships have also been reported for coffee consumers who were nonsmokers, which suggests that the elevated risks of bladder cancer among coffee consumers are not due to confounding by smoking.

B. Brain Cancer

1. The studies regarding coffee consumption and brain cancer yield mixed results and are too few in number to allow causal assessment. Furthermore, none of the studies controlled for cell phone use which is likely to be the major confounder when assessing brain cancer risk.

C. Breast Cancer

1. Some studies indicate an elevated risk of breast cancer, a few show an inverse relation. Vatten 1990 shows an inverse relation among women who had a BMI < 24 and a positive association among those with a BMI > 24. Most studies show no association, including the recent EPIC cohort (Gunter 2017).

2. Many confounders of the association between coffee consumption and breast cancer have not been considered because the information was not available in the data set used for evaluation of risk, the association was not known at the time of the study, or the investigators chose not to assess it.

D. Childhood Acute Leukemia

1. Eight epidemiologic studies have evaluated the risk of childhood acute leukemia (CAL) from maternal consumption of coffee during pregnancy. All of these studies except Petridou report increased risks of childhood acute leukemia. Bonaventure (2013) was particularly well conducted as it controlled for numerous factors that could potentially confound the results. It shows a dose-response for both ALL and AML separately. Several of the studies demonstrate statistically significant dose-response relationships. All four studies that evaluated cigarette smoking demonstrated the highest risk of childhood leukemia among nonsmoking mothers, so the studies do not appear to be confounded by smoking.

2. Four meta-analyses of these studies have been published.

    a. The first meta-analysis by Milne (2011) showed a significantly increased risk of childhood acute leukemia among mothers who consumed more than 3 cups of coffee per day.

    b. In the second meta-analysis, Cheng (2014) reported significantly elevated risks for childhood acute lymphocytic leukemia and childhood acute myelogenous leukemia Dose-response relationships were also significant.

    c. In the third meta-analysis, Thomopoulous (2015) reported a significantly increased risk of CL when comparing highest versus never-lowest consumption.

    d. In the fourth meta-analysis, Yan (2015 and 2016) reported a significantly increased risk of childhood ALL from maternal consumption of coffee during pregnancy.

3. A mechanism for the development of childhood acute leukemia from maternal consumption of coffee during pregnancy has been described.

4. The published epidemiologic studies and mechanistic studies provide strong evidence to support a carcinogenic effect of maternal coffee consumption during pregnancy on the developing fetus, with the resultant development of childhood acute leukemia.

E. Childhood Brain Cancer

1. Four studies have evaluated childhood central nervous system tumors in relation to maternal consumption of coffee during pregnancy.

2. Cordier reported a 90% non-significant increase in the risk of any childhood brain tumor.

3. Plichart reported a 40% non-significant in the risk of childhood brain tumors and a 170% non-significant increase in the risk of ependymomas.

4. Greenop reported a significant 76% increase in the risk of childhood brain tumors for maternal consumption of coffee during the last 6 months of pregnancy, and a 2.5-fold significant increase for consumption of 2 or more cups of coffee per day.

5. Bailey reported that any coffee consumption during the first trimester showed a statistically significant increase in childhood brain tumors.

F. Colorectal Cancer

1. A number of case-control studies indicate an elevated risk of colorectal cancer (CRC) among coffee consumers.

2. Cohort studies also demonstrate increased risks of CRC. The recent EPIC cohort indicates a significant positive trend in the risk of colorectal cancer in relation to coffee consumption. (Gunter 2017).

3. Some meta-analyses (mostly based on case-control studies) show an inverse relationship between coffee consumption and colorectal cancer.

G. Endometrial Cancer

1. Some studies show positive associations for coffee consumption and endometrial cancer that are not statistically significant, while others show no association.

2. Although most studies report significantly reduced risks of endometrial cancer, the antiestrogenic effect of cigarette smoking and other factors that have been reported to reduce the risk of endometrial cancer may well explain the reported inverse associations.

H. Esophageal Cancer

1. Three case-control studies have reported non-significant increased risks of esophageal cancer for consumption of coffee.

2. One cohort study reported an increased risk of squamous cell carcinoma of the esophagus, but a decreased risk of adenocarcinoma of the esophagus for consumption of coffee. (Ren 2010).

3. One meta-analysis showed a non-significant increased risk, while two reported decreased risks, one of which was statistically significant.

4. Subsequent studies reported mixed results.

I. Gastric Cancer

1. About half of 16 hospital-based case-control studies show a significantly elevated risk of gastric cancer. About half of 8 population-based case-control studies show non-significantly elevated risk of gastric cancer.

2. Eight of sixteen cohort studies showed an elevated risk, with four studies showing a significantly elevated risk. None showed a significant deficit overall, however, one study showed a significant deficit in women only.

3. Of 10 meta-analyses, all showed increased risks with 6 demonstrating significantly elevated risks.

J. Kidney Cancer (Renal Cell Carcinoma)

1. Some case-control studies have reported significantly increased risks of kidney cancer in relation to coffee consumption. At least 5 case-control studies have demonstrated a positive dose-response. In the most recent study, Mayo Clinic investigators observed an inverse association with caffeinated coffee, but an increased risk with decaffeinated coffee, particularly with the more aggressive subtype. (Antwi 2017). Other case-control studies have reported increased risks of kidney cancer for coffee consumption that did not achieve statistical significance.

2. While most cohort studies have not reported increased risks for coffee consumption, the recent EPIC cohort study reported a monotonic increase in the risk of kidney cancer for both men and women. (Gunter 2017).

3. Meta-analyses regarding coffee consumption and kidney cancer have not reported either significant increased or decreased risks of kidney cancer.

K. Laryngeal Cancer

1. Of 13 case-control studies evaluating the risk of coffee consumption and laryngeal cancer, 9 reported increased risks (3 statistically significant) and 3 nonsignificantly decreased risks.

2. One cohort study indicated a risk close to unity.

3. Four meta-analyses regarding coffee consumption and laryngeal cancer have been published. All of these report increased risks, one of which is statistically significant.

L. Liver Cancer (Hepatocellular Carcinoma)

1. Epidemiologic studies generally report decreased risks of liver cancer in association with consumption of coffee.

2. Many of the studies did not control for hepatitis infections, liver disease, and other chronic diseases that have been associated with liver cancer.

3. Several studies report an inverse relationship between coffee drinking and liver cirrhosis. Individuals with liver cirrhosis have been reported to decrease their coffee consumption, which suggests that the inverse association between coffee consumption and liver cancer may be due to reverse causation, as is mentioned by the authors of several of the studies.

4. The inverse association between coffee consumption and liver cancer may also be due to exposure misclassification.

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

6. The inverse association between coffee consumption and liver cancer may also be due to confounding by uncontrolled or unknown factors. For example, none of the epidemiologic studies regarding consumption of coffee have evaluated whether the decreased risks of liver cancer may be due to consumption of heat-purified water from brewing or boiling coffee which results reduction of intake of waterborne microorganisms that have been associated with the development of liver disease and liver cancer.

M. Lung Cancer

1. Five case-control studies demonstrate significantly increased risks of lung cancer in relation to coffee consumption. Three indicate a dose-response.

2. Most cohort studies indicate elevated risks of lung cancer; 9 of the studies report significantly increased risks, with 3 indicating a dose response.

3. Four of five meta-analyses regarding coffee consumption and lung cancer demonstrate significantly elevated risks. In some studies, adjustment for cigarette smoking decreased the risk to a non-statistically significant excess or no excess at all, while in other studies adjustment for cigarette smoking resulted in the elevated risk remaining statistically significant.

4. The recent EPIC cohort study adjusted for cigarette smoking and still showed a significant positive monotonic dose response. (Gunter 2017).

N. Non-Hodgkin Lymphoma

1. The risk of NHL was significantly elevated in 5 of 12 case-control studies. Two of these studies demonstrated a significant dose-response.

2. Of the 3 cohort studies regarding coffee consumption and NHL, increased risks were reported in two studies, one of which found a 3-fold significant excess for consumption of 3 to 4 cups of coffee per day. (Stensvold 1994).

3. Two meta-analyses of coffee consumption and NHL reported elevated risks ranging between 1.23 and 1.29 that were not statistically significant.

4. Overall, the studies suggest an elevated risk for consumption of coffee, but too few studies have been published to determine causality.

O. Oropharyngeal Cancer

1. Some case-control and cohort studies have reported significantly reduced risks of oropharyngeal cancer, while others have shown nonsignificantly increased risks.

2. The studies have neither controlled nor adjusted for many factors that have been reported to significantly reduce or increase the risk of oropharyngeal cancer. Therefore, one cannot conclude scientifically that the decreased risks are causally related to consumption of coffee.

P. Ovarian Cancer

1. Most of the case-control studies of coffee consumption and ovarian cancer reported increased risks for the highest level of consumption.

2. Most of the cohort studies regarding coffee consumption and ovarian cancer reported nonsignificantly increased risks for the highest level of consumption. However, the recent EPIC cohort study of participants from 10 European countries reported a statistically significant positive dose response for coffee consumption and ovarian cancer. (Gunter 2017).

3. Three meta-analyses have been published, all reporting nonsignificantly increased risks of ovarian cancer in relation to consumption of coffee.

Q. Pancreatic Cancer

1. Twelve case-control studies indicate statistically significant elevated risks of pancreatic cancer. Eleven show dose-response relationships. Other studies indicate non-significant elevated risks, while none show a significant deficit. Four studies show significant associations in non-smokers.

2. More than 20 cohort studies regarding coffee consumption and pancreatic cancer have been published. Two report significant increased risks and also demonstrate dose-response relationships. Eight studies indicate risks above unity, with 5 indicating statistically significant elevated risks.

3. Of 5 meta-analyses based on cohort studies, 3 indicate a significantly decreased risk of pancreatic cancer and 2 show risks at unity. One meta-analysis based on 37 case-control studies and 17 cohort studies indicated a borderline significant increase in risk.

R. Prostate Cancer

1. Some case-control studies indicate significantly elevated risks of prostate cancer in relation to coffee consumption.

2. Cohort studies indicate no association and in some cases a reduced risk. The EPIC cohort indicates a risk around unity (Gunter 2017).

3. Meta-analyses based on case-control studies indicate increased risks for prostate cancer, while those meta-analyses based on cohort studies report lower risks that are sometimes statistically significant.

S. Skin Cancer

1. Of the few case-control studies regarding coffee consumption and skin cancer, one study reported increased risks of basal cell carcinoma in men and women and another reported increased risks of cutaneous melanoma.

2. An early cohort study reported a 3½-fold increased risk of melanoma in association with coffee consumption, with a statistically significant linear trend. Other cohort studies have reported increased risks in men, but not women and for decaffeinated, but not caffeinated, coffee.

3. Six meta-analyses, all published in 2016 and largely based on the same studies, report inverse associations of coffee consumption and skin cancer.

4. Epidemiologic studies of coffee consumption and skin cancer are subject to multiple confounding factors, especially cigarette smoking which has been reported to reduce the risk of melanoma in three meta-analyses.

T. Thyroid Cancer

1. Case-control and cohort studies regarding coffee consumption and thyroid cancer have not indicated any significantly elevated or decreased risks.

2. The only meta-analysis published regarding coffee consumption and thyroid cancer likewise reports no significant association.

U. Total Cancer

1. Of 14 cohort, 4 studies showed a significant positive association, 3 studies indicated non-significant elevated risks, 6 studies showed no association, and 1 study showed an inverse association with total cancer mortality.

2. The recent large EPIC cohort study demonstrated a significant increase in total cancer 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). (Gunter 2017).

III. CONCLUSIONS

A. Epidemiological studies regarding consumption of coffee have reported increased risks for bladder cancer, childhood acute leukemia, childhood brain cancer, colorectal cancer, gastric cancer, kidney cancer, laryngeal cancer, lung cancer, non-Hodgkin lymphoma, ovarian cancer, pancreatic cancer, and prostate cancer.

B. Epidemiological studies regarding consumption of coffee have reported inverse associations for endometrial cancer, liver cancer, skin cancer.

C. Epidemiological studies regarding consumption of coffee have reported little association for brain cancer, breast cancer, esophageal cancer, oropharyngeal cancer, and thyroid cancer.

D. The epidemiologic studies regarding coffee consumption and cancer are all observational studies that suffer from confounding by known and unknown factors, measurement error and numerous other forms of bias, as well as chance.

E. Nutritional epidemiology studies present special problems in attempting to determine causal effects of coffee, because it is generally considered to be extremely difficult, if not impossible, to evaluate the effect of a single food item among all foods and beverages that people consume as part of their diet in observational studies, no matter how large and how well they attempt to control for innumerable dietary and other confounding factors as well as bias.

Appendix: Confounding Factors for Cancer Sites

Bladder Cancer

Factors Reported to Increase Risk
2-mercaptobenzothiazole
2-naphthylamine
4-Aminobiphenyl
4-chloro-ortho-toluidine
aluminum production
arsenic and inorganic arsenic compounds
auramine production
benzidine
benzidine based dyes
beta-naphthalene
chlornaphazine
cigarette smoking
coal-tar pitch
cyclophosphamide
dry cleaning
engine exhaust, diesel
gamma irradiation
hairdressers and barbers, occupational exposure
magenta production
ortho-toluidine
painting
perchloroethylene
pioglitazone
printing processes
rubber production industry
schistosoma haematobium
soot
textile manufacturing
x-radiation

Factors Reported to Decrease Risk
tea
uncontaminated water

Brain Cancer

Factors Reported to Increase Risk
radiofrequency, electromagnetic fields (including from wireless phones)
gamma-radiation
x-radiation

Factors Reported to Decrease Risk
Tea

Breast Cancer

Factors Reported to Increase Risk
alcohol intake
cigarette smoking
dieldren
diethylstilbestrol
digoxin
early menarche
estrogen-progestogen contraceptives
estrogen-progestogen menopausal therapy
ethylene oxide
high total energy intake
later age at menopause
obesity
polychorinated biphenyls
saturated fat
shiftwork that involves circadian disruption
x-radiation, gamma radiation

Factors Reported to Decrease Risk
black tea
breast feeding
calcium
carotenoids
dietary fiber
early age at first pregnancy
fatty acids
fish
flavan-3-ols
folate
fruit
green tea
mediterranean diet
multiple pregnancies
physical activity
soy
uncontaminated water
vegetables
vitamin B, vitamin C, vitamin D

Childhood Leukemia

Factors Reported to Increase Risk
benzene
gasoline
ionizing radiation
petrochemical exposures

Factors Reported to Decrease Risk
Tea

Colorectal Cancer

Factors Reported to Increase Risk
alcohol
asbestos
cigarette smoking
cooking meats at high temperature
familial diagnosis of colorectal cancer or polyps
gamma radiation
inflammatory bowel disease
obesity
processed meat
red meat
type-2 diabetes
x-radiation

Factors Reported to Decrease Risk
aspirin
bisphosphonates
cruciform vegetables
dietary fiber
flavonoids
fruits
garlic
green tea
isoflavones
Mediterranean diet
menopausal hormone therapy
nuts
omega-3 fatty acids
oral contraceptives
physical activity
soy
statins
uncontaminated water
vitamins (B2, D, magnesium, zinc)
whole grain

Endometrial Cancer

Factors Reported to Increase Risk
diabetes
estrogen and estrogen-progestogen menopausal therapy
obesity
tamoxifen

Factors Reported to Decrease Risk
aspirin
bisphosphonates
breastfeeding.
cigarette smoking
dietary fiber increase
fruits
green tea
increased age at last birth
Intrauterine devices
latest age menarchy
mediterranean diet
oral contraceptives.
parity (more pregnancies)
physical activity
tea
vegetables

Esophageal Cancer

Factors Reported to Increase Risk
alcoholic beverages
betel quid
cigarette smoking
drycleaning
gamma-radiation
obesity
rubber production industry
smokeless tobacco
very hot temperature beverages
x-radiation

Factors Reported to Decrease Risk
fresh fish
fruits
green tea
Mediterranean diet
vegetables

Gastric Cancer

Factors Reported to Increase Risk
asbestos
cigarette smoking
Epstein-Barr virus
gamma radiation
helicobacter pylori
inorganic lead compounds

n-nitroso-compounds
nitrite in food
obesity
pickled vegetables (traditional Asian)
processed meat
rubber production industry
salted fish (Chinese style)
uncontaminated water
x-radiation

Factors Reported to Decrease Risk
garlic
green tea

Kidney Cancer (Renal Cell Carcinoma)

Factors Reported to Increase Risk
aristolochic acid, plants containing
arsenic and inorganic arsenic compounds
cadmium and cadmium compounds
cigarette smoking
diabetes mellitus
family history of kidney cancer
gamma radiation
height
hypertension
hysterectomy
obesity
parity (high)
pentachlorophenol
phenacetin analgesic mintures
printing processes
prior kidney stones
trichloroethylene
use of analgesics
x-radiation

Factors Reported to Decrease Risk
alcohol consumption
consumption of cruciferous vegetables
consumption of dietary fiber
folic acid
oral contraceptive use
physical activity
Vitamin E
Vitamin B2, B6, and B12

Laryngeal Cancer

Factors Reported to Increase Risk
alcoholic beverages
asbestos
cigarette smoking
tobacco smoke, second hand
acid mists, strong inorganic
human papilliomavirus type 16
rubber production industry

Liver Cancer (Hepatocellular Carcinoma)

Factors Reported to Increase Risk
1,2- dichloropropane
aflatoxins
alcohol
androgenic (anabolic) steroids
betel quid
chronic liver disease
cigarette smoking
cyanotoxins
DDT
dichloromethane
estrogen-progestogen contraceptives
gamma radiation
hepatitis viruses
HIV type 1
inorganic arsenic
obesity
road, ditch and river water
schistosome japonicum
trichloroethylene
type-2 diabetes
vinyl chloride
x-radiation

Factors Reported to Decrease Risk
green tea
tea
uncontaminated water

Lung Cancer

Factors Reported to Increase Risk
arsenic
asbestos
beryllium

bischloromethyl ether
cadmium
chloromethyl methyl ether
chromium
cigarette smoking
coal gasification
coal-tar pitch
coke production
diesel engine exhaust
environmental tobacco smoke
hematite mining
iron and steel founding
MOPP
nickel
painting
radon daughters
rubber production
silica dust
silicon carbide fibers
soot

Factors Reported to Decrease Risk
black tea
green tea
tea

Non-Hodgkin Lymphoma

Factors Reported to Increase Risk
2,4-D
benzene
benzene-containing petrochemicals
dichloromethane
Epstein-Barr virus
ethylene oxide
gamma radiation
glyphosate
Hepatitis B virus
Hepatitis C virus
lindane
obesity
organic solvents
other insecticides
phenoxyacetic acid herbicides
trichloroethylene
x-radiation

Oropharyngeal Cancer

Factors Reported to Increase Risk
alcoholic beverages
asbestos
betel quid
cigarette smoking
human papilloma virus types 16 and 18
smokeless tobacco

Factors Reported to Decrease Risk
antioxidant vitamins
calcium supplements
carotenoid intake
egg consumption among never-smokers
fats dietary pattern
fiber
flavan-3-ols
folate
fruit
garlic
good oral hygiene
high recreational physical activity among persons 45 years or older
Mediterranean diet
moderate recreational physical activity
tea
vegetables
Vitamin E
Vitamin C

Ovarian Cancer

Factors Reported to Increase Risk
asbestos (serous subtype)
BRCA 1 and BRCA 2 gene mutation
cigarette smoking (mucinous subtype)
estrogen hormone replacement
family history of ovarian cancer
fertility diagnosis
obesity
polycystic ovary syndrome
talc (serous type)

Factors Reported to Decrease Risk
Tea
Green tea
Parity

Pancreatic Cancer

Factors Reported to Increase Risk
alcoholic beverages
chronic pancreatitis
cigarette smoking
cirrhosis of the liver
diabetes
helicobacter pylori infection
hepatitis B virus
obesity
red meat
saturated fats
sedentary lifestyle
smokeless tobacco

Factors Reported to Decrease Risk
dietary folate
tea

Prostate Cancer

Factors Reported to Increase Risk
alphalinolenic acid
androgenic (anabolic) steriods
cadmium and cadmium compounds
calcium
dairy products
family history prostate cancer
fish
inorganic arsenic
malathion
multivitamin supplements (aggressive form prostate cancer)
obesity
phytoestrogens
red meat (aggressive form of prostate cancer)
rubber production industry
Vitamin D, Vitamin E

Factors Reported to Decrease Risk
green tea
physical activity

Skin Cancer

Factors Reported to Increase Risk
arsenic in drinking water
azathioprine
coal tar pitch
coal-tar distillation
creosotes
cyclosporine
fair skin
family history of skin cancer
freckling
gamma radiation
HPV types 5 and 8,
hydrochlorothiazide
light hair
methoxsalen plus ultraviolet A
mineral oils
nevi
nitrogen mustard
petroleum refining
polychlorinated biphenyls
shale oils
solar radiation
soot
ultraviolet-emitting tanning devices
x-radiation

Factors Reported to Decrease Risk
antioxidants and mineral supplementation
aspirin
carrots
cigarette smoking
cruciferous and leafy vegetables
fruits
non-steroidal anti-inflammatory drugs
vegetables

Thyroid Cancer

Factors Reported to Increase Risk
gamma radiation
radioiodines, including iodine-131
x-radiation

Factors Reported to Decrease Risk
tea

EXHIBIT “C”

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT NO. 323 HON. ELIHU M. BERLE, JUDGE

COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS,

PLAINTIFF,

VS. NO. BC435759

STARBUCKS CORPORATION, ET AL.,

DEFENDANTS.

AND CONSOLIDATED ACTION.

REPORTER'S TRANSCRIPT OF TRIAL PROCEEDINGS

MONDAY, OCTOBER 20, 2014

MORNING SESSION

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OFFICIAL REPORTER PRO TEM

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MORNING SESSION

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1 CASE NUMBER: BC435759
2 CASE NAME: CERT VS. STARBUCKS
3 DEPARTMENT: 323 HON. ELIHU M. BERLE
4 REPORTER: DANA SHELLEY, RPR, CSR #10177
5 LOS ANGELES, CALIFORNIA MONDAY, OCTOBER 20, 2014
6 TIME: 9:40 A.M.
7 APPEARANCES: (AS HERETOFORE NOTED.)
8
9 THE COURT: GOOD MORNING, AGAIN, ON THE CERT VS.
10 STARBUCKS CASE. WE'RE BACK ON THE RECORD. ALL COUNSEL
11 ARE PRESENT, AND WE'RE READY FOR THE NEXT WITNESS.
12 BEFORE WE DO THAT, LET ME DISCUSS --
13 HAVE A SEAT. MAKE YOURSELVES COMFORTABLE.
14 LET ME DISCUSS A COUPLE OF OTHER MATTERS.
15 WE HAVE PLAINTIFF'S REQUEST FOR A JUDICIAL
16 NOTICE OF PORTIONS OF WHAT'S CALLED A BRIEFING BINDER
17 AND ACCOMPANYING PUBLICATIONS FROM THE U.S. EPA.
18 ANYONE WISH TO BE HEARD ON THAT?
19 MR. METZGER: YES, YOUR HONOR.
20 SO IN PARTICULAR, WE'RE SEEKING JUDICIAL
21 NOTICE OF A FEW DOCUMENTS, GOVERNMENT DOCUMENTS. AND
22 THE BASIS FOR THE LISTING OF ACRYLAMIDE AS KNOWN TO THE
23 STATE TO CAUSE CANCER, IT'S BECOME ESPECIALLY RELEVANT
24 IN THIS CASE.
25 BECAUSE YOU MAY RECALL THAT THE REGULATIONS
26 INDICATE THAT IF ONE IS GOING TO DO A RISK ASSESSMENT
27 THAT'S NOT BASED ON A -- A QUANTITATIVE RISK ASSESSMENT,
28 AS PROVIDED IN THE REGULATIONS, SUCH AN ASSESSMENT HAS

1 TO BE BASED ON EVIDENCE AND STANDARDS OF COMPARABLE
2 SCIENTIFIC VALIDITY TO THOSE EVIDENCE AND STANDARDS
3 WHICH FORM THE BASIS OF THE LISTING.
4 SO WE NEED TO KNOW WHAT THE BASIS OF THE
5 LISTING WAS -- THE COURT NEEDS TO KNOW THAT, IN
6 EVALUATING THE CASE. SO THAT'S WHY WE'RE REQUESTING
7 JUDICIAL NOTICE.
8 THE COURT: WELL, I DIDN'T HEAR A REASON WHY --
9 BUT WHAT'S THE STORY ABOUT THIS BRIEFING BINDER? WHAT
10 KIND OF DOCUMENT IS THAT?
11 MR. METZGER: WELL, THIS IS JUST A BINDER THAT THE
12 OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT PUT
13 TOGETHER WHEN THEY WERE DOING AN EVALUATION OF
14 ACRYLAMIDE IN 2003.
15 AND IT'S NOT SO MUCH THE BINDER THAT WE'RE
16 SEEKING JUDICIAL NOTICE OF. IT'S REALLY THE MEMORANDUM,
17 WHICH WAS PART OF IT. IF YOU LOOK, THERE'S A MEMORANDUM
18 DATED FEBRUARY 27, 1990.
19 THE COURT: RIGHT. I MEAN, SO WHAT'S THE DIGNITY
20 WE HAVE TO GIVE TO A MEMORANDUM?
21 MR. METZGER: WELL, THIS IS A MEMORANDUM PREPARED
22 BY THE -- IS IT THE "DEPUTY"; IT'S HARD TO READ -- THE
23 DEPUTY HEAD OF THE DEPARTMENT OF HEALTH SERVICES OF THE
24 STATE OF CALIFORNIA, WHICH SETS FORTH THE BASIS FOR THE
25 LISTING.
26 THE COURT: I'LL HEAR FROM THE DEFENDANT --
27 MR. METZGER: IF YOU SEE, IT SAYS THAT -- IN THE
28 MEMORANDUM:

1 "THE ENVIRONMENTAL PROTECTION AGENCY HAS
2 PUBLISHED CANCER POTENCY EVALUATIONS FOR
3 SEVERAL CHEMICALS LISTED AS CARCINOGENS UNDER
4 THE ACT."
5 SO WE HAVE THIS, WHICH SHOWS THAT AND WHEN
6 THAT OCCURRED.
7 THE COURT: WELL --
8 MR. METZGER: AND THEN, IN PARTICULAR, THERE'S THE
9 REFERENCES LISTED, WHICH INCLUDES THE INTEGRATED RISK
10 INFORMATION SYSTEM, REFERENCE NO. 1 OF THE EPA. AND
11 THAT IS THEN ATTACHED. AND THAT SHOWS THE BASIS FOR THE
12 LISTING.
13 THE COURT: ALL RIGHT. THANK YOU.
14 DEFENDANTS?
15 MS. CORASH: YES. GOOD MORNING, YOUR HONOR.
16 YOUR HONOR, THIS MEMORANDUM WHICH PLAINTIFF
17 SEEKS TO HAVE JUDICIALLY NOTICED IS A MEMORANDUM WRITTEN
18 NOT BY THE DEPUTY SECRETARY AT ALL BUT BY SOMEONE WHO
19 DESCRIBES HIMSELF AS "SCIENCE ADVISOR TO THE SECRETARY."
20 IT REFLECTS THE VIEWS OF A SINGLE STAFF MEMBER. IT'S
21 NOTHING BUT HEARSAY.
22 ACRYLAMIDE -- THE LISTING OF ACRYLAMIDE IS A
23 REGULATORY ACT. AND IF MR. METZGER WANTS TO TALK ABOUT
24 THE BASIS FOR LISTING ACRYLAMIDE AND REFER THE COURT TO
25 THE BASIS FOR THAT LISTING, THOSE MATERIALS ARE
26 AVAILABLE AS PART OF THE RECORD FOR LISTING ACRYLAMIDE.
27 THESE MATERIALS WERE ASSEMBLED BY OEHHA
28 STAFF IN CONNECTION WITH A PROPOSED RULE-MAKING. THE

1 RULE-MAKING PROPOSED WAS WITHDRAWN, ALONG WITH THE
2 MATERIALS THAT WERE PREPARED IN SUPPORT OF IT.
3 SO THESE MATERIALS ARE NOT AN OFFICIAL ACT,
4 WHICH IS A REQUIREMENT FOR JUDICIAL NOTICE. THEY ARE
5 SIMPLY THE VIEWS OF A SINGLE STAFFER. NONE OF US COULD
6 RELY ON THEM, WHETHER IT'S PROSECUTORS OR WHETHER IT'S
7 DEFENDANTS.
8 NONE OF US WOULD BE ENTITLED TO RELY ON
9 THESE MATERIALS BECAUSE THEY ARE NOT THE ACT OF THE
10 AGENCY OR OF ANY OTHER PART OF GOVERNMENT.
11 THE COURT: THE COURT IS GOING TO SUSTAIN THE
12 OBJECTION TO THE REQUEST FOR JUDICIAL NOTICE. IT DOES
13 NOT APPEAR THAT THESE MATERIALS, THIS BRIEFING BINDER
14 AND ACCOMPANYING MEMORANDUM, ARE OFFICIAL GOVERNMENT
15 PUBLICATIONS; AND THEREFORE, THEY'RE NOT OFFICIAL ACTS,
16 UNDER EVIDENCE CODE SECTION 452.
17 MR. METZGER: YOUR HONOR --
18 THE COURT: THE NEXT ITEM IS A REQUEST FOR
19 JUDICIAL NOTICE OF U.S. EPA GUIDELINES.
20 MR. METZGER: YOUR HONOR, COULD I JUST REQUEST
21 THAT THAT RULING BE WITHOUT PREJUDICE TO US BRINGING A
22 REQUEST FOR JUDICIAL NOTICE JUST OF THE IRIS DOCUMENT,
23 THE EPA DOCUMENT --
24 THE COURT: YES.
25 MR. METZGER: -- WHICH IS ATTACHED?
26 THE COURT: YES.
27 MR. METZGER: THANK YOU.
28 THE COURT: AND IT'S WITHOUT PREJUDICE.

1 AND THEN THE NEXT REQUEST IS FOR JUDICIAL
2 NOTICE OF U.S. EPA GUIDELINES.
3 ANYONE WISH TO BE HEARD ON THAT?
4 MR. METZGER: YES, YOUR HONOR.
5 THIS IS -- THE COURT HAS ALREADY GRANTED
6 JUDICIAL NOTICE OF OTHER EPA GUIDELINES FOR RISK
7 ASSESSMENT. IN PARTICULAR, THIS ONE ON PAGE 5, STATES
8 THAT, REGARDING TRANSPLACENTAL CARCINOGENESIS, THAT IT
9 IS CONSIDERED APPROPRIATE TO USE THE GUIDELINES FOR
10 CARCINOGEN RISK ASSESSMENT FOR ASSESSING THAT RISK.
11 AND THE COURT HAS ALREADY JUDICIALLY NOTICED
12 THOSE GUIDELINES FOR CARCINOGEN RISK ASSESSMENT. WE'RE
13 SEEKING JUDICIAL NOTICE OF THIS DOCUMENT, IN PARTICULAR,
14 BECAUSE THIS EXPRESSES THE VIEW OF THE EPA, THE U.S.
15 EPA, THAT FOR TRANSPLACENTAL CARCINOGENESIS RISK
16 ASSESSMENT, ONE SHOULD USE THE GUIDELINES FOR CARCINOGEN
17 RISK ASSESSMENT.
18 THE COURT: ALL RIGHT. THANK YOU.
19 DEFENDANTS?
20 MS. CORASH: YES.
21 YOUR HONOR, IT IS CERTAINLY THE CASE THAT
22 THERE ARE INSTANCES IN WHICH IT IS APPROPRIATE TO LOOK,
23 IN INTERPRETING PROP 65, TO HOW OTHER HEALTH REGULATORY
24 AGENCIES OR TO HOW INTERNATIONAL AGENCIES DEAL WITH A
25 SUBJECT WHICH IS DESCRIBED IN SUBJECTIVE TERMS.
26 HERE, PLAINTIFF SEEKS JUDICIAL NOTICE OF
27 THESE EPA GUIDELINES AND ASSERTS, AS THE RELEVANCE OF
28 THOSE GUIDELINES, THAT THEY'RE RELEVANT TO INTERPRETING

1 HOW TRANSPLACENTAL CARCINOGENICITY IS DEALT WITH UNDER
2 PROPOSITION 65.
3 IN THIS INSTANCE, THAT ISSUE HAS BEEN
4 DIRECTLY AND EXPLICITLY ADDRESSED BY OEHHA BY THE FINAL
5 STATEMENT OF REASONS UNDERLYING THE REGULATIONS AND BY
6 THE SCIENCE PANEL'S OWN GUIDELINES.
7 THERE IS NO AMBIGUITY HERE. IT IS PERFECTLY
8 CLEAR HOW PROPOSITION 65 DEALS WITH TRANSPLACENTAL
9 CARCINOGENICITY. AND IN THOSE CIRCUMSTANCES, THE FACT
10 THAT EPA OR ANYONE ELSE HAS A DIFFERENT VIEW IS
11 IRRELEVANT TO THE ISSUE BEFORE THIS COURT.
12 AND ONE THING THE PARTIES DO AGREE ON IS
13 THAT JUDICIAL NOTICE IS APPROPRIATE AND CAN BE GIVEN
14 ONLY AS TO RELEVANT MATERIALS. THESE MATERIALS ARE NOT
15 RELEVANT TO THE ISSUE OF TRANSPLACENTAL CARCINOGENICITY.
16 THE COURT: THANK YOU.
17 THE COURT IS GOING TO GRANT JUDICIAL NOTICE
18 OF THESE DOCUMENTS, WHICH ARE U.S. EPA'S GUIDELINES,
19 UNDER EVIDENCE CODE SECTION 452, AS BEING OFFICIAL
20 PUBLICATIONS AND THEREFORE ACTS OF GOVERNMENTAL
21 AUTHORITY.
22 HOWEVER, IT'S WITHOUT PREJUDICE TO
23 DEFENDANTS ARGUING THAT THEY'RE NOT RELEVANT AND NOT
24 CONCLUSIVE ON THIS COURT AND NOT -- WITHOUT PREJUDICE TO
25 ARGUING WHAT WEIGHT, IF ANY, SHOULD BE GIVEN TO THOSE
26 DOCUMENTS.
27 MS. CORASH: THANK YOU, YOUR HONOR.
28 THE COURT: ALL RIGHT. MR. METZGER, ARE YOU GOING

1 TO CALL YOUR NEXT WITNESS?
2 MR. METZGER: YES. THE PLAINTIFFS WOULD CALL DR.
3 PETER INFANTE, WHO IS ON THE STAND.
4 THE COURT: GOOD MORNING.
5 THE CLERK: SIR, WILL YOU PLEASE STAND AND RAISE
6 YOUR RIGHT HAND.
7
8 PETER FRANCIS INFANTE,
9 CALLED AS A WITNESS BY THE PLAINTIFF, WAS SWORN AND
10 TESTIFIED AS FOLLOWS:
11 THE CLERK: THANK YOU. PLEASE BE SEATED.
12 WILL YOU STATE AND SPELL YOUR NAME FOR THE
13 RECORD.
14 THE WITNESS: YES. PETER FRANCIS INFANTE: I-N-F,
15 AS IN FRANK, -A-N-T-E.
16 THE COURT: GOOD MORNING, DR. INFANTE.
17 THE WITNESS: GOOD MORNING, YOUR HONOR.
18 THE COURT: COUNSEL, MR. METZGER, YOU MAY PROCEED.
19 MR. METZGER: THANK YOU, YOUR HONOR.
20
21 DIRECT EXAMINATION
22 BY MR. METZGER:
23 Q GOOD MORNING, DR. INFANTE.
24 A GOOD MORNING.
25 Q YOU'RE AN EPIDEMIOLOGIST?
26 A YES.
27 Q I'D LIKE TO SHOW YOU WHAT'S BEEN MARKED AS
28 EXHIBIT 214. AND WOULD YOU CONFIRM THAT THIS IS YOUR

1 CURRICULUM VITAE.
2 A YES, IT IS. I'M JUST CHECKING TO SEE IF YOU
3 HAVE THE MOST UPDATED VERSION.
4 Q THAT'S OKAY.
5 AND DOES THIS CURRICULUM VITAE LIST YOUR
6 QUALIFICATIONS, YOUR EDUCATIONAL BACKGROUND, THE
7 POSITIONS THAT YOU'VE HELD, AND YOUR PUBLICATIONS?
8 A YES.
9 MR. METZGER: ALL RIGHT. YOUR HONOR, I WOULD
10 OFFER EXHIBIT 214 IN EVIDENCE.
11 THE COURT: ANY OBJECTION?
12 MR. SCHURZ: NO OBJECTION, YOUR HONOR.
13 THE COURT: EXHIBIT 214 IS ADMITTED INTO EVIDENCE.
14 (EXHIBIT 214 MARKED FOR IDENTIFICATION
15 AND RECEIVED IN EVIDENCE.)
16 Q BY MR. METZGER: DR. INFANTE, I'M GOING TO
17 SHOW YOU SOME DOCUMENTS SO THAT WE CAN HAVE THEM BE
18 IDENTIFIED.
19 FIRST I'M GOING TO SHOW YOU WHAT'S BEEN
20 MARKED AS EXHIBIT 215. AND WOULD YOU CONFIRM FOR THE
21 COURT THAT THIS IS A LIST OF WRITTEN OPINIONS THAT YOU
22 FORMED FOR THIS CASE THAT WAS PRODUCED AT YOUR
23 DEPOSITION.
24 A (REVIEWS DOCUMENT.)
25 YES.
26 Q OKAY.
27 A YES, IT IS.
28 (EXHIBIT 215 MARKED FOR IDENTIFICATION.)

1 Q BY MR. METZGER: I'M GOING TO SHOW YOU
2 WHAT'S BEEN MARKED AS EXHIBIT 222. AND WOULD YOU
3 CONFIRM FOR THE COURT THAT THIS IS A -- THAT THESE ARE
4 NOTES SETTING FORTH DATA REGARDING EPIDEMIOLOGIC STUDIES
5 OF MATERNAL COFFEE CONSUMPTION AND CHILDHOOD LEUKEMIA
6 THAT YOU PREPARED FOR THIS CASE.
7 A (REVIEWS DOCUMENT.)
8 Q ACTUALLY, LET ME REPHRASE THAT. THIS
9 ACTUALLY CONTAINS SEVERAL MATERIALS.
10 DO THE FIRST -- ARE THESE NOTES REGARDING
11 VARIOUS EPIDEMIOLOGIC STUDIES THAT YOU PREPARED FOR THIS
12 CASE?
13 A YES. I PREPARED THIS -- THESE LISTS.
14 (EXHIBIT 222 MARKED FOR IDENTIFICATION.)
15 Q BY MR. METZGER: OKAY. RIGHT. AND IF WE
16 JUST TAKE A LOOK AT -- THE FIRST TWO PAGES ARE
17 CONCERNING MATERNAL CONSUMPTION OF COFFEE DURING
18 PREGNANCY, AND CHILDHOOD LEUKEMIA; IS THAT CORRECT?
19 A YES.
20 Q I SEE AT THE BOTTOM OF THE SECOND PAGE YOU
21 HAVE SOME NOTES REGARDING CENTRAL NERVOUS SYSTEM TUMORS
22 FROM MATERNAL CONSUMPTION OF COFFEE; IS THAT CORRECT?
23 A YES.
24 Q ALL RIGHT. AND THEN THE THIRD PAGE IS --
25 THIRD, FOURTH, AND FIFTH PAGE AND SIXTH PAGE CONCERN
26 EPIDEMIOLOGIC STUDIES OF COFFEE CONSUMPTION AND BLADDER
27 CANCER; IS THAT CORRECT?
28 A YES. THOSE ARE THE RESULTS OF THOSE

1 STUDIES.
2 Q RIGHT. THIS IS ALSO IMPORTANT DATA THAT YOU
3 EXTRACTED FROM THE STUDIES?
4 A CORRECT.
5 Q AND THEN THE LAST PAGES ARE CONCERNING THE
6 EPIDEMIOLOGIC STUDIES OF COFFEE CONSUMPTION AND
7 PANCREATIC CANCER; IS THAT CORRECT?
8 A YES.
9 Q VERY GOOD.
10 I'LL SHOW YOU WHAT'S BEEN MARKED AS EXHIBIT
11 223. WOULD YOU CONFIRM FOR THE COURT THAT THESE ARE
12 LIKEWISE NOTES THAT YOU MADE OF DATA FROM THE
13 EPIDEMIOLOGIC STUDIES REGARDING COFFEE CONSUMPTION AND
14 LUNG CANCER.
15 A YES, THEY ARE.
16 (EXHIBIT 223 MARKED FOR IDENTIFICATION.)
17 Q BY MR. METZGER: ALL RIGHT. AND WOULD YOU
18 CONFIRM FOR THE COURT THAT EXHIBIT 224 ARE NOTES THAT
19 YOU PREPARED REGARDING META-ANALYSES OF COFFEE
20 CONSUMPTION AND VARIOUS CANCERS?
21 A (REVIEWS DOCUMENT.)
22 YES, I PREPARED THIS LIST.
23 (EXHIBIT 224 MARKED FOR IDENTIFICATION.)
24 Q BY MR. METZGER: OKAY. WOULD YOU ALSO
25 CONFIRM FOR THE COURT THAT EXHIBIT 225 IS A SINGLE PAGE
26 OF YOUR NOTES REGARDING COFFEE CONSUMPTION STUDIES AND
27 BLADDER CANCER, REGARDING THOSE STUDIES CONCERNING
28 DOSE-RESPONSE RELATIONSHIPS?

1 A (REVIEWS DOCUMENT.)
2 YES, I PREPARED THIS LIST.
3 Q AND IS THAT WHAT IT IS?
4 A YES.
5 (EXHIBIT 225 MARKED FOR IDENTIFICATION.)
6 Q BY MR. METZGER: ALL RIGHT. AND WOULD YOU
7 CONFIRM FOR COURT THAT EXHIBIT 226 IS A LIST OF STUDIES
8 THAT YOU PREPARED CONCERNING COFFEE CONSUMPTION AND
9 PANCREATIC CANCER, STUDIES SHOWING A POSITIVE DOSE
10 RESPONSE?
11 A YES, THAT'S WHAT IT IS. AND I PREPARED THE
12 LIST.
13 (EXHIBIT 226 MARKED FOR IDENTIFICATION.)
14 Q BY MR. METZGER: OKAY. WOULD YOU CONFIRM
15 FOR THE COURT ALSO THAT EXHIBIT 227 ARE NOTES THAT YOU
16 PREPARED REGARDING THE DATA FROM THE EPIDEMIOLOGIC
17 STUDIES OF COFFEE CONSUMPTION AND PANCREATIC CANCER.
18 A (REVIEWS DOCUMENT.)
19 YES, AND SEPARATED BY THE VARIOUS TYPES OF
20 ANALYSES THAT WERE DONE.
21 MR. METZGER: YES. ALL RIGHT.
22 (EXHIBIT 227 MARKED FOR IDENTIFICATION.)
23 Q BY MR. METZGER: AND WOULD YOU ALSO TAKE A
24 LOOK AT EXHIBIT 228 AND CONFIRM THAT THESE ARE NOTES
25 THAT YOU PREPARED REGARDING YOUR REVIEW OF EPIDEMIOLOGIC
26 STUDIES CONCERNING ACRYLAMIDE AND CANCER.
27 A (REVIEWS DOCUMENT.)
28 Q REGARDING POTATO CONSUMPTION AND CANCER, I

1 SHOULD SAY.
2 A YES, REGARDING POTATO CONSUMPTION AND
3 CANCER. THIS IS MY LIST.
4 (EXHIBIT 228 MARKED FOR IDENTIFICATION.)
5 Q BY MR. METZGER: ALL RIGHT. AND LASTLY,
6 WOULD YOU CONFIRM FOR THE COURT THAT EXHIBIT 229 ARE
7 YOUR NOTES REGARDING STUDIES -- EPIDEMIOLOGIC STUDIES OF
8 DIETARY EXPOSURE TO ACRYLAMIDE AND CANCER.
9 A YES, THIS IS MY LIST RELATED TO THE DIETARY
10 EPIDEMIOLOGY, MINUS THE POTATO STUDIES. THE PREVIOUS
11 ONE INCLUDED THE POTATO STUDIES.
12 (EXHIBIT 229 MARKED FOR IDENTIFICATION.)
13 Q BY MR. METZGER: AND DID YOU PRODUCE ALL OF
14 THESE NOTES, EXHIBITS 222 THROUGH 229, AT YOUR
15 DEPOSITION IN THIS CASE?
16 A YES, I DID.
17 Q AND WERE THEY MARKED AS EXHIBITS TO YOUR
18 DEPOSITION?
19 A YES.
20 Q ALL RIGHT. HAVE YOU PREPARED A POWERPOINT
21 PRESENTATION TO ELUCIDATE YOUR TESTIMONY FOR THIS CASE?
22 A YES.
23 Q DOES THAT POWERPOINT PRESENTATION TAKE THE
24 DATA THAT YOU HAVE IN THESE NOTES AND PUT IT IN THAT
25 POWERPOINT SO THAT WE CAN ALL SEE THE DATA AS WE'RE
26 GOING THROUGH YOUR TESTIMONY?
27 A YES.
28 Q ALL RIGHT.

1 AND WHAT IS THE EXHIBIT FOR THE POWERPOINT?
2 EXHIBIT -- HERE WE GO.
3 WOULD YOU CONFIRM THAT EXHIBIT 253 IS THE
4 POWERPOINT PRESENTATION THAT YOU PREPARED.
5 A YES, IT IS.
6 (EXHIBIT 253 MARKED FOR IDENTIFICATION.)
7 Q BY MR. METZGER: ALL RIGHT. WE'LL TALK
8 FIRST ABOUT SOME OF YOUR QUALIFICATIONS AND EXPERIENCE.
9 DR. INFANTE, WOULD YOU TELL US --
10 A EXCUSE ME. HOW DO I GET THIS ON?
11 Q I DON'T KNOW. IT SHOULD TURN ON.
12 (DISCUSSION HELD OFF THE RECORD.)
13 Q BY MR. METZGER: CAN YOU LOOK AT THE SCREEN
14 OVER THERE?
15 A YES.
16 MR. METZGER: PERHAPS WE COULD MOVE THE SCREEN
17 BACK A LITTLE BIT.
18 (DISCUSSION HELD OFF THE RECORD.)
19 Q BY MR. METZGER: IS THAT A LITTLE BIT MORE
20 VISIBLE?
21 A YES, I CAN SEE.
22 Q OKAY. ALL RIGHT. WOULD YOU TELL THE COURT
23 BRIEFLY ABOUT YOUR EDUCATIONAL BACKGROUND, DR. INFANTE.
24 A YES. I DON'T KNOW HOW FAR BACK YOU WANT ME
25 TO START, BUT --
26 Q WELL, JUST YOUR PROFESSIONAL -- YOUR COLLEGE
27 AND BEYOND THAT.
28 A YES. WELL, I GUESS I COULD GO BACKWARDS.

1 I HAVE A DOCTORATE IN PUBLIC HEALTH FROM THE
2 DEPARTMENT OF EPIDEMIOLOGY, THE UNIVERSITY OF MICHIGAN.
3 THEN ALSO, OF COURSE, A MASTER'S OF PUBLIC HEALTH I
4 RECEIVED BEFORE THE DOCTORAL DEGREE.
5 THEN FROM OHIO STATE UNIVERSITY,
6 GRADUATED --
7 THE COURT: ANY IRRECONCILABLE CONFLICT ON
8 MICHIGAN AND OHIO STATE?
9 THE WITNESS: WELL, ONE TIME A YEAR, I HAVE TO
10 DECIDE WHO TO ROOT FOR.
11 THE COURT: OKAY. COUNSEL.
12 Q BY MR. METZGER: SO DR. INFANTE, YOUR
13 GRADUATE WORK WAS IN PUBLIC HEALTH AND EPIDEMIOLOGY?
14 A YES, THAT'S CORRECT.
15 Q ALL RIGHT. AND BEFORE THAT, DID YOU HAVE
16 SOME OTHER EDUCATION IN THE MEDICAL FIELD?
17 A YES, I DID.
18 Q TELL US ABOUT THAT.
19 A WELL, I GRADUATED FROM OHIO STATE
20 UNIVERSITY, COLLEGE OF DENTISTRY, IN '66. AND THEN I
21 DID A TWO-YEAR INTERNSHIP AT THE CHILDRENS HOSPITAL OF
22 THE UNIVERSITY, FOR TWO YEARS, WHERE I TOOK CARE OF
23 CHILDREN FOR TWO YEARS.
24 AND I ALSO DID GENERAL ANESTHESIA AND WHAT
25 WAS CALLED AT THE TIME A HANDICAP CLINIC, WHERE HALF OF
26 A DAY EVERY DAY OF THE WEEK I TOOK CARE OF CHILDREN WHO
27 HAD VARIOUS TYPES OF HANDICAPPING CONDITIONS LIKE
28 LEUKEMIA, MENTAL RETARDATION, DOWN'S SYNDROME --

1 Q OKAY.
2 A -- EPILEPSY. HYDROCEPHALUS, AT THE TIME,
3 BECAUSE THERE WASN'T A WAY TO TREAT CHILDREN THAT HAD
4 BLOCKAGE OF FLUID IN THEIR BRAIN AT THAT TIME.
5 SO CHILDREN THAT HAD JUST ABOUT ANY TYPE OF
6 HANDICAPPING CONDITION, I TOOK CARE OF THEM IN THE
7 DENTAL CLINIC FIVE HALF-DAYS A WEEK.
8 Q AND EARLY IN YOUR CAREER, DID YOU PROVIDE
9 PUBLIC SERVICE TO CHILDREN FOR DENTAL ISSUES? DID YOU
10 DO SOME RESEARCH IN THAT AREA?
11 A YES. I DID RESEARCH IN CHILD GROWTH AND
12 DEVELOPMENT. I WAS PART OF THE NATIONAL PRESCHOOL
13 NUTRITIONAL SURVEY FROM 1968 TO 1970, WHERE I WENT ALL
14 OVER THE UNITED STATES EXAMINING PRESCHOOL CHILDREN.
15 AND I WAS LOOKING AT THEIR DENTAL
16 DEVELOPMENT AND DENTAL ISSUES IN RELATION TO THEIR
17 HEIGHT, WEIGHT, HEAD CIRCUMFERENCE, AND DIETARY INTAKE.
18 I WAS PART OF A TEAM THAT DID THAT.
19 Q OKAY. NOW, YOU SPENT MOST OF YOUR CAREER
20 PROVIDING GOVERNMENT -- FEDERAL GOVERNMENT SERVICE; IS
21 THAT CORRECT?
22 A STATE AND FEDERAL GOVERNMENT, YES.
23 Q OKAY.
24 A MOSTLY FEDERAL GOVERNMENT.
25 Q ALL RIGHT. WOULD YOU TELL US WHAT YOUR
26 FIRST POSITION WAS WITH THE FEDERAL GOVERNMENT AND WHAT
27 YOU DID.
28 A YES. BEGINNING IN 1975 TO 1978, I WORKED

1 FOR THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND
2 HEALTH.
3 AND I WAS AN EPIDEMIOLOGIST IN THE BIOMETRY
4 SECTION, WHICH IS A SECTION THAT DOES STUDIES OF WORKERS
5 EXPOSED TO VARIOUS SUBSTANCES AND CHEMICALS IN THE
6 WORKPLACE, TO DETERMINE WHETHER THEIR RISK IS OF VARIOUS
7 TYPES OF DISEASES; MOSTLY CANCER, HEART DISEASE.
8 AND THEN ALSO LOOKING AT REPRODUCTIVE
9 HAZARDS, AS WELL, IS ANOTHER AREA I SPECIALIZED IN
10 BECAUSE OF MY TRAINING IN CHILD GROWTH AND DEVELOPMENT
11 AND MY INTEREST IN THAT FIELD.
12 Q OKAY. AND WHAT WAS YOUR NEXT POSITION IN
13 THE FEDERAL GOVERNMENT?
14 A WELL, AFTER WORKING AT MY NIOSH FOR THREE
15 YEARS -- AND ONE OF THOSE YEARS, I WAS ACTING CHIEF OF
16 THE BIOMETRY SECTION, RESPONSIBLE FOR ALL OF THE
17 EPIDEMIOLOGICAL STUDIES THAT NIOSH WAS CARRYING OUT
18 THROUGHOUT THE COUNTRY -- THE INDUSTRYWIDE STUDIES
19 BRANCH WAS.
20 AND THEN SUBSEQUENT TO THAT, THEN I WAS
21 OFFERED A JOB AT OSHA, THE OCCUPATIONAL SAFETY AND
22 HEALTH ADMINISTRATION. SO I WENT TO OSHA. AND MY FIRST
23 JOB THERE WAS, I WAS DIRECTOR OF THE OFFICE OF
24 CARCINOGEN IDENTIFICATION AND CLASSIFICATION.
25 Q AND WHAT DID THAT INVOLVE?
26 A WELL, THAT, JUST AS THE DESCRIPTION OF THE
27 OFFICE IMPLIES, IS THE OFFICE THAT WOULD IDENTIFY AND
28 CLASSIFY SUBSTANCES FOUND IN THE OCCUPATIONAL SETTING AS

1 TO THEIR DEGREE OF CARCINOGENICITY; AND THEN MAKE
2 RECOMMENDATIONS TO THE SECRETARY OF LABOR, WHICH WAS
3 RECOMMENDED THAT SHOULD -- IN TERMS OF WHAT SHOULD BE
4 THE PRIORITY FOR REGULATING THEM.
5 Q AND DID YOU HAVE SUBSEQUENT POSITIONS WITH
6 OSHA?
7 A YES. THEN SUBSEQUENT TO THAT -- I THINK,
8 FOR THE NEXT 19 YEARS -- I WAS DIRECTOR OF THE OFFICE OF
9 STANDARDS REVIEW, IN THE HEALTH STANDARDS PROGRAM.
10 AND AS PART OF THAT -- WELL, THE JOB OF THAT
11 OFFICE WAS TO EVALUATE DATA FOR SUBSTANCES AND TO
12 DETERMINE RISK AND THEN TO SET STANDARDS FOR EXPOSURE TO
13 THOSE SUBSTANCES IN THE WORKPLACE BASED ON
14 EPIDEMIOLOGICAL DATA, INDUSTRIAL HYGIENE DATA, RISK
15 ASSESSMENTS.
16 AND SO I WAS INVOLVED IN ALL OF THOSE
17 ISSUES, EVALUATING STUDIES AS TO THE RISK OF CANCER,
18 MOSTLY. AND I WOULD QUANTIFY THAT RISK AND MAKE
19 RECOMMENDATIONS TO THE SECRETARY.
20 AND THEN I WOULD FOLLOW THROUGH ON THAT AND
21 WORK ON THE DEVELOPMENT OF STANDARDS IN TERMS OF
22 ANALYSES, THAT WOULD BE PRESENTED IN THE PREAMBLE TO THE
23 STANDARD, THAT WOULD JUSTIFY THE ACTION THAT WAS BEING
24 TAKEN BY THE SECRETARY OF LABOR.
25 Q OKAY. DID YOU RETIRE FROM GOVERNMENT
26 SERVICE IN 2002?
27 A YES, I DID.
28 Q AND THEN DID YOU BECOME A PROFESSOR?

1 A YES.
2 Q AT WHAT INSTITUTION?
3 A AT GEORGETOWN -- OR AT GEORGE WASHINGTON
4 UNIVERSITY, IN WASHINGTON, D.C. I WAS ADJUNCT PROFESSOR
5 THERE. AND ALSO, I WAS INVOLVED IN CONSULTING IN
6 OCCUPATIONAL AND ENVIRONMENTAL HEALTH.
7 Q YOU WERE A PROFESSOR OF ENVIRONMENTAL AND
8 OCCUPATIONAL HEALTH?
9 A YES.
10 Q OKAY. BRIEFLY, WOULD YOU TELL THE COURT
11 ABOUT SOME OF THE AWARDS THAT YOU'VE RECEIVED OVER YOUR
12 CAREER -- VERY BRIEFLY.
13 A WELL, I RECEIVED A SPECIAL COMMENDATION FROM
14 THE PUBLIC HEALTH SERVICE CENTER FOR DISEASE CONTROL FOR
15 MY CONTRIBUTIONS TOWARD THE UNDERSTANDING OF THE
16 TOXICITY OF BENZENE AND BERYLLIUM TO HUMANS.
17 I RECEIVED A -- WELL, I RECEIVED A
18 SPECIAL -- I WAS AWARD TRAINEESHIP TO STUDY PUBLIC
19 HEALTH AT THE UNIVERSITY OF MICHIGAN.
20 AND THEN I RECEIVED OTHER -- LIKE THE
21 SECRETARY'S EXCEPTIONAL ACHIEVEMENT AWARD, IN '93, AND
22 SPECIAL ACHIEVEMENT AWARD.
23 Q ALL RIGHT. AND HAVE YOU PROVIDED
24 CONSULTATION TO SUCH ORGANIZATIONS AS THE AMERICAN
25 PUBLIC HEALTH ASSOCIATION, THE NATIONAL RESEARCH
26 COUNCIL, NATIONAL ACADEMY OF SCIENCES, THE INTERNATIONAL
27 AGENCY FOR RESEARCH ON CANCER, AND VARIOUS OTHER FEDERAL
28 AGENCIES -- AND THE WORLD HEALTH ORGANIZATION?

A YES, I HAVE.

Q AND DO YOU HAVE MORE THAN A HUNDRED PEER-REVIEWED PUBLICATIONS TO YOUR NAME?

A YES.

Q ALL RIGHT. AND HAVE YOU PUBLISHED REGARDING THE AGENCIES THAT EVALUATE CARCINOGENIC RISKS TO HUMANS?

A YOU MEAN "AGENTS"?

Q HAVE YOU PUBLISHED ARTICLES THAT ARE ABOUT THAT?

A YES.

Q OKAY. AND HAVE YOU PUBLISHED ARTICLES REGARDING CARCINOGENICITY TESTING?

A YES.

Q AND REGARDING CARCINOGENICITY?

A YES.

Q AND MUTAGENICITY?

A YES.

Q EXPOSURE ASSESSMENT?

A YES.

Q RISK ASSESSMENT?

A YEAH. AND DOSE-RESPONSE ANALYSES IS PART OF THAT.

Q AND ETHICS AND BIAS IN PUBLICATION?

A DO I HAVE ONE IN THERE ON THAT?

Q WELL, GO AHEAD TO THE LAST ONE. SLIDE 14.

APPARENTLY, YOU DON'T RECALL YOUR PUBLICATIONS.

SO I SEE IN 1993 AN ARTICLE --

1 A OH, YES. YES.
2 Q "MEDICAL AND ETHICAL ISSUES RELATED TO
3 CHRONIC BERYLLIUM DISEASE," "OSHA'S VIEW OF GENETIC
4 SCREENING," AND TWO OTHER ARTICLES REGARDING ETHICS AND
5 BIAS?
6 A YES.
7 Q OKAY. SO NOW LET'S TALK ABOUT YOUR SUBJECT
8 OF EXPERTISE, EPIDEMIOLOGY. WILL YOU TELL US, FIRST:
9 WHAT IS EPIDEMIOLOGY?
10 A YES. WELL, I PUT A SLIDE IN HERE ON THE
11 DERIVATION OF THE NAME: "EPI," MEANING "AMONG"; AND
12 "DEMOS," "PEOPLE"; AND "OLOGY" IS "THE STUDY." SO
13 EPIDEMIOLOGY IS THE STUDY OF PEOPLE.
14 AND THE WAY IT'S PRACTICED TODAY, IT'S THE
15 STUDY OF DISEASES OR THE DETERMINANTS OF DISEASES, LIKE
16 IN THE HUMAN POPULATIONS.
17 Q OKAY. ARE THERE -- DO EPIDEMIOLOGISTS NEED
18 TO KNOW SOMETHING ABOUT VARIOUS ASPECTS OF MEDICAL
19 SCIENCE?
20 A YES. IT CERTAINLY HELPS IN INTERPRETING
21 YOUR DATA.
22 Q AND WHAT TYPES OF MEDICAL SCIENCE DATA DO
23 EPIDEMIOLOGISTS NEED TO KNOW SOMETHING ABOUT?
24 A WELL, YOU HAVE TO KNOW SOMETHING ABOUT
25 MEDICINE. AND I LEARNED THAT FROM -- DURING MY
26 INTERNSHIP AND RESIDENCY AT CHILDRENS HOSPITAL. I WAS
27 ALSO IN GRADUATE SCHOOL FOR A SUMMER AT -- MEDICAL
28 SCHOOL, AT OHIO STATE UNIVERSITY.

1 AND IT HELPS TO KNOW ABOUT -- WELL,
2 CERTAINLY, YOU HAVE TO KNOW ABOUT STATISTICS. AND YOU
3 HAVE TO KNOW -- WELL, MORE SPECIFICALLY NOW, TODAY, IT'S
4 HOW TO DO DOSE-RESPONSE ANALYSIS. SO IT'S IMPORTANT TO
5 KNOW HOW TO EVALUATE EXPOSURE DATA.
6 BECAUSE WHEN YOU'RE DOING DOSE-RESPONSE
7 ANALYSIS, THE DOSE IS THE EXPOSURE, AND THE RESPONSE IS
8 THE RELATIVE RISK. SO YOU HAVE TO KNOW SOMETHING ABOUT
9 STATISTICS, CERTAINLY.
10 Q OKAY. LET'S TALK ABOUT EPIDEMIOLOGIC
11 STUDIES. ARE THERE A FEW TYPES OF -- BASIC TYPES OF
12 EPIDEMIOLOGIC STUDIES THAT YOU CAN INFORM THE COURT OF?
13 A YES.
14 Q SO TELL US ABOUT THOSE.
15 A WELL, THERE ARE CASE-CONTROL STUDIES, COHORT
16 STUDIES, AND INTERVENTION STUDIES, ARE THE MAIN THREE
17 THAT ARE MOSTLY LINKED TO TRYING TO DETERMINE CAUSALITY.
18 Q OKAY.
19 A I MEAN, THERE ARE OTHER MORE DESCRIPTIVE
20 STUDIES, BUT THEY'RE USUALLY -- THE PURPOSE IS TO THEN
21 FOLLOW THOSE UP WITH MORE DETAILED STUDIES, LIKE A
22 CASE-CONTROL STUDY.
23 Q ALL RIGHT. AND CAN YOU EXPLAIN TO THE COURT
24 WHAT A CASE-CONTROL STUDY IS.
25 A YES. A CASE -- I THINK I HAVE SOME -- WELL,
26 YEAH. A CASE-CONTROL STUDY IS THE TYPE OF STUDY WHERE
27 YOU'RE IDENTIFYING INDIVIDUALS WHO HAVE THE DISEASE.
28 THEY'RE THE CASES. THEN YOU'RE LOOKING AT THE EXPOSURE

1 THAT YOU'RE INTERESTED IN AMONG THE CASES.
2 Q OKAY.
3 A AND THEN FOR THE CASES, YOU PICK CONTROLS
4 THAT DO NOT HAVE THE DISEASE, THAT ARE MATCHED AS
5 CLOSELY AS YOU CAN TO THE CASES IN TERMS OF SEX, RACE,
6 SOCIOECONOMIC STATUS; TRYING MATCH THEM TO THE CASE AS
7 CLOSELY AS YOU CAN.
8 AND THEN YOU LOOK TO SEE THERE WHAT THEIR
9 EXPOSURE IS, OF THE EXPOSURES OF INTEREST. AND THEN YOU
10 LOOK AT THE RATIO OF THOSE EXPOSURES IN THE CASES VERSUS
11 THOSE IN THE CONTROLS. AND THAT ENDS UP BEING AN ODDS
12 RATIO.
13 SO IT'S THE ODDS OF EXPOSURE TO THE CASES
14 VERSUS THE ODDS OF EXPOSURE TO THE SUBSTANCES OR
15 SUBSTANCE YOU'RE INTERESTED IN IN THE CONTROLS.
16 Q ALL RIGHT.
17 A AND THEN THAT ODDS RATIO IS A SURROGATE FOR
18 WHAT'S CALLED THE RELATIVE RISK OF THE DISEASE.
19 Q OKAY. AND WILL YOU TELL THE COURT BRIEFLY
20 WHAT A COHORT STUDY IS.
21 A YES. WELL, I HAVE SOME SLIDES HERE THAT --
22 Q WE'LL GET TO IT, THEN.
23 A OKAY. A COHORT STUDY IS WHERE YOU IDENTIFY
24 A GROUP OF PEOPLE -- I THINK THE WORD COMES FROM LIKE
25 THE ROMAN DAYS, OF ROMAN COHORTS AND LEGIONS.
26 AND THEN YOU IDENTIFY THEM AT A CERTAIN
27 PERIOD OF TIME. AND THEN YOU CAN DO IT RETROSPECTIVELY
28 OR PROSPECTIVELY.

1 MEANING AS IF LIKE, SAY, TODAY I WANTED TO
2 DO A STUDY, A COHORT STUDY OF CANCER, I WOULD HAVE TO GO
3 BACK IN TIME FAR ENOUGH TO ALLOW THAT CANCER TO BECOME
4 MANIFEST, SO THERE'S AN ADEQUATE LATENCY PERIOD, AND
5 THEN IDENTIFY INDIVIDUALS EXPOSED TO THAT SUBSTANCE.
6 LIKE, FOR EXAMPLE, WHICH I'VE DONE MY WHOLE
7 LIFE IN OCCUPATIONAL EPIDEMIOLOGY AND OCCUPATIONAL
8 COHORT STUDY. LET'S SAY IF YOU WERE INTERESTED IN
9 WORKERS EXPOSED TO BENZENE AND WHAT THEIR RISK WAS FROM,
10 SAY, LEUKEMIA OR OTHER CANCERS, YOU WOULD TRY TO
11 IDENTIFY A GROUP OF WORKERS EXPOSED TO BENZENE, GOING
12 BACK AS FAR AS YOU CAN -- SAY, IN THE '40S OR '50S, IF
13 YOU COULD FIND THEM BACK THAT FAR; AND THE '60S.
14 YOU IDENTIFY THEM FROM EMPLOYMENT RECORDS
15 FROM THE COMPANY, OR YOU USED TO BE ABLE TO USE SOCIAL
16 SECURITY RECORDS. THEN YOU IDENTIFY THAT GROUP, AND
17 THEN YOU FOLLOW THAT GROUP FORWARD.
18 AND YOU SAY, "OKAY. NOW I'M GOING TO LOOK
19 AND SEE WHAT KIND OF -- WHAT DISEASES -- WHAT CANCERS
20 ARE THEY DYING FROM?"
21 AND LET'S SAY YOU'RE FOLLOWING A COHORT, AND
22 YOU HAVE TEN CASES OF LEUKEMIA. YOU MIGHT SAY, ALL
23 RIGHT; BUT NOW, IF YOU COMPARE THEM TO, LET'S SAY, AN
24 UNEXPOSED POPULATION -- WHICH QUITE OFTEN IS THE GENERAL
25 POPULATION.
26 OR BETTER YET, WOULD BE OTHER WORKERS NOT
27 EXPOSED TO THE SUBSTANCE YOU'RE INTERESTED IN. AND IT'S
28 BETTER IF YOU CAN FIND THEM, BECAUSE THEY'RE MORE

1 MATCHED SOCIOECONOMICALLY TO THE EXPOSURE GROUP YOU'RE
2 INTERESTED IN.
3 SO YOU LOOK AT THE RATE OF DEATH IN THE
4 EXPOSED GROUP, AND YOU COMPARE THAT TO THE RATE OF DEATH
5 IN THE UNEXPOSED GROUP.
6 AND IF IT'S A MORTALITY STUDY, THAT'S CALLED
7 A STANDARDIZED MORALITY RATIO, OR SMR; OR YOU COULD CALL
8 IT A RELATIVE RISK, IF YOU WANT. IT'S ALL
9 INTERCHANGEABLE.
10 SO AN ODDS RATIO FROM A CASE-CONTROL STUDY
11 AND AN SMR, OR RELATIVE RISK, FROM A COHORT STUDY --
12 THOSE ESSENTIALLY ARE THE SAME MEASURE OF RISK.
13 Q OKAY.
14 A SO YOU CAN EQUATE -- SAY, AN ODDS RATIO OF 2
15 WOULD BE A RELATIVE RISK OF 2 OR AN SMR OF 2.
16 Q ALL RIGHT. NOW, OVER YOUR CAREER, WHAT TYPE
17 OF EPIDEMIOLOGIC STUDY HAVE YOU DONE MORE OF THAN
18 OTHERS?
19 A COHORT STUDIES.
20 Q OKAY. NOW, ALTHOUGH MOST OF THE
21 EPIDEMIOLOGIC STUDIES THAT YOU HAVE DONE OVER YOUR
22 CAREER ARE COHORT STUDIES, DO YOU STILL CONSIDER
23 CASE-CONTROL STUDIES IN ASSESSING RISK AND CAUSALITY?
24 A YES. NOT ONLY DO I DO IT, BUT ANYONE. IT
25 DEPENDS ON WHAT THE QUESTION IS YOU'RE ASKING. OF
26 COURSE, YOU WOULD USE COHORT STUDIES. AND YOU WOULD USE
27 CASE-CONTROL STUDIES.
28 AND I SUPPOSE IF YOU WERE AT FOOD AND DRUG

1 ADMINISTRATION, YOU WOULD -- THEY'RE THE STANDARD -- THE
2 BEST STANDARD -- THE GOLD STANDARD WOULD BE INTERVENTION
3 STUDIES.
4 Q OKAY. WHAT IS AN INTERVENTION STUDY?
5 A AN INTERVENTION STUDY IS A STUDY WHERE YOU
6 ARE GOING TO, SAY, DISPENSE THE AGENT YOU'RE CONCERNED
7 ABOUT -- THE VITAMIN OR WHATEVER IT IS THAT YOU'RE
8 CONCERNED ABOUT -- TO A GROUP YOU'VE IDENTIFIED. AND
9 THEN YOU'RE GOING TO IDENTIFY ANOTHER GROUP THAT YOU'RE
10 NOT GOING TO GIVE THAT AGENT TO.
11 AND THEN YOU'RE GOING TO FOLLOW THEM OVER
12 TIME AND SEE WHAT PARTICULAR DISEASE ARE YOU INTERESTED
13 IN STUDYING, TO SEE IF THERE'S A PROTECTIVE EFFECT FROM
14 THAT CHEMICAL.
15 LIKE, FOR EXAMPLE, I MEAN, I THINK ONE OF
16 THE FAMOUS EXAMPLES IS LIKE BETA CAROTENE AND LUNG
17 CANCER. THERE WERE THOSE COHORT AND CASE-CONTROL
18 STUDIES WHICH SHOWED BENEFITS FROM DIETARY CAROTENE
19 SUPPLEMENTS OR PEOPLE WITH HIGH BETA CAROTENE DIETS, AND
20 THE RISK OF LUNG CANCER WAS SUPPOSEDLY REDUCED.
21 SO PEOPLE WERE PROMOTING BETA CAROTENE AND
22 VITAMIN A FOR PEOPLE TO TAKE, TO REDUCE RISK OF LUNG
23 CANCER, BECAUSE THAT'S WHAT THE COHORT AND CASE-CONTROL
24 STUDIES SHOWED.
25 THEN WHEN THEY DID AN INTERVENTION STUDY, IN
26 FACT, THEY FOUND JUST THE OPPOSITE: THAT IN THE GROUP
27 THEY WERE STUDYING, THOSE THAT WERE ADMINISTERED THE
28 BETA CAROTENE VERSUS THOSE THAT WERE NOT, THEY FOUND, IN

1 FACT, IT WAS PRODUCING MORE LUNG CANCER.
2 Q OKAY.
3 A THE BETA CAROTENE, WHICH WAS SUPPOSED TO BE
4 PROTECTIVE IN THE OTHER STUDIES, IN THE INTERVENTION
5 STUDIES, IT SHOWED HARMFUL EFFECTS. SO I DIDN'T WORK AT
6 FDA, BUT I'M SAYING, IF I WAS AT THE FDA, THAT WOULD BE
7 THE GOLD STANDARD.
8 Q ALL RIGHT. NOW, ARE EPIDEMIOLOGIC STUDIES
9 SOMETIMES CLASSIFIED AS BEING EITHER RETROSPECTIVE OR
10 PROSPECTIVE?
11 A YES, THEY CAN BE EITHER.
12 Q OKAY.
13 A I MEAN, MOST ARE RETROSPECTIVE; BUT THERE
14 ARE SOME ALSO THAT ARE ONGOING, THAT ARE PROSPECTIVE.
15 Q SLIDE 25.
16 AND WOULD YOU EXPLAIN TO THE COURT WHAT THIS
17 SLIDE 25 IS SHOWING.
18 A CASE CONTROL -- YES. IF YOU LOOK OVER ON
19 THE RIGHT-HAND COLUMN, YOU SEE WHERE IT SAYS "STUDY
20 POPULATION." SO THIS IS A CASE-CONTROL STUDY, LIKE I
21 SPOKE OF BEFORE.
22 AND ON THE TOP, YOU SEE CASES OF DISEASE.
23 YOU SEE CONTROLS, NO DISEASE. SO WHEN YOU IDENTIFY THE
24 CASES AND THE CONTROLS, THEN YOU EVALUATE THOSE
25 INDIVIDUALS TO SEE WHAT THE DIFFERENCES IN THEIR
26 EXPOSURE IS, TO THE EXPOSURE OF INTEREST THAT YOU WANT
27 TO STUDY, OR THE EXPOSURES OF INTEREST.
28 Q AND THAT'S THE FACTOR PRESENT OR ABSENT HERE

1 ON THIS?
2 A YES; RIGHT.
3 Q ALL RIGHT.
4 A AND SO THE RATIO OF THAT, THEN, WOULD BE --
5 THE RATIO OF THE EXPOSURE IN THE CASES TO THE EXPOSURE
6 IN THE CONTROLS WOULD BE CALLED AN ODDS RATIO. IT'S THE
7 ODDS OF EXPOSURE FOR A CASE VERSUS THE CONTROL.
8 Q AND ON --
9 A WHICH IS THE SAME -- IT GENERATES THE SAME
10 STATISTIC, ESSENTIALLY, AS A SURROGATE FOR THE RELATIVE
11 RISK OF THE DISEASE.
12 Q ARE CASE-CONTROL STUDIES RETROSPECTIVE
13 STUDIES?
14 A WELL, YES, THEY WOULD HAVE TO BE BY NATURE,
15 BECAUSE YOU'RE IDENTIFYING INDIVIDUALS THAT ALREADY HAVE
16 THE DISEASE OR THE CANCER OR WHATEVER YOU'RE STUDYING.
17 Q ARE THERE CERTAIN ADVANTAGES OF CASE-CONTROL
18 STUDIES?
19 A YES.
20 Q WHAT ARE SOME OF THEM?
21 A WELL, SOME OF THE ADVANTAGES OF THE
22 CASE-CONTROL STUDIES ARE THAT THEY DON'T TAKE AS LONG TO
23 DO AS A COHORT STUDY, SO THEY'RE CHEAPER TO DO.
24 THEY CAN HAVE A LOT MORE STATISTICAL POWER,
25 IF THERE ARE SPECIFIC CANCERS THAT YOU'RE INTERESTED IN,
26 OR YOU DON'T HAVE TO WAIT FOR A LATENCY PERIOD LIKE YOU
27 WOULD IN A -- CERTAINLY, IN A PROSPECTIVE COHORT STUDY.
28 SO YOU CAN IDENTIFY THE CASES MUCH MORE QUICKLY FROM A

1 CANCER REGISTRY OR FROM OTHER SOURCES.
2 SO THEY'RE LESS EXPENSIVE, AND THEY HAVE
3 MORE STATISTICAL POWER IN TERMS LOOKING AT PARTICULAR
4 CANCERS BECAUSE YOU CAN IDENTIFY A LARGE NUMBER OF THE
5 CANCERS.
6 IN PARTICULAR, WHEN YOU'RE TALKING ABOUT
7 CANCER, A LOT OF CANCERS ARE RARE DISEASES. SO IF YOU
8 WERE TO FOLLOW A COHORT, YOU MIGHT HAVE TO HAVE A VERY
9 LARGE COHORT WHICH YOU'D HAVE TO ENROLL AND THEN FOLLOW
10 OVER TIME. AND YOU'RE NOT GOING TO FIND NEARLY AS MANY
11 RARE CANCERS IN A COHORT STUDY.
12 Q OKAY. AND ARE THERE CERTAIN LIMITATIONS OF
13 CASE-CONTROL STUDIES?
14 A YES, THERE ARE LIMITATIONS. I THINK I -- I
15 HAVE A SLIDE. HERE IT IS, YES.
16 SO IF YOU LOOK AT THE BOTTOM BULLET THERE.
17 SO THEY'RE DIFFICULT FOR STUDYING UNCOMMON EXPOSURES
18 BECAUSE YOUR CASES MIGHT NOT HAVE ANY OF THE EXPOSURE
19 THAT YOU WANT TO EVALUATE. SO IT'S DIFFICULT TO DO FOR
20 UNCOMMON EXPOSURES.
21 AND THERE'S -- YOU WOULD HAVE TO BE
22 CONCERNED, ALSO, ABOUT THE MISCLASSIFICATION OF THE
23 EXPOSURE BECAUSE THESE ARE RETROSPECTIVE EXPOSURE
24 DETERMINATIONS. SO YOU MAY BE ASKING SOMEBODY ABOUT
25 WHAT THEY WERE EXPOSED TO 5, 10, 15, 20 YEARS AGO. AND
26 SOME MAY RECALL, AND SOME RECALL BETTER THAN OTHERS.
27 SO YOU HAVE SOME DIFFICULTIES IN EXPOSURE
28 MISCLASSIFICATION, AND YOU CAN ALSO HAVE RECALL BIAS.

1 Q OKAY. LET'S TALK ABOUT COHORT STUDIES.
2 GO TO SLIDE 30, PLEASE.
3 AND WOULD YOU TELL THE COURT ABOUT SOME OF
4 THE ADVANTAGES OF COHORT STUDIES.
5 A WELL, I HAVE DIFFERENT NUMBERED SLIDES THAN
6 YOU DO.
7 THE ADVANTAGES OF COHORT STUDIES IS, YOU CAN
8 LOOK AT MULTIPLE DISEASES AT ONE TIME, WHEREAS IN A
9 CASE-CONTROL STUDY, YOU'RE LOOKING AT A SINGLE DISEASE,
10 LOOKING AT THE ODDS OF THE EXPOSURE. IN A COHORT STUDY,
11 YOU CAN STUDY SEVERAL DISEASES AT ONE TIME.
12 Q WHAT ARE SOME OF THE LIMITATIONS OF COHORT
13 STUDIES?
14 A WELL, IN COHORT STUDIES SOMETIMES, BECAUSE
15 OF -- MANY OF THESE ARE MORTALITY STUDIES, AND THE CAUSE
16 OF DEATH MAY NOT BE CORRECTLY LISTED ON THE DEATH
17 CERTIFICATE; WHEREAS IN A CASE-CONTROL STUDY, USUALLY
18 YOU'RE GETTING THAT KNOWLEDGE FROM THE CANCER REGISTRY.
19 SO THE PERSON HAS BEEN TREATED FOR THEIR CANCER, SO
20 YOU'RE GOING TO HAVE PRETTY GOOD INFORMATION ON THE TYPE
21 OF CANCER THAT THEY HAVE.
22 SO IT'S A DISADVANTAGE.
23 THE OTHER THING ABOUT COHORT STUDIES, AS I
24 MENTIONED BEFORE, YOU HAVE TO FOLLOW THEM FOR A LONG
25 ENOUGH PERIOD OF TIME TO ALLOW THE CANCER TO BECOME
26 MANIFEST. AND SOME CANCERS MAY TAKE 30, 40 YEARS --
27 SAY, 20 TO 40 YEARS TO MANIFEST THEMSELVES CLINICALLY.
28 SO IF YOU DON'T FOLLOW THE COHORT LONG

1 ENOUGH, YOU'RE NOT GOING TO BE ABLE TO OBSERVE WHETHER
2 OR NOT THAT COHORT IS, IN FACT, DEVELOPING THOSE
3 CANCERS. SO THAT'S ONE OF THEM.
4 AND THEY HAVE LOW STATISTICAL POWER IN TERMS
5 OF THE INDIVIDUAL CANCERS BECAUSE YOU MAY NOT HAVE
6 ENOUGH CANCERS TO GIVE YOU ENOUGH STATISTICAL POWER TO
7 IDENTIFY, SAY, A CANCER RISK IF, IN FACT, IT'S PRESENT.
8 Q SO ALTHOUGH A COHORT STUDY MAY HAVE SEVERAL
9 HUNDRED THOUSAND PEOPLE AS PARTICIPANTS, ONLY A SMALL
10 NUMBER OF THOSE WILL GET CANCERS, AND THEN YOU'RE
11 EVALUATING THAT SMALL NUMBER. IS THAT HOW THAT WORKS?
12 MR. SCHURZ: OBJECTION; LEADING.
13 THE COURT: OVERRULED.
14 THE WITNESS: AS YOU'RE FOLLOWING THEM, YES. YES.
15 AND THE RARER THE CANCER, THE FEWER YOU WILL HAVE.
16 Q BY MR. METZGER: OKAY. ARE COHORT STUDIES
17 PRACTICABLE OR FEASIBLE TO DO FOR RARE CANCERS?
18 A IT'S VERY DIFFICULT FOR RARE CANCERS BECAUSE
19 YOU JUST SIMPLY WOULDN'T HAVE ENOUGH -- YOU WOULDN'T
20 HAVE ENOUGH STATISTICAL POWER. YOU WOULDN'T IDENTIFY
21 ENOUGH OF THEM.
22 Q CAN YOU GIVE US AN EXAMPLE.
23 A YEAH, SURE. LIKE IF YOU WERE, SAY, STUDYING
24 ANGIOSARCOMA OF THE LIVER IN A COHORT STUDY. I THINK
25 THERE ARE ONLY ABOUT 50 CASES A YEAR IN THE UNITED
26 STATES. AND SO IF YOUR -- 50 CASES IN THE ENTIRE UNITED
27 STATES, WHICH IS OVER, WHAT, 200 MILLION PEOPLE.
28 SO IF YOU'RE DOING A COHORT STUDY OF 3,000

1 PEOPLE, LET'S SAY -- 5,000 PEOPLE, 10,000 PEOPLE -- AND
2 YOU'RE FOLLOWING IT FOR 30 YEARS, YOU WOULD PROBABLY
3 EXPECT LESS THAN ONE TO DEVELOP.
4 Q OKAY.
5 A AND EVEN IF YOU FOUND ONE, I MEAN, WHAT ARE
6 YOU GOING TO SAY BASED ON ONE CANCER? YOU'RE GOING TO
7 SAY, "THIS IS WHAT THE RISK IS FOR ANGIOSARCOMA"? SO IN
8 THAT SITUATION, YOU WOULD NEED TO IDENTIFY CASES OF
9 ANGIOSARCOMA.
10 Q WHAT ARE --
11 A THE EXCEPTION BEING -- LET ME JUST EXPLAIN
12 IT. BECAUSE, IN FACT, VINYL CHLORIDE EXPOSED WORKERS
13 BEING STUDIED DID DEMONSTRATE AN ELEVATED RISK OF LIVER
14 CANCER, FOR WHICH ANGIOSARCOMA WAS THE MAIN LIVER CANCER
15 EARLY ON, BUT THAT'S BECAUSE THE EXPOSURES WERE SO HIGH
16 AMONG THOSE WORKERS.
17 THAT'S HOW -- IT WAS SUCH A RARE CANCER. IT
18 WAS LATER CONFIRMED IN AN EPIDEMIOLOGICAL STUDY. BUT IT
19 WAS FIRST IDENTIFIED BY A PATHOLOGIST, WHO SAID, "HEY,
20 I'VE SEEN THREE OF THESE RARE LIVER CANCERS IN MY
21 PRACTICE HERE COMING FROM THIS ONE PLANT, AND THERE ARE
22 ONLY LIKE MAYBE 50 IN THE ENTIRE UNITED STATES A YEAR.
23 MAYBE SOMETHING -- THIS IS RARE. SOMETHING MUST BE
24 GOING ON."
25 SO IT WAS SO RARE AND IT WAS SO OUTSTANDING
26 AT THE COMPANY THAT IT WAS IDENTIFIED BY, REALLY, A
27 PATHOLOGIST. AND THEN IT WAS CONFIRMED BY ANIMAL
28 STUDIES THAT SHOWED THAT ADMINISTERING VINYL CHLORIDE TO

1 ANIMALS, THEY DEVELOPED ANGIOSARCOMA.
2 Q OKAY.
3 A BASED ON THAT, IN FACT, OSHA SET AN
4 EMERGENCY STANDARD.
5 Q ALL RIGHT. WHAT ABOUT FOR A CANCER LIKE
6 CHILDHOOD LEUKEMIA, THAT'S NOT QUITE AS RARE AS
7 ANGIOSARCOMA OF THE LIVER. ARE COHORT STUDIES FEASIBLE
8 TO EVALUATE THAT?
9 A I THINK YOU WOULD HAVE TO DO CASE-CONTROL
10 STUDIES BECAUSE IT'S SO RARE. LIKE CHILDHOOD LEUKEMIAS
11 UNDER THE AGE OF 19 IS ABOUT 4 PER 100,000 DEATHS A
12 YEAR; 4, 4.5 PER 100,000 DEATHS. SO YOU WOULD HAVE TO
13 FOLLOW -- IF YOU WANTED TO FOLLOW -- BECAUSE YOU WANT TO
14 FOLLOW CHILDHOOD LEUKEMIA AND MOTHERS. IS THAT WHAT
15 YOU'RE SPEAKING ABOUT?
16 Q YES, FROM A -- YEAH.
17 A YOU WOULD NEED AN IMPOSSIBLY LARGE COHORT TO
18 DO A COHORT STUDY OF THAT. IN FACT, I DID A
19 CALCULATION.
20 Q LET'S TAKE A LOOK AT THAT. CAN YOU EXPLAIN
21 THE CALCULATION.
22 A EXCUSE ME. AN EXAMPLE.
23 HERE WE GO. THAT SLIDE IS A LITTLE CROOKED.
24 I CAN'T READ THE READING ON IT.
25 Q LET ME SEE IF I CAN MOVE THIS JUST A LITTLE
26 TO TRY TO GET IT --
27 (DISCUSSION HELD OFF THE RECORD.)
28 Q BY MR. METZGER: MAYBE THAT'S GOOD. LET'S

1 LEAVE IT THERE. I THINK YOU CAN SEE IT.
2 A SO I WAS SAYING, WELL, THIS IS A CASE THAT
3 IF YOU WANTED TO ENROLL MOTHERS IN A COHORT STUDY AND
4 SAY, "OKAY. NOW I WANT TO STUDY CHILDHOOD LEUKEMIA IN
5 THEIR OFFSPRING," HOW MANY WOULD YOU NEED?
6 SO IF YOU LOOK AT -- THERE'S A DECIMAL POINT
7 OFF IN THAT FIRST LINE THERE, IN THE U.S. BIRTH RATE.
8 IT'S REALLY 14.1 PER 100,000.
9 THE BIRTH RATE IN THE UNITED STATES -- THIS
10 IS FOR ALL WOMEN -- IS 14.1 PER 100,000 WOMEN PER YEAR.
11 AND THE INCIDENCE OF LEUKEMIA IS 4.5 PER 100,000. SO IT
12 WOULD TAKE 1,000 WOMEN TO GIVE YOU 14.1 CHILDREN.
13 AND IF THE LEUKEMIA INCIDENCE IS 4.5 PER
14 100,000, IT WOULD TAKE ESSENTIALLY A MILLION -- OVER
15 1,500,000 WOMEN TO PRODUCE ONE LEUKEMIA CASE.
16 Q SO IF YOU WANTED TO DO A STUDY OF MATERNAL
17 CONSUMPTION OF COFFEE AND CHILDHOOD LEUKEMIA, AND YOU
18 WANTED TO HAVE, SAY, 500 CASES, HOW MANY -- WHAT SIZE
19 COHORT WOULD YOU NEED? OR JUST A HUNDRED CASES. LET'S
20 MAKE IT EASY.
21 A WELL, YOU WOULD NEED TO DO A CASE-CONTROL
22 STUDY. YOU WOULD NEVER BE ABLE TO GENERATE A HUNDRED
23 CASES BY LOOKING AT A COHORT OF WOMEN WHO, SAY, DRANK
24 COFFEE VERSUS A COHORT WHO DIDN'T.
25 Q ALL RIGHT. NOW, LET'S MOVE ON TO SLIDE 34.
26 AND I THINK HERE YOU HAVE A -- YOU DEPICT AN
27 INTERVENTION STUDY. CAN YOU BRIEFLY EXPLAIN THAT TO THE
28 COURT.

1 A WELL, AN INTERVENTION STUDY -- AND THESE ARE
2 THE ONES LIKE FDA REQUIRES IF YOU'RE, SAY, LOOKING AT
3 VITAMINS OR DRUGS OR NUTRITIONAL SUPPLEMENTS. IF YOU
4 WANT TO PUT A CLAIM THAT THERE'S A BENEFIT TO THIS -- TO
5 TAKING OF THIS WHATEVER IT IS, YOU WOULD HAVE TO DO AN
6 INTERVENTION STUDY.
7 AND BY DOING THAT, WHAT YOU WOULD DO IS, YOU
8 WOULD IDENTIFY -- WITH A CLINICAL TRIAL, YOU WOULD
9 IDENTIFY INDIVIDUALS THAT YOU WOULD GIVE THAT AGENT TO.
10 AND YOU WOULD LOOK AT THE OUTCOME OF THEM, LOOK AT THE
11 RATE OF WHATEVER YOU'RE EVALUATING IN THEM. AND THEN
12 YOU WOULD HAVE A CONTROL GROUP THAT YOU WOULD NOT GIVE
13 THAT DRUG TO.
14 AND THEN YOU WOULD FOLLOW THEM OVER TIME AND
15 SAY, "OKAY. WHAT IS THE DIFFERENCE IN" -- IF YOU'RE
16 INTERESTED IN HEART DISEASE, "WHAT'S THE DIFFERENCE IN
17 THE RATE OF HEART DISEASE? IS THERE A BENEFIT, OR IS
18 THERE A HARM TO TAKING -- IN THIS CASE, LIKE THE BETA
19 CAROTENE?"
20 Q OKAY. HAVE ANY INTERVENTION STUDIES BEEN
21 DONE TO ASSESS COFFEE AND CANCER?
22 A NOT TO MY KNOWLEDGE, NO.
23 Q OKAY. ALL RIGHT.
24 LET'S MOVE ON TO MEASURES OF ASSOCIATION.
25 A I JUST WANTED TO MAKE ONE POINT.
26 Q GO AHEAD.
27 A I HAVE IT ON MAYBE SLIDE 35, WHILE WE'RE ON
28 THE INTERVENTION STUDIES.

1 JUST THAT THE ADVANTAGES, THAT YOU'RE
2 AVOIDING MISCLASSIFICATION OF EXPOSURE BECAUSE YOU'RE
3 GIVING THE EXPOSURE TO THE GROUP, TO THE EXPOSED GROUP.
4 Q RIGHT.
5 A AND YOU'RE NOT GIVING IT TO THE CONTROL
6 GROUP. SO, IN FACT, YOU KNOW THAT THE CONTROL GROUP
7 ISN'T GETTING IT.
8 AND SO THEN YOU DON'T HAVE TO DEAL WITH
9 RECALL BIAS BECAUSE YOU'RE ADMINISTERING WHATEVER IT IS
10 TO THE TWO GROUPS.
11 AND YOU'RE AVOIDING ANY SELECTION BIAS
12 BECAUSE YOU'RE SELECTING THEM AHEAD OF TIME, BEFORE YOU
13 ADMINISTER THE AGENT TO THE GROUP THAT GETS IT VERSUS
14 THE CONTROLS THAT DON'T GET IT.
15 SO IT -- BUT IT'S VERY EXPENSIVE AND TIME
16 CONSUMING.
17 Q OKAY. THANK YOU.
18 LET'S GO ON TO MEASURES OF ASSOCIATION,
19 SLIDE 40. COULD YOU TELL THE COURT WHAT MEASURES OF
20 ASSOCIATION ARE.
21 A YES. THESE ARE MEASURES OF ASSOCIATION.
22 THEY'RE MEASURING LIKE RISK OR RELATIVE RISK IN GROUPS
23 THAT YOU'RE STUDYING.
24 SO IN A CASE-CONTROL STUDY, YOU WOULD
25 MEASURE THE ODDS RATIO, WOULD BE THE ESTIMATE OF
26 RELATIVE RISK. IN, SAY, AN OCCUPATIONAL STUDY, WHERE
27 YOU'RE LOOKING AT THE DISEASE INCIDENCE IN THE
28 OCCUPATIONALLY EXPOSED TO THAT AGENT VERSUS, LET'S SAY,

1 OTHER WORKERS WHO WEREN'T EXPOSED TO IT, THERE YOU WOULD
2 GENERATE A RELATIVE RISK.
3 IF YOU WERE DOING A MORTALITY STUDY, YOU
4 WOULD CALL THE SAME ESTIMATE A STANDARDIZED -- I'M
5 SORRY. IT WOULD BE A STANDARDIZED MORTALITY RATIO,
6 WHICH IS THE SECOND BULLET FROM THE BOTTOM.
7 IF YOU'RE LOOKING AT THE INCIDENCE OF
8 DISEASE, IT WOULD BE A STANDARDIZED INCIDENCE RATIO.
9 AND THEN WE HAVE SOME THINGS THAT ARE CALLED
10 PROPORTIONATE MORTALITY RATIOS, WHERE ONLY LOOKING AT
11 DEATHS IN THE TWO GROUPS.
12 THEY'RE ALL MEASURES OF ASSOCIATION, AND
13 THEY CAN ALL BE USED INTERCHANGEABLY AS ESTIMATES OF
14 RELATIVE RISK.
15 Q OKAY. LET'S TALK ABOUT HOW ONE CALCULATES
16 AN ODDS RATIO. CAN YOU GO TO SLIDE 42 AND EXPLAIN THIS
17 TO THE COURT.
18 A NOW, THIS IS A SIMPLE TWO BY TWO. IN OTHER
19 WORDS, YOU'RE LOOKING AT THE ODDS OF EXPOSED OVER THE
20 ODDS OF THE -- I'M SORRY, THE ODDS OF EXPOSURE TO THOSE
21 WITH THE DISEASE VERSUS THE ODDS OF EXPOSURE TO THOSE
22 WITHOUT THE DISEASE.
23 SO, FOR EXAMPLE, IF YOU LOOK UNDER
24 "EXPOSURE," THE FIRST BLUE BOX SAYS "PRESENT," AND THE
25 OUTCOME IS "PRESENT." SO THAT'S A.
26 SO -- AND THEN, OF COURSE, THE OPPOSITE
27 EXTREME IS, IF THERE'S THE ABSENCE OF EXPOSURE, THERE'S
28 ABSENCE OF THE DISEASE. THAT'S IN BOX D. WHAT YOU DO

1 IS, YOU MULTIPLY A TIMES D, AND YOU DIVIDE THAT BY B
2 TIMES C, AND THAT BECOMES THE ODDS RATIO.
3 Q OKAY. AND HOW DOES ONE INTERPRET THE NUMBER
4 THAT ONE GETS IN DOING THAT CALCULATION?
5 A WELL, YOU LOOK AND SEE, WELL, IS THERE AN
6 INCREASE IN THE ODDS OF EXPOSURE AMONG THOSE WITH THE
7 DISEASE, OR IS THERE A DECREASE IN EXPOSURE THAT YOU'RE
8 INTERESTED IN AMONG THOSE WITH THE DISEASE? IT CAN GO
9 EITHER WAY.
10 OR THERE COULD BE -- THE ODDS RATIO COULD BE
11 1, WHICH MEANS THERE'S NO ASSOCIATION AT ALL, EITHER
12 WAY.
13 Q SO IF THE ODDS RATIO IS ABOVE 1, THE RISK IS
14 INCREASED. AND IF IT'S BELOW 1, IT'S DECREASED. IS
15 THAT THE ESSENCE OF IT?
16 A RIGHT.
17 Q OKAY. ALL RIGHT. I DON'T WANT TO GO
18 THROUGH ALL OF THESE. BUT LET'S GO TO SLIDE 48, IF WE
19 COULD, WHICH YOU'VE INDICATED HERE HOW RISK IS
20 EXPRESSED. AND COULD YOU EXPLAIN THAT TO THE COURT.
21 A YES. WELL, IN THE ODDS RATIO -- YOU MIGHT
22 SAY LIKE, FOR EXAMPLE, THE ODDS RATIO IS 2, WHICH MEANS
23 THE CASES HAVE TWICE AS MUCH EXPOSURE AS THE NON-CASES.
24 AND THEN YOU CALCULATE A CONFIDENCE INTERVAL AROUND THAT
25 ESTIMATE, SO FOR -- A 95 PERCENT CONFIDENCE INTERVAL.
26 WHICH MEANS THAT WHEN YOU GENERATE THE ODDS
27 RATIO -- LET'S SAY IN THIS CASE IT'S 2. THEN YOU WANT
28 TO SAY, OKAY, IT'S 2. BUT THEN -- AND ALSO, YOU'RE --

1 FROM THE DATA ANALYSIS, THAT YOU'RE 95 PERCENT SURE THAT
2 THE RANGE WOULD BE SOMEWHERE BETWEEN 1.5 AND 2.5.
3 WHICH MEANS THAT 95 TIMES OUT OF 100, THAT
4 THAT ODDS RATIO WOULD BE SOMEWHERE BETWEEN 1.5 AND 2.5,
5 SINCE IT'S THE 95 PERCENT CONFIDENCE INTERVAL.
6 Q OKAY. AND WHERE YOU HAVE UP THERE, FOR
7 EXAMPLE, "ODDS RATIO EQUALS 2.0, 95 PERCENT CONFIDENCE
8 INTERVAL, 1.5 TO 2.5," WOULD YOU EXPLAIN TO THE COURT
9 WHAT THAT MEANS.
10 A WELL, WHAT THAT INDICATES IS THAT THE RESULT
11 IS STATISTICALLY SIGNIFICANT, IF THE LOWER BOUND OF THE
12 CONFIDENCE INTERVAL IS ABOVE 1.0.
13 Q OKAY.
14 A AND THEN THE RESULT WOULD BE STATISTICALLY
15 SIGNIFICANT IF YOU'RE USING A 95 PERCENT CONFIDENCE
16 INTERVAL, WITH THE 95 PERCENT LEVEL OF CONFIDENCE.
17 I MEAN, SOMETIMES YOU'LL SEE RESULTS THAT
18 ARE 1.0, AND YOU'RE NOT QUITE SURE, IS THAT
19 STATISTICALLY SIGNIFICANT? IS IT ROUNDING OFF? BECAUSE
20 1.0 -- 1.04 WOULD BE ROUNDED OFF TO 1.0.
21 Q OKAY.
22 A SOMETIMES AUTHORS WILL GIVE YOU MORE
23 DECIMALS IN THE ODDS RATIO SO YOU CAN SEE WHETHER OR NOT
24 IT'S SIGNIFICANT IF THE LOWER BOUND IS CLOSE TO 1.
25 Q ALL RIGHT. SO IN LOOKING AT EPIDEMIOLOGIC
26 STUDIES AND THESE ODDS RATIOS, OR RELATIVE RISKS, ONE
27 WANTS TO LOOK AT WHETHER THE RATIO -- WHETHER THE RISK
28 IS INCREASED OR DECREASED AND WHETHER IT IS

1 SIGNIFICANTLY INCREASED OR DECREASED; IS THAT CORRECT?
2 A CORRECT. AND THEN THE ODDS -- THE
3 CONFIDENCE INTERVAL CAN TELL YOU THAT.
4 Q OKAY. WOULD YOU GO TO SLIDE 52.
5 AND WOULD THE TELL THE COURT ABOUT SOME
6 OTHER THINGS OR FACTORS THAT EPIDEMIOLOGISTS LOOK FOR IN
7 EVALUATING EPIDEMIOLOGIC STUDIES.
8 A YES. I HAVE THIS LIST HERE.
9 YOU LOOK, FIRST OF ALL, ON THE -- YEAH,
10 QUALITY OF THE EXPOSURE ASSESSMENT. SO IN OTHER WORDS,
11 ARE THOSE THAT YOU'RE STUDYING THAT ARE SUPPOSED TO BE
12 EXPOSED, ARE THEY ACTUALLY EXPOSED.
13 THEN IF YOU'RE MEASURING THE EXPOSURE, DID
14 YOU ACTUALLY -- DOES THE STUDY REALLY INDICATE THAT
15 YOU'RE GETTING THE EXPOSURE CORRECT OR NOT; OR ARE YOU
16 BASING THE EXPOSURE ON, SAY, FOR CERTAIN PERIODS WHEN
17 YOU DON'T HAVE ANY EXPOSURE DATA, WHICH QUITE OFTEN
18 HAPPENS, AND YOU'RE ESTIMATING IT FROM TIME PERIODS
19 LATER ON WHERE YOU DO HAVE EXPOSURE?
20 SO YOU'RE DOING RETROSPECTIVE EXPOSURE
21 ESTIMATION. SO YOU MAY NOT HAVE DATA FOR SOME OF YOUR
22 COHORT MEMBERS THAT, SAY, BEGAN IN THE '50S AND '60S, OR
23 EVEN '70S, SO YOU HAVE TO ESTIMATE THAT. SO YOU HAVE TO
24 LOOK AT WHAT THE ESTIMATION PROCEDURES ARE, TO SEE IF
25 THAT'S BEEN PROPERLY DONE.
26 OR SOMETIMES THE INVESTIGATORS DO THEM AS
27 BEST AS THEY CAN DO, BUT -- IT MAY BE GOOD; OR IN OTHER
28 CASES, IT JUST MAY NOT BE GOOD ENOUGH, BUT THEY DID THE

1 BEST THEY COULD DO.
2 SO YOU HAVE TO EVALUATE THE QUALITY OF THE
3 EXPOSURE ASSESSMENT, PARTICULARLY IN STUDIES WHERE
4 YOU'RE TRYING TO DETERMINE A DOSE-RESPONSE RELATIONSHIP.
5 IF YOU'RE DOING A STUDY WHERE YOU'RE JUST
6 SAYING, "EXPOSED; WHAT'S THE RISK?" VERSUS A COMPARISON
7 GROUP, THEN IT'S NOT AS IMPORTANT TO KNOW WHAT THE --
8 THE EXPOSURE ASSESSMENT DOESN'T HAVE TO BE QUITE AS
9 GOOD, IF YOU KNOW THEY WERE EXPOSED.
10 YOU MAY NOT KNOW HOW MUCH THEY WERE EXPOSED
11 TO, BUT YOU KNOW THEY WERE EXPOSED OVER SOME THRESHOLD
12 OF AT LEAST A DAY OR A WEEK OR A YEAR, BUT YOU DON'T
13 KNOW HOW MUCH.
14 THAT'S A QUALITATIVE EXPOSURE ESTIMATE, AND
15 YOU'RE LOOKING AT THE RISK OF DISEASE.
16 IN THE STUDY I PUBLISHED IN 1977 ON BENZENE
17 AND LEUKEMIA, THE INITIAL STUDY, I KNEW THEY WERE -- THE
18 WORKERS WERE EXPOSED, BUT I DIDN'T KNOW EXACTLY HOW MUCH
19 BENZENE EXPOSURE THEY HAD.
20 BUT I KNEW THEY WORKED IN THIS PROCESS WHERE
21 THEY WERE ALL EXPOSED TO BENZENE. AND I FOLLOWED THEM
22 AND FOUND THAT THEY HAD A FIVE- TO TEN-FOLD RISK OF
23 LEUKEMIA.
24 AND FOR THE TIME THAT IT WAS DONE, IN 1977,
25 THAT WAS ADEQUATE. THEN SUBSEQUENT TO THAT, IF YOU WANT
26 TO DETERMINE, WELL, HOW MUCH BENZENE EXPOSURE CAUSES HOW
27 MUCH RISK OF LEUKEMIA, NOW IT BECOMES IMPORTANT TO KNOW
28 HOW MUCH BENZENE EXPOSURE THEY HAD AND HOW THAT WAS

1 DETERMINED.
2 Q OKAY.
3 A SO IT DEPENDS ON WHAT THE ANALYSIS IS THAT
4 YOU'RE DOING. BUT YOU HAVE TO LOOK AT THE QUALITY OF
5 THE EXPOSURE ASSESSMENT.
6 Q WHAT ELSE DO YOU HAVE TO LOOK FOR, AS AN
7 EPIDEMIOLOGIST?
8 A PARDON ME?
9 Q WHAT ELSE DO YOU HAVE TO LOOK FOR, AS AN
10 EPIDEMIOLOGIST?
11 A WELL, YOU WANT TO LOOK AT THE -- AS WE
12 MENTIONED EARLIER, IS THE LATENCY PERIOD ADEQUATE? IN
13 OTHER WORDS, HAS THE GROUP BEEN FOLLOWED LONG ENOUGH TO
14 ALLOW CANCERS -- PARTICULARLY THOSE WITH LONG LATENCY
15 PERIODS -- TO BECOME CLINICALLY MANIFEST.
16 THEN THE OTHER THING YOU LOOK AT IS THE
17 STRENGTH OF THE ASSOCIATION.
18 Q WHAT DOES THAT MEAN?
19 A THAT'S WHAT I WAS TALKING ABOUT BEFORE:
20 WHAT IS THE RELATIVE RISK OF THE GROUP? IS IT
21 SIGNIFICANTLY ELEVATED, OR ISN'T IT? IS IT CLOSE?
22 AND THEN THE NEXT ONE IS CONSISTENCY OF THE
23 RESULTS. ARE THERE OTHER STUDIES THAT SHOW SIMILAR
24 OBSERVATIONS, OR IS THIS THE ONLY STUDY?
25 Q OKAY.
26 A THEN DOSE-RESPONSE RELATIONSHIPS, THAT'S
27 IMPORTANT. BECAUSE IF YOU CAN IDENTIFY DOSE RESPONSE IN
28 AN EPIDEMIOLOGICAL STUDY, IT'S A PRETTY POWERFUL TOOL IN

1 TERMS OF CAUSALITY.
2 BECAUSE MOST OF YOUR ERRORS IN EXPOSURE
3 ASSESSMENT ARE GOING TO BIAS YOU TOWARDS NOT FINDING A
4 DOSE RESPONSE. SO YOU'VE GOT TO -- SO IF YOU'RE
5 DOING -- SO IF YOU CAN, IF THE DATA ARE ADEQUATE TO DO A
6 DOSE-RESPONSE ANALYSIS, THAT HELPS IN THE INTERPRETATION
7 OF DATA.
8 Q OKAY.
9 A ON THE OTHER HAND, YOU COULD STILL DO A
10 DOSE-RESPONSE ANALYSIS AND DON'T HAVE VERY GOOD DATA.
11 AND YOU MIGHT BE STUDYING A POPULATION THAT,
12 IN FACT, YOU KNOW SUBSTANCE A CAUSES DISEASE B, AND YOU
13 FIND IT OVERALL, BUT YOU DON'T FIND IT IN YOUR
14 DOSE-RESPONSE ANALYSIS. AND YOU WONDER, WELL, WHY IS
15 THAT?
16 WELL, ONE THING, IT COULD BE A REFLECTION OF
17 A POOR DOSE ESTIMATION, BECAUSE YOUR ERRORS IN YOUR
18 EXPOSURE ESTIMATION WILL FLATTEN THE DOSE RESPONSE.
19 Q OKAY. AND WHAT ELSE, AS AN EPIDEMIOLOGIST,
20 DO YOU LOOK FOR IN EVALUATING EPIDEMIOLOGIC STUDIES?
21 A WELL, YOU WOULD SEE IF THE STUDY ACCOUNTED
22 FOR KNOWN CONFOUNDERS RELATED TO THE DISEASE.
23 Q OKAY.
24 A BUT THEN, ON THE OTHER HAND, THAT'S WHY DOSE
25 RESPONSE IS IMPORTANT, BECAUSE A LOT OF STUDIES, THEY'RE
26 ABLE TO MAYBE ADJUST -- STATISTICALLY ADJUST FOR
27 CONFOUNDERS, AND THEY HAVE VARYING DEGREES OF QUALITY OF
28 THE DATA RELATED TO CONFOUNDERS.

1 SO THAT'S WHY, WHEN YOU HAVE A DOSE-RESPONSE
2 ANALYSIS, IT OVERCOMES A LOT OF THAT.
3 Q WHAT ELSE DO YOU CONSIDER?
4 A WELL, IS THERE ADEQUATE STATISTICAL POWER?
5 LIKE FOR THE -- SAY, IF YOU'RE DOING A STUDY FOR THE
6 RISK YOU MIGHT EXPECT FROM THIS EXPOSURE, DO YOU HAVE
7 ENOUGH PEOPLE ENROLLED IN YOUR STUDY TO BE ABLE TO
8 IDENTIFY A 30 PERCENT INCREASE, A 50 PERCENT INCREASE, A
9 100 PERCENT INCREASE? THAT HAS TO DO WITH STATISTICAL
10 POWER.
11 AND WHEN YOU LOOK AT STATISTICAL POWER, IT
12 HAS TO DO WITH BETA ERROR. YOU HAVE ALPHA ERROR, AND
13 ALPHA ERROR HAS TO DO WITH LIKE STRENGTH OF THE
14 ASSOCIATION: IS THE RESULT STATISTICALLY SIGNIFICANT?
15 BUT WHEN YOU DO A STUDY AND YOU DON'T FIND
16 ANY INCREASE IN RISK, THEN THE QUESTION YOU WANT TO ASK:
17 WELL, WHAT'S THE BETA ERROR? WHAT WAS THE STRENGTH OF
18 THE STUDY? WHAT WAS THE STATISTICAL POWER THAT WAS
19 PROVIDED BY THE STUDY TO BE ABLE TO EVALUATE VARIOUS
20 ESTIMATES OF RELATIVE RISK IN THE STUDY?
21 Q OKAY. ANYTHING ELSE THAT YOU CONSIDER, AS
22 AN EPIDEMIOLOGIST, IN EVALUATING EPIDEMIOLOGIC STUDIES?
23 A WELL, THE FINAL THING IS -- AND I THINK
24 THIS -- ACTUALLY, THE LAST BULLET REALLY HAS TO DO WITH
25 INTERPRETATION IN EVALUATING THE STUDIES.
26 SO THE BIOLOGICAL PLAUSIBILITY REALLY HAS
27 MORE TO DO WITH YOUR INTERPRETATION OF THE
28 EPIDEMIOLOGICAL STUDY RESULTS. DOES IT MAKE SENSE FROM

1 THE OTHER TOXICITY OR MANIFESTATIONS OF TOXICITY THAT WE
2 KNOW ABOUT THE SUBSTANCE?
3 SO YOU NEED TO KNOW SOMETHING A LITTLE BIT
4 MORE THAN JUST DOING STATISTICAL ASSOCIATIONS. I
5 SUPPOSE ANYBODY CAN DO THAT. YOU HAVE TO TRY TO MAKE
6 SENSE OUT OF IT IN TERMS OF WHAT ELSE IS KNOWN ABOUT THE
7 SUBSTANCE THAT YOU'RE STUDYING.
8 Q OKAY.
9 A SO THE TOXICITY RELATED TO, LET'S SAY, THE
10 CANCER OR OTHER DISEASE THAT YOU MIGHT BE STUDYING.
11 Q LET'S TALK A LITTLE ABOUT DOSE-RESPONSE
12 RELATIONSHIPS. FIRST OF ALL, HAVE YOU PUBLISHED
13 ARTICLES REGARDING THAT TOPIC?
14 A YES, I HAVE.
15 Q OKAY. AND ARE THERE DIFFERENT MODES OF
16 EXPOSURE THAT CAN BE ASSESSED IN EVALUATING DOSE-
17 RESPONSE RELATIONSHIPS?
18 A WELL, YES. AND THEY ALL HAVE THEIR
19 STRENGTHS AND WEAKNESSES.
20 Q WOULD YOU TELL US ABOUT THESE.
21 A YES. WELL, THESE ARE THE MOST COMMONLY USED
22 ONES, CERTAINLY, IN COHORT STUDIES.
23 Q OKAY.
24 A YOU HAVE LIKE DURATION -- SAY, IN AN
25 OCCUPATIONAL STUDY, YOU HAVE DURATION OF EMPLOYMENT. SO
26 YOU MIGHT EVALUATE YOUR DATA BY, SAY, INDIVIDUALS
27 EXPOSED FOR 5 YEARS, THEN 5 TO 10 YEARS, THEN 10 TO 15
28 YEARS, TO SEE IF YOU CAN FIND -- I'M SORRY. I'M TALKING

1 ABOUT EMPLOYMENT NOW. THAT'S THE MOST CRUDE ONE.
2 Q RIGHT.
3 A AND EVALUATE THE DATA TO SEE, WITH AN
4 INCREASE IN EMPLOYMENT, IS THERE AN INCREASE IN THE
5 RISK? BUT THERE ARE HAZARDS TO THAT, AS I'LL POINT OUT
6 LATER.
7 Q OKAY.
8 A THEN NEXT IS DURATION OF EXPOSURE. YOU LOOK
9 AT THE NUMBER OF YEARS THEY'RE EXPOSED AND SEE IF YOU
10 HAVE -- WHEN YOU HAVE AN INCREASE IN THE EXPOSURE, DO
11 YOU HAVE AN INCREASE IN RISK?
12 Q OKAY.
13 A SO THAT'S ANOTHER ONE.
14 BUT THERE ARE PROBLEMS WITH DURATION OF
15 EXPOSURE. FOR EXAMPLE, WE KNOW THAT OVER TIME IN THE
16 INDUSTRIAL SETTING THAT EXPOSURES HAVE PRETTY MUCH
17 DECLINED OVER TIME BECAUSE THERE HAVE BEEN STANDARDS.
18 COMPANIES HAVE IMPROVED THEIR INDUSTRIAL HYGIENE.
19 SO AS PEOPLE ARE EMPLOYED, THE EXPOSURES ARE
20 REDUCED. SO YOU DON'T HAVE AS HIGH EXPOSURES, LET'S
21 SAY, TODAY IN THE WORKPLACE TO MANY, MANY SUBSTANCES
22 THAT YOU DID 50, 40 YEARS AGO.
23 Q OKAY.
24 A SO WHEN YOU'RE LOOKING AT DURATION OF
25 EXPOSURE, THE QUESTION IS, WELL -- AND YOU ONLY SEE AN
26 ANALYSIS BY THAT, THE QUESTION IS, WELL, WHEN WERE THEY
27 EXPOSED? BECAUSE 5 YEARS' DURATION OF EXPOSURE, SAY,
28 FROM 1950 TO 1955 MAY BE A LOT MORE THAN 20 YEARS'

1 EXPOSURE FROM 1970 TO 1990.
2 SO BY JUST DOING AN ANALYSIS BY DURATION OF
3 EXPOSURE, YOU HAVE TO GET A SENSE OF, WELL, WHEN THIS
4 COHORT WAS EXPOSED.
5 NOW, DURATION OF EXPOSURE WOULD BE A VERY
6 GOOD MEASURE OF EXPOSURE IF THE EXPOSURE WAS THE SAME
7 THROUGHOUT THE ENTIRE EMPLOYMENT PERIOD, BUT THAT'S
8 USUALLY NOT THE CASE IN THE OCCUPATIONAL SETTING. BUT
9 IT WOULD BE, IF THAT WERE THE CASE; BUT IT ISN'T.
10 Q WHAT ARE THE OTHER MODES OF EXPOSURE FOR
11 DOSE-RESPONSE ANALYSIS?
12 A WELL, YOU CAN ANALYZE DATA BY THE AVERAGE
13 LEVEL OF EXPOSURE OR BY THE MAXIMUM LEVEL OF EXPOSURE OR
14 BY CUMULATIVE EXPOSURE.
15 Q AND WHAT DOES THAT MEAN?
16 A CUMULATIVE EXPOSURE WOULD BE -- IT WOULD BE
17 DETERMINED BY MEASURING THE DURATION OF EXPOSURE BY THE
18 LEVEL OF EXPOSURE DURING THAT DURATION TIME PERIOD.
19 Q OKAY.
20 A AND AS YOU'RE DOING CUMULATIVE EXPOSURE, OF
21 COURSE, THAT WILL CHANGE OVER TIME, DEPENDING ON WHEN
22 THE EXPOSURES OCCURRED.
23 FOR EXAMPLE, LET'S SAY THAT BETWEEN 1950 TO
24 1960 -- THAT'S TEN YEARS -- YOU WERE EXPOSED TO 5 PARTS
25 PER MILLION OF BENZENE, 5 PARTS PER MILLION FOR TEN
26 YEARS IN THAT PERIOD.
27 SO LET'S SAY, OKAY, A WORKER THAT WORKED
28 THERE DURING THAT TEN-YEAR PERIOD WAS EXPOSED TO 5 PARTS

1 PER MILLION TIMES TEN YEARS. THAT PERSON'S EXPOSURE
2 WOULD BE 50 PARTS PER MILLION YEARS. IT'S SIMPLY A
3 PRODUCT OF THOSE TWO NUMBERS.
4 AND YOU COULD SAY THE SAME PERSON, HE WAS
5 EXPOSED FROM 1980 TO 1990, ANOTHER TEN-YEAR PERIOD, BUT
6 TO 1 PART PER MILLION. SO YOU WOULD MULTIPLY THE 1 PART
7 PER MILLION TIMES 10, AND YOU'D GET 10 PARTS PER MILLION
8 FOR THAT EXPOSURE PERIOD.
9 SO IF YOU ADD IT ALL UP, THEN IT WOULD BE 60
10 PARTS PER MILLION OF CUMULATIVE EXPOSURE -- 60 PARTS PER
11 MILLION YEARS OF CUMULATIVE EXPOSURE.
12 Q ALL RIGHT. NOW, ARE DOSE-RESPONSE
13 RELATIONSHIPS IMPORTANT IN ASSESSING CAUSALITY?
14 A YES.
15 Q WHO SAYS SO?
16 A WELL, I MEAN, THERE ARE A LOT OF -- I MEAN,
17 IT'S GENERALLY ACCEPTED IN THE FIELD OF EPIDEMIOLOGY.
18 AND I KNOW I POINTED UP SOME CITATIONS HERE.
19 Q INCLUDING THE INTERNATIONAL AGENCY FOR
20 RESEARCH ON CANCER?
21 A YES.
22 Q WHICH SAYS, SLIDE 57:
23 "IF THE RISK OF THE DISEASE IN QUESTION
24 INCREASES WITH THE AMOUNT OF EXPOSURE, THIS IS
25 CONSIDERED TO BE A STRONG INDICATION OF
26 CAUSALITY."
27 A YES; CORRECT.
28 MR. SCHURZ: OBJECTION; HEARSAY. HE'S JUST

1 READING.
2 THE COURT: OVERRULED.
3 Q BY MR. METZGER: AND DO YOU AGREE WITH THAT?
4 A YES, ABSOLUTELY. I MEAN, I'VE LECTURED --
5 SOME OF THOSE PAPERS AND LECTURES YOU HAD EARLIER, THESE
6 ARE SOME OF THE POINTS I RAISE -- I PRESENT IN THOSE
7 LECTURES.
8 Q OKAY. LET'S TALK ABOUT THIS CASE AND START
9 WITH ACRYLAMIDE, IF WE COULD. LET ME FIRST ASK YOU TO
10 TELL THE COURT WHAT --
11 THE COURT: WELL, IF WE'RE MOVING TO A NEW
12 SUBJECT, WE'RE GOING TO TAKE OUR MORNING RECESS AT THIS
13 TIME.
14 MR. METZGER: VERY GOOD, YOUR HONOR.
15 THE COURT: AND THEN I'LL CALL SOME OTHER CASES.
16 WE'LL BE IN RECESS FOR TEN MINUTES.
17 DR. INFANTE, YOU MAY STEP DOWN FOR A FEW
18 MINUTES.
19 THE WITNESS: THANK YOU.
20 (RECESS.)
21 THE COURT: GOOD MORNING AGAIN. BACK ON THE
22 RECORD IN CERT VS. STARBUCKS. ALL COUNSEL ARE PRESENT.
23 DR. INFANTE IS BACK ON THE STAND.
24 DO YOU UNDERSTAND YOU'RE STILL UNDER OATH?
25 THE WITNESS: YES.
26 THE COURT: RESTATE YOUR NAME FOR THE RECORD.
27 THE WITNESS: PETER FRANCIS INFANTE.
28 THE COURT: MR. METZGER WAS INQUIRING.

1 COUNSEL, YOU MAY PROCEED.
2 MR. METZGER: THANK YOU, YOUR HONOR.
3 Q DR. INFANTE, WOULD YOU INFORM THE COURT WHAT
4 I ASKED YOU TO DO INITIALLY FOR THIS CASE.
5 A YES. YOU ASKED ME TO EVALUATE THE RISK OF
6 CANCER AMONG ACRYLAMIDE-EXPOSED POPULATIONS.
7 Q AND DID YOU DO THAT?
8 A YES.
9 Q AND HOW DID YOU GO ABOUT DOING THAT?
10 A WELL, BY SELECTING POPULATIONS EXPOSED TO
11 ACRYLAMIDE AND EVALUATING THOSE STUDIES.
12 Q AND WHAT TYPES OF POPULATIONS WERE THEY?
13 A WELL, THE FIRST ONE THAT I SELECTED FOR
14 EVALUATION WAS OCCUPATIONAL EXPOSURES TO ACRYLAMIDE.
15 Q AND WHY DID YOU SELECT THAT FIRST?
16 A I SELECTED THE WORKERS BECAUSE THEY HAVE THE
17 HIGHEST EXPOSURES TO ACRYLAMIDE.
18 Q AND WHAT TYPE THE WORKERS ARE THOSE? THOSE
19 ARE INDUSTRIAL WORKERS INVOLVED IN THE PRODUCTION OF
20 ACRYLAMIDE?
21 A YES.
22 MR. METZGER: OKAY.
23 THE COURT: WHEN YOU SAY "PRODUCTION OF
24 ACRYLAMIDE," IS IT ACTUAL PRODUCTION OF THE CHEMICAL FOR
25 SOME PURPOSE, OR IS IT AN OFFSHOOT OF PRODUCTION OF
26 SOMETHING ELSE?
27 MR. METZGER: ACRYLAMIDE IS A MAJOR COMMODITY
28 CHEMICAL USED IN --

1 THE COURT: YOU DON'T HAVE TO ANSWER THE QUESTION.
2 LET THE WITNESS ANSWER IT.
3 MR. METZGER: OH, I'M SORRY; I'M SORRY.
4 THE COURT: WHEN YOU SAY "PRODUCTION OF
5 ACRYLAMIDE," WHAT DO YOU MEAN BY THAT?
6 THE WITNESS: WELL, THEY'RE MANUFACTURING
7 ACRYLAMIDE. IT'S BEEN USED AS -- LIKE IT'S A VERY GOOD
8 AGENT TO USE FOR GROUT, FOR EXAMPLE.
9 THE COURT: SO IT'S A SPECIFIC PRODUCTION FOR THE
10 PURPOSE OF PRODUCING ACRYLAMIDE; IT'S NOT AN OFFSHOOT
11 CHEMICAL OF SOMETHING ELSE?
12 THE WITNESS: CORRECT.
13 THE COURT: ALL RIGHT. THANK YOU.
14 COUNSEL.
15 Q BY MR. METZGER: AND WHAT WAS THE NEXT
16 ACRYLAMIDE-EXPOSED POPULATION THAT YOU CONSIDERED?
17 A I LOOKED AT THE EPIDEMIOLOGY RELATED TO THE
18 CONSUMPTION OF POTATOES.
19 Q AND CANCER?
20 A YES.
21 Q AND WHY DID YOU LOOK AT THAT NEXT?
22 A BECAUSE FRIED POTATOES HAVE THE HIGHEST
23 LEVELS IN ACRYLAMIDES IN THEM, OF FOODS.
24 Q OKAY. AND WHAT WAS THE THIRD POPULATION
25 THAT YOU CONSIDERED IN EVALUATING THE RISK OF CANCER
26 FROM ACRYLAMIDE?
27 A I LOOKED AT THE DIETARY STUDIES THAT WERE
28 DONE TO EVALUATE ACRYLAMIDE EXPOSURE AND RISK OF CANCER,

1 MINUS THE POTATO STUDIES.
2 Q ALL RIGHT. SO LET'S START WITH THE
3 OCCUPATIONAL STUDIES. AND WHAT STUDIES -- OR HOW MANY
4 STUDIES DID YOU IDENTIFY?
5 A I IDENTIFIED -- WELL, I HAVE A SLIDE WITH
6 THAT ON IT.
7 Q GO TO SLIDE 62.
8 A YES. THESE ARE THE STUDIES THAT I
9 IDENTIFIED OF WORKERS EXPOSED TO ACRYLAMIDE.
10 Q SOBEL --
11 A SOBEL, COLLINS, MARSH '99. THEN MARSH
12 CONTINUED FOLLOW-UP IN 2007. AND THEN THERE'S THE SWAEN
13 2007 STUDY.
14 Q OKAY. AND DID YOU EVALUATE ANY PARTICULAR
15 CANCERS FROM THESE STUDIES?
16 A WELL, I LOOKED AT THE CANCERS THAT WERE
17 PRESENTED IN THE RESULTS, YES.
18 Q WHAT DID YOU FIND?
19 A WELL, I FOUND THAT THERE WAS AN INCREASED
20 RISK OF PANCREATIC CANCER IDENTIFIED.
21 Q ALL RIGHT. AND WOULD YOU TELL THE COURT
22 WHAT THE DATA WAS REGARDING THAT.
23 A WELL, YES. IF YOU LOOK AT THE SOBEL, THE
24 1986 STUDY, YOU SEE THAT THE RELATIVE RISK OF CANCER WAS
25 2.2, AND THAT WAS NOT STATISTICALLY SIGNIFICANT.
26 Q SO IT WAS DOUBLE BUT NOT SIGNIFICANT?
27 A CORRECT.
28 Q GOT IT.

1 A DO YOU'D LOOK AT THE 95 PERCENT CONFIDENCE
2 INTERVAL. IT'S BELOW 1.
3 Q OKAY.
4 A THEN THE '99 STUDY BY COLLINS, ET AL.
5 Q 1989?
6 A 1989; I'M SORRY, YES.
7 AND THAT STUDY WAS OF WORKERS EXPOSED TO
8 ACRYLAMIDE. AND THERE, THEY ALSO DID DOSE ESTIMATIONS,
9 LIKE HOW MUCH ACRYLAMIDE WERE THEY EXPOSED TO?
10 THE COURT: WHEN YOU SAY "EXPOSURE TO ACRYLAMIDE,"
11 ARE THESE JUST BECAUSE ACRYLAMIDE IS IN THE AIR, OR
12 THERE HAS TO BE SOME INGESTION OF ACRYLAMIDE?
13 THE WITNESS: WELL, THAT'S A GOOD POINT. THESE
14 ARE ATMOSPHERIC EXPOSURES. I MEAN, WHETHER THERE'S SOME
15 ADDITIONAL INGESTION OR NOT, THEY DON'T MENTION IN THE
16 STUDY, BUT THAT WOULD --
17 THE COURT: SO THESE WORKERS WEREN'T --
18 THE WITNESS: MOSTLY, IT'S ATMOSPHERIC EXPOSURE.
19 THE COURT: THEY WEREN'T SITTING AROUND DRINKING
20 ACRYLAMIDE --
21 THE WITNESS: NO.
22 THE COURT: -- BUT THEY WERE EXPOSED BY SOME
23 AIRBORNE --
24 THE WITNESS: EXACTLY, YES.
25 THE COURT: ALL RIGHT. THANK YOU.
26 COUNSEL.
27 Q BY MR. METZGER: AND WHAT DID YOU NOTE FROM
28 THE COLLINS 1989 STUDY?

1 A WELL, IN THE COLLINS '89 STUDY, IT SHOWS THE
2 RELATIVE RISK FOR PANCREATIC CANCER, WHICH IS 2.03. IT
3 DIDN'T STATE WHETHER IT WAS SIGNIFICANT OR NOT.
4 BUT WHEN YOU LOOK AT THE DATA -- WAIT A
5 MINUTE. WHEN YOU LOOK AT THE DATA FOR INDIVIDUALS WHO
6 HAD CUMULATIVE EXPOSURES OF GREATER THAN .001 MICROGRAM
7 PER CUBIC METER YEARS, THE RISK WAS SIGNIFICANTLY
8 ELEVATED WHEN YOU ADJUST THE DATA FOR THAT.
9 I MADE THAT ADJUSTMENT BECAUSE I ADJUSTED
10 THE DATA FOR WHAT'S CALLED A "HEALTHY WORKER EFFECT."
11 Q WHAT IS THE "HEALTHY WORKER EFFECT"?
12 A WELL, THE "HEALTHY WORKER EFFECT" IS A
13 PHENOMENON FOUND WHEN YOU STUDY WORKERS, BECAUSE WORKERS
14 ARE HEALTHIER THAN THE GENERAL POPULATION. THEY HAVE TO
15 PASS A PHYSICAL EXAMINATION IN ORDER TO BE EMPLOYED. SO
16 THEY'RE HEALTHIER, IN GENERAL, THAN THE GENERAL
17 POPULATION FOR WHICH THEIR DISEASE RISK IS COMPARED TO.
18 LIKE FOR EXAMPLE, IF I WERE TO, SAY, TAKE
19 THE PEOPLE IN THIS ROOM IN A LARGE GROUP RIGHT NOW AND
20 COMPARE YOUR -- THE MORTALITY IN THIS GROUP TO THE
21 GENERAL POPULATION, THERE ARE PEOPLE RIGHT NOW, AS WE
22 SIT HERE, THAT ARE DYING FROM CANCER. SO WE WOULD BE
23 RELATIVELY HEALTHIER THAN THE GENERAL POPULATION.
24 Q OKAY.
25 A SO IT'S A PHENOMENON THAT IS CORRECTED FOR
26 WHEN YOU ARE REVIEWING DATA, AND THERE ARE TEXTBOOKS
27 THAT INDICATE HOW TO CORRECT FOR THE "HEALTHY WORKER
28 EFFECT."

1 Q AND HOW DID YOU ADJUST FOR THE "HEALTHY
2 WORKER EFFECT" HERE?
3 A WELL, IN THE COLLINS STUDY, WHERE YOU SEE
4 THAT THE RELATIVE RISK WAS 2.03, I ADJUSTED FOR THE --
5 THE "HEALTHY WORKER EFFECT" IN THAT STUDY WAS .081 FOR
6 ALL CAUSES OF DEATH.
7 SO WHAT THAT TELLS YOU IS THAT FOR ALL
8 CAUSES OF DEATH, THE ENTIRE COHORT ONLY HAS 81 PERCENT
9 OF MORTALITY AS COMPARED TO THE GENERAL POPULATION. SO
10 THEY'RE HEALTHIER.
11 IF THEY DIED AT THE SAME RATE AS THE GENERAL
12 POPULATION, THEN THE RELATIVE RISK WOULD BE 1; IT WOULD
13 BE THE SAME. IT'S 0.81. SO IT INDICATES THAT THEY'RE
14 HEALTHIER THAN THE GENERAL POPULATION.
15 THE COURT: IS THERE A REASON THAT YOU CAN
16 ATTRIBUTE WHY THEY'RE HEALTHIER THAN THE GENERAL
17 POPULATION?
18 THE WITNESS: YES. THEY'RE HEALTHIER BECAUSE IN
19 ORDER TO GET A BLUE-COLLAR JOB, YOU HAVE TO PASS A
20 PHYSICAL EXAMINATION. SO YOU'RE HEALTHIER THAN THE
21 GENERAL POPULATION.
22 THE COURT: AND THE FACT THAT THEY'RE WORKING,
23 PERIOD, PSYCHOLOGICALLY, I ASSUME, IS A HEALTHIER
24 ATMOSPHERE.
25 THE WITNESS: YES. AND OF COURSE, THEY HAVE OTHER
26 BENEFITS, TOO. THEY HAVE HEALTH CARE FROM THE JOB,
27 WHICH OTHER PEOPLE DON'T HAVE. AND THESE ARE MORTALITY
28 STUDIES. SO -- BUT IT'S WRITTEN, AND THERE ARE

1 SEVERAL --
2 THE COURT: LET ME ASK YOU THIS: WHEN YOU SAY
3 "HEALTHIER THAN THE GENERAL POPULATION," DOES THE
4 GENERAL POPULATION COVER ALL AGES AND ALL DEMOGRAPHICS?
5 THE WITNESS: THESE STUDIES ARE ADJUSTED FOR AGE,
6 SEX, AND RACE. THESE ARE MEN, SO IT WOULD BE --
7 THE COURT: ALL RIGHT. SO IF YOU HAVE A WORKER
8 GROUP THAT'S GENERALLY WORKERS BETWEEN AGE 25 AND 65,
9 COMPARED TO THE GENERAL POPULATION, DO YOU USE THE SAME
10 FACTORS --
11 THE WITNESS: YOU MATCH -- THAT'S A GOOD POINT.
12 YOU MATCH THEIR AGES TO THE GENERAL POPULATION. YOU
13 TAKE THEIR PERSON-YEARS, HOW OLD THEY ARE. AND THEN YOU
14 TAKE PEOPLE IN THE GENERAL POPULATION OF THAT SAME AGE
15 AND SEX. IF IT WAS MEN, YOU SAY, OKAY, BASED ON THAT,
16 HOW MANY WOULD YOU EXPECT?
17 AND THEN ONE OF THE CALCULATIONS IS HOW MANY
18 DEATHS FROM ALL CAUSES. AND WHEN YOU SEE THAT .81, IT
19 TELLS YOU THAT THERE'S A "HEALTHY WORKER EFFECT," WHICH
20 YOU SEE IN MOST OCCUPATIONAL STUDIES.
21 THE COURT: THANK YOU.
22 THE WITNESS: SO --
23 Q BY MR. METZGER: SO DR. INFANTE -- I'M
24 SORRY. HOW DID YOU ADJUST FOR THE "HEALTHY WORKER
25 EFFECT"? CAN YOU JUST GENERALLY EXPLAIN THAT.
26 A YES. YOU TAKE THE -- YOU'VE GOT THE RISK
27 RATIO OF 2.03. AND SO, IN ESSENCE, YOU DIVIDE THAT BY
28 .81, AND YOU COME UP WITH 2.51.

1 AND THAT RESULT IS STATISTICALLY SIGNIFICANT
2 BECAUSE THE 95 PERCENT CONFIDENCE INTERVAL I CALCULATED
3 FOR IT IS 1.08 TO 4.94.
4 Q OKAY.
5 A SO I'VE MADE THAT ADJUSTMENT FOR THE
6 "HEALTHY WORKER EFFECT."
7 Q ALL RIGHT. AND WHAT IS THE SIGNIFICANCE TO
8 YOU, AS AN EPIDEMIOLOGIST, THAT THE WORKERS WHO HAD A
9 CUMULATIVE EXPOSURE OF GREATER THAN .001 MILLIGRAM PER
10 CUBIC METER YEARS HAD A 2.5-FOLD RISK OF PANCREATIC
11 CANCER THAT WAS STATISTICALLY SIGNIFICANT WHEN ADJUSTED
12 FOR THE "HEALTHY WORKER EFFECT"?
13 A WELL, IT TELLS YOU THEY HAVE AN ELEVATED
14 RISK OF PANCREATIC CANCER IN RELATION TO THE GENERAL
15 POPULATION.
16 Q OKAY. AND DID YOU NOTE ABOUT THE MARSH 1999
17 STUDY?
18 A WELL, IF YOU LOOK AT THE MARSH 1999 STUDY,
19 AND IF YOU TAKE WORKERS THAT HAD IN THAT STUDY THE
20 HIGHEST CUMULATIVE EXPOSURE, YOU SEE THAT FOR THOSE WHO
21 WERE EXPOSED TO GREATER THAN .3 MILLIGRAMS PER CUBIC
22 METER YEARS, THEIR RELATIVE RISK IS 2.26. AND THAT WAS
23 STATISTICALLY SIGNIFICANT.
24 Q OKAY. AND WHAT DID YOU CONSIDER ABOUT THE
25 MARSH 2007 UPDATE?
26 A WELL, THE MARSH 2007 UPDATE, WHEN YOU LOOK
27 AT -- AND I HAD TO GO BY THE CATEGORIES OF EXPOSURE THAT
28 THEY HAD. AND YOU LOOK AT INDIVIDUALS WHO HAD

1 CUMULATIVE EXPOSURES ABOVE 0.001 MILLIGRAMS PER CUBIC
2 METER, THE RISK THAT THEY CALCULATED WAS 1.41. AND THAT
3 RESULT WAS NOT STATISTICALLY SIGNIFICANT.
4 AND THAT WAS BASED ON A COMPARISON TO LOCAL
5 RATES. AND SO WHEN YOU LOOK AT THEIR OVERALL MORTALITY
6 COMPARED TO -- SO ANYHOW, THAT WAS BASED ON USING LOCAL
7 RATES. RATHER THAN NATIONAL RATES, THEY USED LOCAL
8 RATES TO COMPARE IT TO.
9 THEN WHEN I LOOKED AT THOSE WHO WERE
10 UNEXPOSED -- IN THE SAME PLANT, WHO WERE UNEXPOSED TO
11 ACRYLAMIDE, THEIR RATE FOR PANCREATIC CANCER WAS 0.78.
12 SO THAT TELLS ME THAT THESE WORKERS WHO WORK
13 AT THAT PLANT, WERE INDUSTRIAL WORKERS, AND WHO WERE NOT
14 EXPOSED TO ACRYLAMIDE, THEIR BACKGROUND RISK IS 0.78
15 COMPARED TO THE GENERAL POPULATION. IN OTHER WORDS,
16 THEY HAVE A FAVORABLE MORTALITY RATE FROM PANCREATIC
17 CANCER.
18 SO THAT SHOULD BE THE -- THAT'S THE MOST
19 APPROPRIATE COMPARISON POPULATION, OTHER WORKERS WHO ARE
20 NOT EXPOSED. BECAUSE IT MATCHES FOR HEALTH CARE,
21 SOCIOECONOMIC STATUS, OTHER FACTORS THAT YOU CAN'T
22 CONTROL FOR, BECAUSE THEY WORK AT THE SAME PLANT EXCEPT
23 THEY NOT EXPOSED; SAME PLANT, BUT THEY'RE NOT EXPOSED.
24 SO WHEN I TAKE THE DEATH RATE FROM
25 PANCREATIC CANCER FOR THE UNEXPOSED, WHICH WAS .78, AND
26 I TAKE THE 1.41, I DIVIDE IT BY THE .78 AND SAY, LOOK,
27 THEIR RISK, THEN, FOR THE EXPOSED IS 1.81. AND THAT'S
28 STATISTICALLY SIGNIFICANT.

1 Q OKAY.
2 A AND WHEN I HAVE VERSUS UNEXPOSED, THAT MEANS
3 UNEXPOSED IN THE SAME INDUSTRIAL PLANTS. AND IT'S WELL
4 ACCEPTED IN OCCUPATIONAL EPIDEMIOLOGY THAT THE MOST
5 FAVORABLE COMPARISON GROUP ARE OTHER WORKERS AT THE SAME
6 FACILITIES WHO WERE NOT EXPOSED.
7 THE COURT: ALL RIGHT. THANK YOU.
8 MR. METZGER, THIS IS ALL VERY INTERESTING.
9 WHAT IS THE RELEVANCE TO THIS CASE?
10 MR. METZGER: OH, IT IS EXTREMELY RELEVANT, YOUR
11 HONOR. BECAUSE BELIEVE IT OR NOT, THIS CASE IS ACTUALLY
12 ABOUT ACRYLAMIDE AND WHETHER ACRYLAMIDE CAUSES CANCER.
13 THE COURT: ALL RIGHT. BUT PEOPLE WALKING IN THE
14 SUPERMARKET AND BUYING COFFEE OR GOING INTO STARBUCKS,
15 UNLESS THEY'RE SNIFFING AT THE COFFEE- MAKING MACHINE,
16 THEY'RE NOT -- AT LEAST THERE'S NO ALLEGATION ABOUT
17 BEING EXPOSED TO ACRYLAMIDE EXCEPT THROUGH THE PROCESS
18 OF DRINKING COFFEE.
19 MR. METZGER: OKAY. WELL, THERE'S OTHER
20 RELEVANCE, YOUR HONOR. FOR EXAMPLE, DR. BOFFETTA
21 RENDERED AN OPINION THAT ACRYLAMIDE DOES NOT CAUSE HUMAN
22 CANCER. THIS IS SHOWING THAT, IN FACT, ACRYLAMIDE
23 EXPOSURE DOES SIGNIFICANTLY INCREASE THE RISK OF CANCER,
24 AT LEAST PANCREATIC CANCER.
25 SO I MEAN, THERE'S MULTIPLE RELEVANCE TO
26 THIS. I'M NOT SAYING THAT THIS -- THIS IS ONE PIECE OF
27 THE PUZZLE. IT'S A COMPLEX PUZZLE IN THIS CASE.
28 THE COURT: ALL RIGHT. WELL, I GUESS WE'LL

1 EVENTUALLY GET TO A DISCUSSION ABOUT THE EFFECT OF
2 DILUTION IN TERMS OF ACRYLAMIDE.
3 AND I UNDERSTAND YOUR POSITION IS THAT
4 ACRYLAMIDE IS CARCINOGENIC, A TOXIC CHEMICAL; AND IT'S
5 CARCINOGENIC, AND IT'S CARCINOGENIC.
6 BUT THE QUESTION IS -- IT COMES BACK TO THE
7 ISSUE, WHICH I GUESS IS THE MAJOR ISSUE BETWEEN THE
8 PARTIES, AS TO THE EFFECT WITH REGARD TO CONSUMPTION OF
9 COFFEE. ARE WE GOING TO LOOK AT IT ONLY AS ACRYLAMIDE
10 AS ITSELF, AND THEREFORE THE WARNING IS NECESSARY; OR
11 RATHER, IN THE CONTEXT OF IT BEING DILUTED IN COFFEE?
12 MR. METZGER: RIGHT. AND AS WE GET THROUGH THE
13 LOWER EXPOSURE TO ACRYLAMIDE, I THINK WE'LL SEE THIS.
14 BUT RIGHT NOW, THIS IS THE HIGHEST EXPOSED ACRYLAMIDE
15 GROUP.
16 WE'RE THEN GOING TO TALK ABOUT THE POTATO
17 CONSUMPTION, WHICH IS THE NEXT HIGHEST. AND THEN THE
18 DIETARY. SO WE'LL BE GETTING THERE.
19 THE COURT: ALL RIGHT.
20 MR. METZGER: OKAY.
21 THE COURT: GO AHEAD.
22 Q BY MR. METZGER: SO LASTLY, DR. INFANTE, I
23 THINK WE'RE NOW UP TO THE SWAEN 2007 UPDATE. AND THIS
24 IS THE DUTCH ACRYLAMIDE PRODUCTION WORKERS. WHAT DID
25 YOU NOTE OF SIGNIFICANCE IN THAT STUDY?
26 A WELL, IN THIS STUDY, THERE'S AN ELEVATED
27 RISK, LIKE A 2.66-FOLD INCREASED RISK, FOR PANCREATIC
28 CANCER, BUT THE RESULT IS NOT STATISTICALLY SIGNIFICANT;

1 BUT IT'S A HIGH RISK.
2 AND THE REASON IT ISN'T STATISTICALLY
3 SIGNIFICANT WITH SUCH A HIGH RISK IS BECAUSE IT'S A
4 SMALL POPULATION. IT DOESN'T HAVE A LOT OF STATISTICAL
5 POWER.
6 Q ALL RIGHT. NOW, DID YOU ALSO ASSESS DOSE-
7 RESPONSE RELATIONSHIPS FOR THE ACRYLAMIDE PRODUCTION
8 WORKERS IN RELATIONSHIP TO PANCREATIC CANCER?
9 A YES.
10 Q ALL RIGHT. WILL YOU GO TO SLIDE 65 --
11 THE COURT: LET ME ASK DEFENDANTS: DO DEFENDANTS
12 DISPUTE THAT ACRYLAMIDE CAN CAUSE THE RISK OF CANCER,
13 ACRYLAMIDE BY ITSELF?
14 MR. SCHURZ: YES, YOUR HONOR, WE DO. AND WE WILL
15 SHOW -- AND AS THIS TABLE SHOWS, THE OCCUPATIONAL
16 EPIDEMIOLOGY DOES NOT SHOW THAT EXPOSURE TO ACRYLAMIDE
17 CAUSES CANCER IN WORKERS. DR. INFANTE WAS ABLE TO
18 ACHIEVE THE STATISTICAL SIGNIFICANCE BY --
19 THE COURT: WELL, YOU DON'T HAVE TO ARGUE IT. I
20 JUST WANT TO KNOW WHAT YOUR POSITION IS.
21 SO YOU'RE CONTESTING WHETHER ACRYLAMIDE IN
22 ITSELF, IN ITS PUREST FORM -- IF SUCH EXISTS -- WHETHER
23 IT'S IN THE AIR OR IN SOME PRODUCT, THAT YOU'RE
24 CONTESTING THAT IT HAS ANY RISK OF CAUSING CANCER.
25 MR. SCHURZ: TWO-PART ANSWER, YOUR HONOR.
26 FIRST, WE THINK THE RELEVANT EVIDENCE HERE
27 IS COFFEE. WE THINK THE RELEVANT EVIDENCE --
28 THE COURT: I KNOW. WE'RE GOING TO GET TO THAT,

1 WHEN THEY DILUTE IT IN COFFEE, OR WHATEVER.
2 MR. SCHURZ: YES. AND SO WE QUESTION THE
3 RELEVANCE WITH RESPECT TO OCCUPATIONAL STUDIES RELATING
4 TO THOSE WHO ARE EXPOSED TO AIRBORNE ACRYLAMIDE.
5 HAVING SAID THAT, WE -- AS DR. BOFFETTA
6 TESTIFIED, THE DIETARY ACRYLAMIDE STUDIES, AS WELL AS
7 THE OCCUPATIONAL ACRYLAMIDE STUDIES, DO NOT ESTABLISH
8 THAT ACRYLAMIDE, IN THE EXPOSURES THAT ARE EXPERIENCED
9 IN THESE TWO CONTEXTS, RESULT IN INCREASED RISK OF
10 CANCER.
11 THE COURT: ALL RIGHT. THANK YOU.
12 MR. METZGER, YOU MAY PROCEED.
13 MR. METZGER: ALL RIGHT.
14 Q SO WOULD YOU EXPLAIN TO THE COURT HOW YOU
15 WENT ABOUT ASSESSING EXPOSURE -- OR DOSE-RESPONSE
16 RELATIONSHIPS FROM THESE OCCUPATIONAL COHORT STUDIES.
17 A YES. WELL, I TOOK THE DATA FROM THE TABLE.
18 THIS IS FROM TABLE 7 IN MARSH 1999. AND IF YOU LOOK AT
19 IT, YOU'LL GET DURATION OF EXPOSURE.
20 AND THEN YOU LOOK AT THE STANDARDIZED
21 MORTALITY RATIO, YOU CAN SEE THAT -- I MEAN, DURATION OF
22 EMPLOYMENT. AS IT INCREASES, THE RISK OF PANCREATIC
23 CANCER INCREASES.
24 NOW, YOU SAY, WELL, THAT SEEMS LIKE A SMALL
25 RISK. HOWEVER, OF THOSE 44 CASES UNDER DURATION OF
26 EMPLOYMENT, 30 OF THEM ARE ACTUALLY NOT EVEN EXPOSED TO
27 ACRYLAMIDE. SO THAT'S GOING TO -- THAT WILL DILUTE OUT
28 THE FINDINGS FOR THOSE THAT ARE EXPOSED TO ACRYLAMIDE,

1 BECAUSE YOU'VE GOT ALL THE DENOMINATORS FOR THOSE PEOPLE
2 IN THAT POPULATION ALSO.
3 SO NOW, AS YOU GO TO DURATION OF EXPOSURE --
4 Q HOLD ON, DR. INFANTE.
5 A YEAH.
6 Q JUST A MINUTE. SO YOU LOOKED AT DURATION OF
7 EMPLOYMENT, AND YOU LOOKED AT DURATION OF EXPOSURE. AND
8 DID YOU ALSO LOOK AT OTHER FACTORS IN ASSESSING DOSE-
9 RESPONSE RELATIONSHIPS?
10 A YES.
11 Q WHAT OTHER FACTORS?
12 A WELL, I LOOKED AT THE MEAN INTENSITY OF
13 EXPOSURE, WHICH IS PRESENTED IN THIS TABLE, AND ALSO
14 CUMULATIVE EXPOSURE.
15 Q ALL RIGHT. SO YOU LOOKED AT FOUR METRICS OF
16 EXPOSURE IN RELATIONSHIP TO DOSE RESPONSE?
17 A YES, THAT ARE PRESENTED BY THE AUTHORS.
18 Q ALL RIGHT. SO THE FIRST TABLE YOU HAVE HERE
19 IS REGARDING DURATIONS OF EMPLOYMENT. AND YOU HAVE LESS
20 THAN 1 YEAR, 1 TO 14 YEARS, AND 15 OR MORE YEARS. AND
21 THE STANDARDIZED MORTALITY RATIO GOES FROM 0.87 TO 0.95
22 TO 1.19; IS THAT CORRECT?
23 A CORRECT.
24 Q AND WHAT DID THAT INDICATE TO YOU?
25 A WELL, THAT INDICATES A DOSE RESPONSE BY
26 DURATION OF EMPLOYMENT.
27 Q BECAUSE AS THE DURATION OF EMPLOYMENT
28 INCREASES, THE MORTALITY RATIO -- STANDARDIZED MORTALITY

1 RATIO INCREASES?
2 A CORRECT.
3 Q ALL RIGHT. AND IS THAT A STATISTICALLY
4 SIGNIFICANT DOSE RESPONSE?
5 A NO, IT IS NOT STATISTICALLY SIGNIFICANT.
6 Q OKAY.
7 A BUT NEVERTHELESS, IT'S A DOSE RESPONSE. BUT
8 AS I INDICATED, THE REASONS I INDICATED, IT'S DILUTED
9 OUT A LOT BECAUSE THERE ARE 30 INDIVIDUALS IN THAT FIRST
10 ANALYSIS THAT AREN'T EVEN EXPOSED TO ACRYLAMIDE.
11 Q OKAY. NOW, IF WE GO TO THE NEXT METRIC THAT
12 YOU CONSIDERED, DURATION OF EXPOSURE, YOU HAVE HERE THE
13 NUMBER OF YEARS OF EXPOSURE, NOT JUST EMPLOYMENT;
14 CORRECT?
15 A YES; CORRECT.
16 Q ALL RIGHT. AND WHAT YOU HAVE HERE IS FOUR
17 CATEGORIES: THE FIRST ONE "UNEXPOSED," AND THEN THREE
18 INCREASING CATEGORIES OF NUMBER OF YEARS. AND THEN YOU
19 HAVE THE STANDARDIZED MORTALITY RATIO.
20 AND IT GOES FROM 0.80 FOR THE UNEXPOSED, TO
21 1.46 FOR THE FIRST EXPOSURE LEVEL -- DURATION LEVEL, AND
22 THEN 1.79 FOR THOSE EXPOSED 5 TO 15 YEARS -- TO 19
23 YEARS, AND 2.42 FOR THOSE EXPOSED 20 OR MORE YEARS; IS
24 THAT CORRECT?
25 A YES.
26 Q OKAY. AND THE REASON I'M ACTUALLY READING
27 THIS IS BECAUSE THAT WILL NOW BE IN EVIDENCE, JUST SO
28 YOU UNDERSTAND. WHAT'S ON THE SLIDE IS NOT IN EVIDENCE.

1 ALL RIGHT. AND WHAT DID YOU NOTE OF
2 SIGNIFICANCE OR IMPORTANCE TO YOU FROM THE STANDARDIZED
3 MORTALITY RATIOS BY DURATION OF EXPOSURE?
4 A YOU SEE A DOSE RESPONSE BY DURATION OF
5 EXPOSURE. IN OTHER WORDS, AS YOU HAVE AN INCREASE IN
6 THE DURATION OF EXPOSURE, YOU HAVE AN INCREASE IN THE
7 RISK OF PANCREATIC CANCER.
8 Q OKAY. LET'S GO TO THE NEXT SLIDE. AND
9 HERE, YOU EVALUATED MEAN INTENSITY OF EXPOSURE. FIRST,
10 WILL YOU TELL THE COURT WHAT THAT IS.
11 A WELL, THAT WOULD BE THE AVERAGE LEVEL OF
12 EXPOSURE FOR THOSE WORKERS.
13 Q OKAY. YOU HAVE FOUR CATEGORIES HERE, THE
14 FIRST BEING MEAN INTENSITY OF EXPOSURE EXPRESSED IN
15 MILLIGRAMS PER CUBIC METER OF AIR; IS THAT CORRECT?
16 A YES.
17 Q ALL RIGHT. AND THOSE -- YOU HAVE FOUR
18 CATEGORIES, FROM ZERO UP TO 0.3 OR ABOVE; CORRECT?
19 A YES.
20 Q AND THEN THE STANDARDIZED MORTALITY RATIO IS
21 0.80 FOR THE UNEXPOSED, AND 2.31 FOR THOSE EXPOSED TO
22 THE HIGHEST MEAN INTENSITY OF EXPOSURE. AND THE NUMBERS
23 GO -- WOULD YOU EXPLAIN -- WELL, THE NUMBERS GO FROM
24 0.80, TO 1.69, TO 1.50, TO 2.31; IS THAT CORRECT?
25 A YES.
26 Q AND WHAT DID YOU -- WHAT ELSE DID YOU DO
27 HERE REGARDING THE STANDARDIZED MORTALITY RATIO?
28 A WELL, WHAT I DID THERE IS THAT -- IT LOOKS

1 LIKE IT'S A DOSE RESPONSE, BUT IN FACT, IF YOU COMBINE
2 THE TWO LOWER EXPOSURE GROUPS, YOU GET A MONOTONIC DOSE
3 RESPONSE.
4 SO IT GOES FROM .8 TO THE UNEXPOSED, TO 1.57
5 FOR THE TWO LOWEST EXPOSURE GROUPS, THEN UP TO 2.31.
6 Q AND WHERE DID THE 1.57 COME FROM?
7 A IT COMES FROM COMBINING THE DATA FOR THE
8 ZERO POINT -- FOR THE SECOND AND THIRD EXPOSURE GROUPS.
9 Q WHO DID THAT?
10 A WELL, I'M PRESENTING IT HERE. I DID THAT
11 FOR THIS ANALYSIS, BUT I GOT THE IDEA OF COMBINING THAT
12 FROM SHULZ 2001, WHO DID IT FOR, IN FACT, CUMULATIVE
13 EXPOSURE, WHICH IS IN THE NEXT SLIDE.
14 Q AND IS THAT A PUBLISHED STUDY?
15 A YES.
16 Q ALL RIGHT. AND SO SCHULZ DID IT FOR
17 CUMULATIVE EXPOSURE. AND AGAIN, YOU HAVE FOUR
18 CATEGORIES HERE OF CUMULATIVE EXPOSURE, WITH THE
19 STANDARDIZED MORTALITY RATIO GOING FROM 0.80, TO 2.77,
20 TO 0.73, TO 2.26.
21 AND WHAT DID YOU ASSESS FROM THAT?
22 A WELL, I ASSESSED FROM THAT THAT THERE IS A
23 DOSE RESPONSE, AGAIN, BUT THIS TIME BY CUMULATIVE
24 EXPOSURE. AND THAT HIGHEST DOSE GROUP, THE 2.26, THAT
25 RESULT IS STATISTICALLY SIGNIFICANT. I DIDN'T PUT ANY
26 CONFIDENCE INTERVALS, BUT THE 2.26 IS STATISTICALLY
27 SIGNIFICANT.
28 NOW, I COMBINED THE TWO LOWER DOSE GROUPS

1 TOGETHER, THE ONE THAT HAS THREE DEATHS AND THE ONE THAT
2 HAS TWO DEATHS. AND I DID THAT BECAUSE I THOUGHT IT WAS
3 A GOOD ANALYSIS TO DO BECAUSE THE NUMBERS ARE SO SMALL,
4 SO YOU GET A LITTLE MORE STRENGTH FOR THOSE DATA POINTS.
5 AND IN FACT, SCHULZ HAD PUBLISHED THE
6 IDENTICAL ANALYSIS IN 2001, SAYING, "HEY, IF YOU ANALYZE
7 THE DATA IN THE STUDY FOR PROSTATE CANCER, YOU COMBINE
8 THE TWO -- THE DATA IN THE TWO LOWER DOSE GROUPS, YOU,
9 IN FACT, HAVE A MONOTONIC DOSE RESPONSE FOR EXPOSURE TO
10 ACRYLAMIDE AND PANCREATIC CANCER."
11 Q ALL RIGHT. WOULD YOU GO TO THE NEXT SLIDE.
12 AND IS THIS THE TABLE FROM SCHULZ THAT
13 YOU'RE REFERRING TO?
14 A YES, IT IS. AND THAT WAS PUBLISHED IN 2001
15 IN THE "JOURNAL OF OCCUPATIONAL AND ENVIRONMENTAL
16 MEDICINE."
17 Q ALL RIGHT. FOR HIS SECOND EXPOSURE GROUP,
18 HE HAS AN SMR -- STANDARDIZED MORTALITY RATIO -- OF
19 1.31.
20 AND IF YOU GO BACK ONE SLIDE, THAT'S WHERE
21 YOU GOT THAT?
22 A CORRECT.
23 Q ALL RIGHT. GO FORWARD ONE SLIDE.
24 AND I THINK YOU TOLD US THAT IN THE HIGHEST
25 EXPOSURE GROUP, CUMULATIVE EXPOSURE GROUP, THE
26 STANDARDIZED MORTALITY RATIO OF 2.26 WAS STATISTICALLY
27 SIGNIFICANT. AND IS THAT SHOWN HERE IN THE SCHULZ
28 TABLE?

1 A YES, BECAUSE THE LOWER BOUND OF THE 95
2 PERCENT CONFIDENCE INTERVAL IS ABOVE 1.
3 Q OKAY. NOW, DID YOU PERFORM A SIMILAR
4 ANALYSIS FOR THE MARSH 2007 UPDATE OF THE ACRYLAMIDE
5 PRODUCTION WORKER COHORT STUDY?
6 A YES.
7 Q ALL RIGHT. COULD YOU GO TO THE NEXT SLIDE.
8 AND FOR DURATION OF EMPLOYMENT FOR THE THREE
9 CATEGORIES, THE STANDARDIZED MORTALITY RATIO WENT FROM
10 0.82, TO 0.84, TO 1.17; CORRECT?
11 A CORRECT.
12 Q AND WHAT DID YOU CONSIDER ABOUT THAT?
13 A WELL, IT'S SHOWING A SLIGHT DOSE RESPONSE;
14 BUT AGAIN, THERE'S A LOT OF DILUTION IN IT.
15 Q OKAY. AND FOR DURATION OF EXPOSURE FOR THE
16 FOUR EXPOSURE CATEGORIES -- DURATION OF EXPOSURE
17 CATEGORIES, THE STANDARDIZED MORTALITY RATIO WENT FROM
18 0.78, TO 1.12, TO 1.55, TO 1.81 IN THE HIGHEST DURATION
19 OF EXPOSURE GROUP; IS THAT CORRECT?
20 A YES.
21 Q AND WHAT DID YOU MAKE OF THAT?
22 A WELL, IT'S SHOWING A DOSE RESPONSE BY
23 DURATION OF EXPOSURE.
24 Q OKAY. AND IF WE GO TO THE NEXT SLIDE.
25 FOR THE MARSH 2007 UPDATE, DID YOU ALSO SHOW
26 A MEAN INTENSITY OF EXPOSURE DOSE RESPONSE WHEN
27 COMBINING THE MIDDLE EXPOSURE GROUPS, AS SCHULZ DID?
28 A YEAH. WELL, THE TWO LOWER EXPOSURE GROUPS,

1 YES.
2 Q I'M SORRY.
3 A WELL, I GUESS THEY'RE IN THE MIDDLE IF YOU
4 CONSIDER, I GUESS, UNEXPOSED AS AN EXPOSURE; CORRECT.
5 SORRY.
6 Q ALL RIGHT. AND THAT WENT FROM 0.78, TO
7 1.34, TO 1.11, TO 1.85, WITH THE TWO -- WITH THE
8 COMBINED GROUP OF 1.22; IS THAT CORRECT?
9 A YES.
10 Q ALL RIGHT. AND THEN FOR THE CUMULATIVE
11 EXPOSURE, DID YOU FIND A SIMILAR DOSE-RESPONSE
12 RELATIONSHIP?
13 A YES, I DID. AND COMBINING -- AS I'M
14 SHOWING, IF YOU COMBINE THE TWO MIDDLE GROUPS, YOU HAVE
15 A MONOTONIC DOSE RESPONSE: FROM .78, TO 1.15, TO 1.71.
16 Q OKAY. WELL, WHAT WAS YOUR ULTIMATE
17 CONCLUSION, DR. INFANTE, FROM THESE ANALYSES -- THESE
18 DOSE-RESPONSE ANALYSES THAT YOU DID REGARDING THE
19 OCCUPATIONAL COHORT STUDIES FOR ACRYLAMIDE PRODUCTION
20 WORKERS IN RELATIONSHIP TO THEIR DEVELOPMENT OF
21 PANCREATIC CANCER?
22 A WELL, MY CONCLUSION WAS THAT THE DATA SHOW
23 AN INCREASED RISK OF PANCREATIC CANCER AMONG PRODUCTION
24 WORKERS EXPOSED TO ACRYLAMIDE.
25 Q AND WHAT DID YOU CONCLUDE REGARDING DOSE
26 RESPONSE?
27 A WELL, THEY ALSO DEMONSTRATED -- IT'S A
28 LARGER STUDY THAT DEMONSTRATES A DOSE RESPONSE, WHICH IS

1 A POWERFUL TOOL IN EPIDEMIOLOGY.
2 Q WHY IS IT A POWERFUL TOOL?
3 A WELL, IT'S A POWERFUL TOOL, AS I EXPLAINED
4 EARLIER, BECAUSE ALL OF YOUR ERRORS IN EXPOSURE
5 ASSESSMENT ARE GOING TO BIAS YOU TOWARDS NOT FINDING A
6 DOSE RESPONSE.
7 Q OKAY. SO WHAT WAS THE SIGNIFICANCE TO YOU
8 OF FINDING A DOSE RESPONSE IN THESE STUDIES THAT WAS
9 APPARENT USING FOUR DIFFERENT METRICS OF EXPOSURE?
10 A WELL, TO ME, I THINK IT PROVIDES STRONG
11 EVIDENCE OF AN ASSOCIATION AMONG THESE WORKERS BETWEEN
12 EXPOSURE TO ACRYLAMIDE AND RISK OF PANCREATIC CANCER.
13 MR. METZGER: ALL RIGHT. THANK YOU.
14 YOUR HONOR, WE'RE GOING TO START A NEW
15 TOPIC. DO WE HAVE TIME?
16 THE COURT: YES. GO AHEAD.
17 MR. METZGER: ALL RIGHT.
18 Q SO YOU TOLD US, DR. INFANTE, THAT THE NEXT
19 TYPE OF EPIDEMIOLOGIC STUDIES THAT YOU EVALUATED
20 REGARDING ACRYLAMIDE AND CANCER WAS STUDIES REGARDING
21 CANCER AND CONSUMPTION OF POTATOES.
22 A YES.
23 Q OKAY. AND I THINK YOU INDICATED THAT WAS
24 BECAUSE POTATOES CONTAIN THE HIGHEST LEVELS OF
25 ACRYLAMIDE IN THE HUMAN DIET?
26 A THAT'S MY UNDERSTANDING, YES.
27 Q OKAY. NOW, WAS THIS ISSUE OF WHETHER
28 CONSUMPTION OF COOKED POTATOES INCREASES THE RISK OF

1 CANCER SOMETHING THAT HAD BEEN EVALUATED BY DR. BOFFETTA
2 IN HIS 2011 REVIEW?
3 A YES.
4 Q AND DID YOU READ DR. BOFFETTA'S 2011 REVIEW
5 REGARDING THIS ISSUE?
6 A YES. WELL, THERE WERE OTHER CO-AUTHORS ON
7 THIS REVIEW; BUT YES, I DID.
8 Q YES. COULD YOU GO TO THE NEXT SLIDE. GO TO
9 SLIDE 74; I'M SORRY. ALL RIGHT.
10 AND WHAT DID YOU FIND FROM DR. BOFFETTA'S
11 REVIEW REGARDING STUDIES OF POTATO CONSUMPTION AND
12 CANCER?
13 A WELL, HE WAS DOING A REVIEW OF ACRYLAMIDE IN
14 THE DIET AND CANCER RISK, AND THERE'S ONE SECTION WHERE
15 HE FOCUSED ON POTATO CONSUMPTION BECAUSE POTATOES HAVE
16 THE HIGHEST AMOUNT OF ACRYLAMIDE IN DIETARY FOODS.
17 AND WHAT I HAD NOTICED IS THAT --
18 THE COURT: IS THAT POTATOES IN THEMSELVES, OR IS
19 IT THE FRYING OF POTATOES?
20 THE WITNESS: THE FRYING OF THE POTATOES. AND THE
21 MORE YOU FRY THEM, THE CRISPER YOU GET, THE MORE
22 ACRYLAMIDE THEY HAVE.
23 THE COURT: BUT THE POTATOES THEMSELVES DON'T
24 CONTAIN ACRYLAMIDE; IS THAT RIGHT?
25 THE WITNESS: I THINK YOU HAVE TO -- IT'S THE
26 HEATING PROCESS THAT FORMS THE ACRYLAMIDE.
27 THE COURT: OKAY.
28 Q BY MR. METZGER: OKAY. AND HOW MANY STUDIES

1 DID DR. BOFFETTA, IN HIS 2011 REVIEW, IDENTIFY REPORTING
2 INCREASED RISKS OF CANCER FROM CONSUMPTION OF POTATOES?
3 A NINE STUDIES.
4 Q ALL RIGHT. AND DID ANY OF THOSE STUDIES
5 THAT DR. BOFFETTA IDENTIFIED IN HIS REVIEW REFLECT A
6 DOSE-RESPONSE RELATIONSHIP?
7 A NO.
8 Q OKAY. AND WHAT WAS DR. BOFFETTA'S
9 CONCLUSION?
10 NEXT SLIDE.
11 A WELL, HE CONCLUDED THAT THE -- HE SAYS:
12 "THE STUDIES ON CANCER RISK FROM INTAKE
13 OF ACRYLAMIDE-RICH FOODS -- AND IN PARTICULAR,
14 POTATOES COOKED AT HIGH TEMPERATURE -- OFFER
15 ONLY A LIMITED CONTRIBUTION TO THE
16 INVESTIGATION OF THE POSSIBLE CARCINOGENIC
17 EFFECT OF ACRYLAMIDE IN HUMANS."
18 Q ALL RIGHT. NOW, DID YOU SEARCH FOR STUDIES
19 EVALUATING CANCERS IN RELATIONSHIP TO CONSUMPTION OF
20 COOKED POTATOES?
21 A YES.
22 Q AND WHAT DID YOU FIND?
23 A WELL, I HAVE A SUMMARY SLIDE HERE THAT I
24 IDENTIFIED LIKE AN ADDITIONAL 18 STUDIES THAT WERE
25 PUBLISHED BEFORE 2011, WHICH WAS THE DATE OF HIS REVIEW,
26 THAT REPORTED INCREASED RISKS OF CANCER IN RELATION TO
27 CONSUMPTION OF POTATOES.
28 Q AND DID ANY OF THOSE STUDIES THAT YOU FOUND

1 REPORT DOSE-RESPONSE RELATIONSHIPS FOR CONSUMPTION OF
2 COOKED POTATOES AND CANCER?
3 A YES. THERE WERE SIX.
4 Q OKAY. AND DID YOU UPDATE -- WELL, DID YOU
5 ALSO LOOK FOR STUDIES POST-DATING 2011, TO SEE WHETHER
6 OTHER EPIDEMIOLOGIC STUDIES, MORE RECENT STUDIES,
7 REPORTED INCREASED RISKS OF CANCER IN RELATIONSHIP TO
8 CONSUMPTION OF COOKED POTATOES?
9 A YES.
10 Q AND WHAT DID YOU FIND?
11 A THERE WERE FIVE ADDITIONAL.
12 Q OKAY. AND DID YOU CHART THE DATA FROM THESE
13 STUDIES IN YOUR NOTES?
14 A YES. THESE WERE THE RESULTS THAT I HAD AT
15 MY DEPOSITION.
16 Q OKAY. COULD WE GO TO THE NEXT SLIDE.
17 SO I'D LIKE YOU TO TELL US ABOUT SOME OF
18 THESE STUDIES. WE'RE NOT GOING TO GO THROUGH EVERY ONE.
19 BUT THE FIRST ONE, FROM 1975, PHILLIPS.
20 BEFORE WE DO THAT, WHAT TYPES OF STUDIES ARE
21 THESE?
22 A WELL, THEY'RE EPIDEMIOLOGICAL STUDIES.
23 THEY'RE CASE-CONTROL STUDIES.
24 Q OKAY. SO THESE ARE STUDIES WHERE
25 INVESTIGATORS GOT TOGETHER A GROUP OF PATIENTS WHO HAD A
26 PARTICULAR CANCER, AND THEY LOOKED RETROSPECTIVELY TO
27 SEE WHETHER THEY LOOKED -- WHAT THEY WERE EXPOSED TO.
28 AND ONE OF THOSE FACTORS WAS COOKED POTATOES?

1 A YES.
2 THE COURT: LET ME ASK THIS: ARE THERE ANY OTHER
3 FOODS BESIDES POTATOES AND COFFEE THAT RELEASE OR CAUSE
4 PRODUCTION OF ACRYLAMIDE IN THE HEATING PROCESS?
5 IN PARTICULAR, WHAT INGREDIENT IN POTATOES
6 CREATES THIS PROCESS? IS IT SOME STARCH PART OF THE
7 POTATO, OR WOULD A SIMILAR REACTION OCCUR IN OTHER FOOD
8 TYPES?
9 THE WITNESS: YOU KNOW, I -- THERE'S TWO ANSWERS
10 TO YOUR QUESTIONS. ONE, IT WAS A SWEDE THAT DETERMINED
11 THIS, I THINK, IN AROUND 2002. AND I DON'T RECALL
12 THE -- LIKE THE CHEMICAL PROCESS OF HOW IT WORKS.
13 SO IT FORMS AS THE POTATOES ARE HEATED. AND
14 THE MORE YOU HEAT THEM -- SO IF YOU WERE TO ORDER A
15 BUNCH OF FRIES, IF YOU ORDERED SOME THAT ARE CRISPY,
16 LIKE A LOT OF PEOPLE LIKE BEST, THEY HAVE A LOT MORE
17 ACRYLAMIDE IN THEM.
18 THE COURT: BUT WHAT ABOUT IF YOU FRIED ONIONS?
19 THE WITNESS: I DON'T KNOW ABOUT ONIONS, BUT BREAD
20 WILL FORM ACRYLAMIDE; NOT AS MUCH AS POTATOES. POTATOES
21 FORMS THE MOST.
22 AND SOME OF THESE SURVEYS THAT HAVE BEEN
23 DONE, LOOKING AT ACRYLAMIDE AND THE DIET OUTSIDE OF
24 POTATOES --
25 THE COURT: YES.
26 THE WITNESS: -- I THINK THEY INCLUDE ANYWHERE
27 FROM LIKE 17 TO 24 ITEMS THAT THEY CONSIDERED HAD
28 ACRYLAMIDE IN THEM.

1 THE COURT: OKAY. THANK YOU.
2 COUNSEL.
3 Q BY MR. METZGER: ALL RIGHT. SO PHILLIPS WAS
4 A STUDY -- NOW, THIS WAS A STUDY DONE, WHAT, 27 YEARS
5 BEFORE IT WAS KNOWN THAT ACRYLAMIDE IS IN THE HUMAN
6 DIET?
7 A YES. 1975.
8 Q ALL RIGHT. AND WHAT PHILLIPS DID IS, HE
9 LOOKED AT BREAST CANCER AND COLON CANCER IN RELATIONSHIP
10 TO VARIOUS FACTORS. IS THAT HOW IT WORKED?
11 A YES.
12 Q ALL RIGHT. AND FOR POTATO CONSUMPTION, WHAT
13 WAS REPORTED IN THAT STUDY THAT YOU FOUND IMPORTANT?
14 A WELL, THEY FOUND A SIGNIFICANT INCREASE IN
15 BREAST CANCER AND COLON CANCER.
16 Q IN RELATIONSHIP TO WHAT?
17 A IN RELATIONSHIP TO POTATO CONSUMPTION.
18 Q OKAY. AND IF WE GO DOWN TO -- WELL, THE
19 NEXT ONE, STEINECK 1990, UROTHELIAL CANCER. WHAT DID
20 YOU FIND OF NOTE IN THAT STUDY?
21 A WELL, THEY REPORTED A SIGNIFICANT INCREASE
22 IN UROTHELIAL CANCERS.
23 Q IN RELATION TO?
24 A TO POTATOES IN THE DIET.
25 Q OKAY. AND FRANCESCHI 1991?
26 A YES.
27 Q WHAT DID YOU FIND OF NOTE IN THAT STUDY?
28 A A SIGNIFICANT INCREASE IN THYROID CANCER.

1 Q IN RELATIONSHIP TO?
2 A TO POTATO CONSUMPTION.
3 Q OKAY. AND FRANCESCHI 1997?
4 A YES. AN INCREASE IN COLORECTAL CANCER, BUT
5 THE DATA ALSO DEMONSTRATE A SIGNIFICANT DOSE RESPONSE.
6 AND THAT'S WHEN I HAVE "YES" UNDER "DOSE RESPONSE."
7 Q I SEE.
8 A BECAUSE IF THE DOSE RESPONSE WAS
9 SIGNIFICANT, I WOULD PUT A "YES."
10 Q WHAT DOES THAT ACTUALLY MEAN, THAT THE DOSE
11 RESPONSE WAS SIGNIFICANT?
12 A IT MEANS THAT WHEN YOU HAD AN INCREASE IN
13 THE AMOUNT OF CONSUMPTION, YOU HAVE AN INCREASE IN THE
14 RISK OF THE CANCER; BUT IN THE DOSE RESPONSE, THE TREND
15 WAS STATISTICALLY SIGNIFICANT.
16 Q IS THERE A CALCULATION THAT ONE DOES TO
17 DETERMINE WHETHER THE TREND IS STATISTICALLY
18 SIGNIFICANT?
19 A YES.
20 Q ALL RIGHT. AND WHEN IT IS STATISTICALLY
21 SIGNIFICANT, DOES IT MEAN THAT THE ODDS OF THAT DOSE-
22 RESPONSE TREND OCCURRING -- BEING DUE TO CHANCE IS LESS
23 THAN 5 PERCENT?
24 A YES.
25 Q ALL RIGHT. NOW, PING 1998. THAT ONE
26 INDICATED AN INCREASED RISK, BUT IT WAS NOT
27 STATISTICALLY SIGNIFICANT?
28 A CORRECT.

1 Q ALL RIGHT. AND HU, 1998, A SIGNIFICANT
2 INCREASE IN GASTRIC CANCER?
3 A YES.
4 Q FROM POTATO CONSUMPTION?
5 A YES.
6 Q ALL RIGHT. BOSETTI 2002, A SIGNIFICANT
7 INCREASE IN LARYNGEAL CANCER FROM -- IN ASSOCIATION WITH
8 POTATO CONSUMPTION. IS THAT WHAT THAT INDICATES?
9 A YES.
10 Q AND WAS THAT -- WAS THERE ANY STATISTICALLY
11 SIGNIFICANT DOSE-RESPONSE RELATIONSHIP BETWEEN
12 CONSUMPTION OF POTATOES AND THE DEVELOPMENT OF LARYNGEAL
13 CANCER?
14 A YES.
15 Q ALL RIGHT. AND DID HU 2002 ALSO REPORT AN
16 INCREASED RISK OF CANCER -- IN THIS CASE, LUNG CANCER --
17 FROM POTATO CONSUMPTION, WITH A SIGNIFICANT DOSE-
18 RESPONSE RELATIONSHIP?
19 A IT WAS BORDERLINE. THE LOWER BOUND IS 1.0,
20 BUT YET.
21 Q OKAY.
22 A AND THERE'S A SIGNIFICANT DOSE RESPONSE --
23 Q OKAY.
24 A -- WHICH IS REALLY MORE POWERFUL THAN THE
25 1.7, THE ONE-POINT ESTIMATE. BECAUSE DOSE RESPONSE,
26 YOU'RE CONSIDERING ALL THE DATA IN THE STUDY, NOT JUST
27 ONE DATA POINT.
28 Q AND LEE 2003 FOUND A STATISTICALLY

1 SIGNIFICANT INCREASED RISK OF BREAST CANCER FROM POTATO
2 CONSUMPTION; IS THAT CORRECT?
3 A YES.
4 Q DE STEFANI 2004, A SIGNIFICANT INCREASE IN
5 GASTRIC CANCER IN WOMEN; TRUE?
6 A YES.
7 Q ALL THIS IS IN RELATIONSHIP TO POTATO
8 CONSUMPTION; RIGHT?
9 A CORRECT.
10 Q AND BUNIN 2005 FOUND MORE THAN A DOUBLING OF
11 THE RISK OF MEDULLOBLASTOMA THAT WAS STATISTICALLY
12 SIGNIFICANT, AND ALSO SHOWED A DOSE-RESPONSE
13 RELATIONSHIP?
14 A YES.
15 Q ALL RIGHT. CHAN 2005, PANCREATIC CANCER
16 INCREASED, AS WELL?
17 A YES.
18 Q AND RADOSAVLJEVIC, FROM SERBIA, IN 2005, A
19 GREATER THAN SIX-FOLD INCREASED RISK OF BLADDER CANCER;
20 IS THAT CORRECT?
21 A YES.
22 Q AND LASTLY, MICHELS 2006, BREAST CANCER
23 SIGNIFICANTLY INCREASED; IS THAT RIGHT?
24 A YES.
25 MR. METZGER: YOUR HONOR, I SEE THAT IT'S ALMOST
26 NOON. SHALL WE BREAK AT THIS POINT?
27 THE COURT: WE'LL TAKE A RECESS AT THIS TIME.
28 MR. METZGER: THANK YOU.

1 THE COURT: HOW MUCH LONGER ARE YOU GOING TO BE
2 WITH DR. INFANTE?
3 MR. METZGER: I WILL BE ALL DAY WITH HIM AND
4 PROBABLY INTO THE NEXT DAY. HE'S GOING TO GO THROUGH
5 ALL THE DATA ON ACRYLAMIDE AND ALL THE DATA ON COFFEE
6 FOR THOSE PARTICULAR TYPES OF CANCER THAT HE'S
7 EVALUATED. IT'S A LOT OF INFORMATION.
8 THE COURT: WHAT'S THE ANTICIPATED LENGTH OF
9 CROSS-EXAMINATION.
10 MR. SCHURZ: IF MR. METZGER TURNS DR. INFANTE OVER
11 BY MID-MORNING TOMORROW, WE WILL -- I WOULD EXPECT WE
12 WOULD CONCLUDE DR. INFANTE BY THE END OF THE DAY. I'M
13 NOT GOING TO GO MUCH --
14 THE COURT: WHO ELSE DO WE HAVE FOR THIS WEEK?
15 MR. METZGER: WE THEN HAVE DR. HUFF, WHO IS COMING
16 IN FROM THE EAST COAST. AND HE'LL BE HERE -- I THINK
17 HE'S ARRIVING TOMORROW NIGHT. HE'LL BE AVAILABLE ON
18 WEDNESDAY.
19 THE COURT: HOW LONG WILL HIS TESTIMONY TAKE?
20 MR. METZGER: I THINK IT WILL TAKE A DAY. BUT I
21 THINK THAT DR. INFANTE IS PROBABLY GOING TO END UP
22 TAKING THREE DAYS, THERE'S SO MUCH INFORMATION. I COULD
23 BE WRONG.
24 THE COURT: OKAY. WE'LL BE IN RECESS TILL 1:30.
25 (AT 11:59 A.M., A LUNCH RECESS WAS TAKEN
26 UNTIL 1:30 P.M. OF THE SAME DAY.)
27 (TRANSCRIPT CONTINUES ON PAGE 151.)
28

EXHIBIT “D”

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT 323 HON. ELIHU M. BERLE, JUDGE

COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS, A CALIFORNIA CORPORATION,

PLAINTIFF,

VS.

STARBUCKS CORPORATION, A CALIFORNIA CORPORATION, ET AL.,

DEFENDANTS.

AND CONSOLIDATED ACTION.

CASE NO. BC435759

REPORTER'S TRANSCRIPT OF TRIAL PROCEEDINGS

MONDAY, OCTOBER 20, 2014

AFTERNOON SESSION

APPEARANCES:

FOR THE PLAINTIFF: METZGER LAW GROUP
BY: RAPHAEL METZGER, ESQ.
KENNETH HOLDREN, ESQ.
401 EAST OCEAN BOULEVARD, SUITE 800
LONG BEACH, CALIFORNIA 90802

FOR THE DEFENDANT: MORRISON & FOERSTER
BY: JAMES SCHURZ, ESQ.
MICHELE B. CORASH, ESQ.
425 MARKET STREET
SAN FRANCISCO, CALIFORNIA 94105

CCROLA JOB NO. 114684

KAREN VILICICH, CSR. NO. 7634
OFFICIAL REPORTER PRO TEMPORE

I N D E X

MONDAY, OCTOBER 20, 2014 (P.M.)

CHRONOLOGICAL AND ALPHABETICAL INDEX OF WITNESSES

PLAINTIFF WITNESS: PAGE

PETER FRANCIS INFANTE, DR.P.H.
DIRECT BY MR. METZGER 151

EXHIBIT INDEX

(NONE OFFERED.)

1 CASE NUMBER: BC435759
2 CASE NAME: CERT VS. STARBUCKS
3 LOS ANGELES, CALIFORNIA MONDAY, OCTOBER 20, 2014
4 DEPARTMENT 323 HON. ELIHU M. BERLE, JUDGE
5 REPORTER: KAREN VILICICH, CSR NO. 7634
6 TIME: P.M. SESSION
7
8 (THE FOLLOWING PROCEEDINGS WERE HELD
9 IN OPEN COURT:)
10
11 THE COURT: BACK ON THE RECORD IN THE CASE OF CERT
12 VERSUS STARBUCKS. ALL COUNSEL ARE PRESENT. DR. INFANTE
13 IS ON THE STAND.
14 DR. INFANTE, YOU UNDERSTAND YOU ARE STILL
15 UNDER OATH?
16 THE WITNESS: YES, SIR.
17 THE COURT: PLEASE RESTATE YOUR NAME FOR THE
18 RECORD.
19 THE WITNESS: PETER FRANCIS INFANTE, I-N-F-A-N-T-E.
20 THE COURT: MR. METZGER WAS INQUIRING.
21 COUNSEL, YOU MAY PROCEED.
22 MR. METZGER: THANK YOU, YOUR HONOR.
23
24 DIRECT EXAMINATION (CONTINUED)
25
26 BY MR. METZGER:
27 Q WHEN WE BROKE FOR LUNCH, WE WERE DISCUSSING
28 THE CASE-CONTROL STUDIES OF CANCER IN RELATIONSHIP TO

1 POTATO CONSUMPTION.
2 YOU HAD MENTIONED, DR. INFANTE, THE CHAN
3 STUDY FROM 2005 WHICH SHOWED AN INCREASED RISK OF
4 PANCREATIC CANCER IN RELATIONSHIP TO POTATO CONSUMPTION.
5 WAS THERE ANYTHING IN THAT STUDY THAT YOU
6 FOUND TO BE PARTICULARLY SIGNIFICANT?
7 A YES.
8 Q WHAT WAS THAT?
9 A IT WAS THAT POTATOES IS THE ONLY VEGETABLE
10 CONSIDERED OR ANALYZED FOR IN THE STUDY THAT DEMONSTRATED
11 AN INCREASE IN RISK WITH AN INCREASE IN CONSUMPTION. IN
12 FACT, IF YOU LOOK AT "TOTAL VEGETABLES WITHOUT POTATOES,"
13 IT SHOWED AN INVERSE RELATION, MEANING THAT THE MORE YOU
14 CONSUMED, THE LOWER WAS YOUR RISK FOR PANCREATIC CANCER.
15 Q IS THAT SET FORTH IN TABLE 2 OF THE CHAN
16 STUDY?
17 A I DON'T KNOW -- YES, IT IS.
18 Q COULD WE HAVE THE NEXT SLIDE.
19 IS THAT THE STUDY TITLED, "VEGETABLE AND
20 FRUIT INTAKE AND PANCREATIC CANCER IN A POPULATION-BASED
21 CASE-CONTROL STUDY IN THE SAN FRANCISCO BAY AREA"?
22 A YES, IT IS.
23 Q AND TABLE 2 PROVIDES THE ODDS RATIOS OF 95
24 PERCENT, CONFIDENCE INTERVALS BY QUARTILE OF VEGETABLE
25 INTAKE IN THE STUDY; IS THAT CORRECT?
26 A YES, BY THE TYPE OF VEGETABLE.
27 Q IF WE LOOK AT THE TABLE, I SEE THAT POTATOES
28 IS AT THE VERY BOTTOM AND ALL THE OTHER VEGETABLES ARE

1 ABOVE IT; IS THAT CORRECT?
2 A YES.
3 Q ALL RIGHT. IF WE LOOK AT THE FIRST THREE
4 ROWS, "TOTAL FRUITS AND VEGETABLES," "TOTAL VEGETABLES"
5 AND "TOTAL VEGETABLES WITHOUT POTATOES," IF WE LOOK AT
6 THE TREND, IT IS HARD TO SEE, BUT -- WELL, LET'S LOOK AT
7 THE FIRST ROW, "TOTAL FRUITS AND VEGETABLES."
8 FOR THE FIRST QUARTILE, 1.0 RISK. FOR THE
9 SECOND QUARTILE, 0.83. FOR THE THIRD QUARTILE, 0.70.
10 FOR THE FOURTH QUARTILE, 0.47.
11 THOSE NUMBERS ARE DECREASING?
12 A CORRECT.
13 MR. SCHURZ: OBJECTION. THE DOCUMENT SPEAKS FOR
14 ITSELF. ALSO A HEARSAY OBJECTION. COUNSEL IS READING
15 THE TABLE INTO THE RECORD.
16 THE COURT: I ASSUME WE WILL GET TO A QUESTION.
17 Q BY MR. METZGER: IS THAT WHAT YOU MEANT BY
18 AN INVERSE RELATIONSHIP?
19 A YES, IT IS. THE MORE YOU CONSUME, THEN THE
20 LOWER IS YOUR RISK FOR PANCREATIC CANCER.
21 Q AND THE LAST COLUMN INDICATES A P-TREND OF
22 LESS THAN 0.0001.
23 WHAT DOES THAT INDICATE?
24 A THAT MEANS THAT THAT TREND WOULD OCCUR DUE
25 TO CHANCE ONE TIME OUT OF 10,000. DUE TO CHANCE ALONE,
26 ONE TIME OUT OF 10,000.
27 Q ALL RIGHT. AND IF YOU LOOK AT THE DATA FOR
28 ALL OF THE VEGETABLE CATEGORIES EXCEPT POTATOES, IS THERE

1 A GENERAL RESULT THAT YOU SEE HERE?
2 A YES.
3 Q WHAT IS THAT?
4 A THAT THE MORE YOU CONSUME, THE LOWER AND
5 LOWER IS YOUR RISK FOR DEVELOPING PANCREATIC CANCER.
6 Q OKAY. AND THEN IF YOU LOOK AT POTATOES, THE
7 LAST ROW IN THE TABLE SHOWS THE RISK FOR QUARTILE 1 AT
8 1.0. QUARTILE 2 AT 1.3. QUARTILE 3 AT 1.1. QUARTILE 4
9 AT 1.4. AND THE ODDS RATIO -- I'M SORRY, THE 95 PERCENT
10 CONFIDENCE INTERVAL FOR THE 1.4 VALUE, THE POTATOES IN
11 THE HIGHEST CONSUMPTION CATEGORY IS 1.0 TO 1.9; IS THAT
12 CORRECT?
13 MR. SCHURZ: OBJECTION; HEARSAY.
14 THE COURT: THE OBJECTION IS SUSTAINED. I READ THE
15 CHART. ALL THE WITNESS IS SAYING, "YES. YES." I
16 THOUGHT THIS WAS LEADING TO SOME ANALYTICAL QUESTION.
17 MR. METZGER: IT IS, YOUR HONOR. I DON'T KNOW HOW
18 TO DO THIS OTHER -- BECAUSE WE NEED A RECORD. THIS
19 DOCUMENT IS NOT -- THE POWERPOINT IS NOT COMING INTO
20 EVIDENCE. I THINK I NEED TO GET THE RESULTS INTO
21 EVIDENCE.
22 THE COURT: WELL, TRY TO SHORTEN IT WITHOUT
23 RECITING EVERYTHING THAT IS ON THE CHART.
24 MR. METZGER: I WILL TRY, YOUR HONOR. THANK YOU.
25 Q DR. INFANTE, WHAT IS THE SIGNIFICANCE TO YOU
26 OF THAT DATA FOR POTATOES IN THIS CASE-CONTROL STUDY OF
27 PANCREATIC CANCER?
28 A IT WAS THE ONLY -- IT IS THE ONLY FOOD ITEM

1 ANALYZED FOR THAT SHOWS AN INCREASE IN THE RISK WITH AN
2 INCREASE IN CONSUMPTION WHEREAS ALL THE OTHERS, AND
3 PARTICULARLY THE THIRD ENTRY, "TOTAL VEGETABLES WITHOUT
4 POTATOES," SHOWS AN INVERSE RELATION. SO IT IS VERY
5 STRIKING THAT IT IS THE ONLY ONE OF ALL THE FOOD ITEMS
6 MENTIONED THAT GOES IN THE OPPOSITE DIRECTION.
7 Q THE ONLY ONE OF ALL THE VEGETABLES?
8 A OF ALL THE VEGETABLES, YES.
9 Q ALL RIGHT. NOW, WE HAD NOT QUITE FINISHED
10 WITH THE STUDIES THAT YOU EVALUATED REGARDING CANCER IN
11 RELATIONSHIP TO CONSUMPTION OF POTATOES. I THINK WE LEFT
12 OFF WITH MICHELS AT 2006.
13 ARE THERE MORE STUDIES?
14 A YES.
15 Q COULD WE HAVE THE NEXT SLIDE.
16 YOU HAVE ISO FROM JAPAN IN 2007 SHOWING AN
17 INCREASED RISK FOR COLON CANCER IN RELATIONSHIP TO POTATO
18 CONSUMPTION; IS THAT CORRECT?
19 A YES.
20 Q AND DID THAT STUDY REPORT A DOSE-RESPONSE
21 RELATIONSHIP FOR CONSUMPTION OF POTATOES AND COLON
22 CANCER?
23 A YES, IN BOTH MEN AND WOMEN SEPARATELY.
24 Q AND MARCHIONI 2007, WHAT DID YOU -- A
25 2.2-FOLD INCREASED RISK OF ORAL CANCER?
26 A YES, IT WAS DEMONSTRATED THE DOSE-
27 RESPONSE --
28 MR. SCHURZ: OBJECTION; HEARSAY. HE IS READING

1 TABLES AGAIN.
2 THE COURT: I COULD NOT HEAR A THING. EVERYONE WAS
3 TALKING OVER EACH OTHER. START OVER, ASK THE QUESTION,
4 TAKE A BREATH SO I CAN HEAR IF THERE IS AN OBJECTION.
5 Q BY MR. METZGER: DR. INFANTE, WHAT DID YOU
6 NOTE FROM THE MARCHIONI STUDY OF 2007?
7 A THAT IT DEMONSTRATED A SIGNIFICANT INCREASE
8 OF RISK OF ORAL CANCER, AND ALSO THERE WAS A
9 DOSE-RESPONSE INDICATING THAT THE MORE POTATO
10 CONSUMPTION, THE HIGHER THE RISK.
11 Q WHAT DID YOU NOTE REGARDING THE LUCENTEFORTE
12 STUDY FROM 2008 IN ITALY?
13 A IT DEMONSTRATED A SIGNIFICANT INCREASE IN
14 STOMACH CANCER, AND ALSO A DOSE-RESPONSE BY THE AMOUNT OF
15 POTATOES CONSUMED.
16 Q WHAT DID YOU NOTE REGARDING THE NASHAR STUDY
17 FROM 2008 IN SAUDI ARABIA?
18 A IT SHOWS A HIGHER RISK, BUT THE RESULT IS
19 NOT QUITE -- IT IS ONLY SIGNIFICANT AT THE .14 LEVEL, SO
20 IT IS NOT AT THE .05 LEVEL. SO THAT RESULT ONLY OCCURRED
21 14 TIMES OUT OF 100 DUE TO CHANCE.
22 Q OKAY. SONESTEDT 2008, SWEDEN, REGARDING
23 BREAST CANCER. WHAT DID YOU NOTE REGARDING THAT STUDY?
24 A WELL, I NOTICED THAT FOR THE BREAST CANCER
25 THAT IS NOT SENSITIVE TO ESTROGENS -- THERE ARE DIFFERENT
26 KINDS OF BREAST CANCER, AND THE ONE THAT IS NOT SENSITIVE
27 TO ESTROGENS, THERE IS A SIGNIFICANT INCREASE IN RELATION
28 TO POTATO CONSUMPTION.

1 THE COURT: LET ME ASK THIS, MR. METZGER: IS THERE
2 A REASON WHY WE HAVE TO GO THROUGH ALL OF THESE STUDIES
3 AND HAVE DR. INFANTE TESTIFY WHAT THESE STUDIES MEAN AND
4 WHAT THEY FOUND IN EACH STUDIES?
5 MR. METZGER: I THINK SO, YOUR HONOR.
6 THE COURT: WHY?
7 MR. METZGER: THESE STUDIES ARE SHOWING THAT THE --
8 ONE --
9 THE COURT: THEY MAY. WHATEVER THEY SHOW, THEY
10 SHOW. THOSE STUDIES ARE NOT IN EVIDENCE. DR. INFANTE IS
11 ON THE STAND, HE WILL TESTIFY TO HIS OPINIONS AND THE
12 BASES OF HIS OPINIONS. DO WE NEED TO GO INTO THE STUDY?
13 THE WITNESS CAN COME INTO COURT AND SAY, "I
14 COME TO THE CONCLUSION THAT THE MOON IS MADE OUT OF SWISS
15 CHEESE."
16 "FINE. WHAT DO YOU BASE THE OPINION ON?"
17 "BEING ADVISED BY READING THE ENCYCLOPEDIA
18 BRITANNICA FROM COVER TO COVER."
19 OKAY. DOES THAT MEAN WE ARE GOING TO HAVE
20 SOMEONE TESTIFY AS TO WHAT EVERY -- WHAT IS IN EVERY
21 VOLUME, I DON'T KNOW IF IT EVEN EXISTS ANYMORE, OF THE
22 ENCYCLOPEDIA BRITANNICA?
23 MR. METZGER: I UNDERSTAND YOUR POINT, YOUR HONOR.
24 THE COURT: LET'S TRY TO SHORTEN IT UP.
25 MR. METZGER: I WILL TRY TO SHORTEN IT UP, YES.
26 Q WE WILL TALK ABOUT A FEW OF THESE. THERE IS
27 ANOTHER STUDY HERE REGARDING PANCREATIC CANCER BY POLESEL
28 IN 2010.

1 FIRST, WOULD YOU TELL US WHAT THE RESULTS
2 WERE OF -- THE MAIN RESULT OF THAT STUDY WAS REGARDING
3 POTATO CONSUMPTION, DR. INFANTE?
4 A IT DEMONSTRATES A SIGNIFICANT INCREASED RISK
5 OF PANCREATIC CANCER AND ALSO A SIGNIFICANT
6 DOSE-RESPONSE.
7 Q WAS THERE ANYTHING IN PARTICULAR ABOUT THAT
8 STUDY THAT YOU FOUND IMPORTANT IN THIS CONTEXT?
9 A YES.
10 Q IS THAT INFORMATION THAT IS SET FORTH IN
11 TABLE 4 OF THE POLESEL STUDY?
12 A YES, IT IS.
13 Q COULD WE HAVE THE NEXT SLIDE.
14 WOULD YOU TELL US WHAT THAT IS?
15 A WHEN YOU LOOK AT POTATO CONSUMPTION, YOU SEE
16 AT THE BOTTOM, YOU SEE A POSITIVE DOSE-RESPONSE BY
17 CONSUMPTION CATEGORY, AND RISK OF PANCREATIC CANCER.
18 THEN IF YOU LOOK RIGHT ABOVE IT, FOR EXAMPLE, AT "COOKED
19 VEGETABLES," ALL COOKED VEGETABLES, YOU, IN FACT, SEE AN
20 INVERSE RELATION. THAT THE MORE OF THEM YOU ATE, THE
21 LOWER WAS YOUR RISK FOR PANCREATIC CANCER.
22 Q WHAT IS THE SIGNIFICANCE OF THAT TO YOU?
23 A WELL, IT IS SIGNIFICANT BECAUSE IT LOOKS
24 LIKE, YOU KNOW, EATING COOKED VEGETABLES IS, YOU KNOW,
25 THE MORE THAT YOU EAT, IT LOWERS YOUR RISK OF PANCREATIC
26 CANCER, WITH THE EXCEPTION OF POTATOES, WHERE THE MORE
27 THAT YOU EAT, YOU HAVE A HIGHER AND HIGHER RISK OF
28 DEVELOPING PANCREATIC CANCER.

1 Q OKAY. ALL RIGHT. NOW, IF WE COULD GO BACK
2 ONE SLIDE.
3 ALL OF THE STUDIES UP TO 2010 HERE, THERE
4 WAS A PREVIOUS SLIDE THAT HAD STUDIES GOING BACK TO 1975,
5 ARE MOST OF THESE STUDIES STUDIES THAT DR. BOFFETTA
6 MISSED IN HIS 2011 REVIEW?
7 A YES.
8 Q ALL RIGHT. AND DID YOU ALSO FIND STUDIES
9 SUBSEQUENT TO DR. BOFFETTA'S 2011 REVIEW WHICH REPORTED
10 INCREASED RISKS OF VARIOUS CANCERS IN RELATIONSHIP TO
11 POTATO CONSUMPTION?
12 A YES.
13 Q AND HOW MANY SUCH STUDIES WERE THERE?
14 A WELL, THERE ARE FOUR INDICATED IN THIS
15 SLIDE, THE BROVI, SHAMSI, STOTT-MILLER AND DE STEFANI.
16 Q HOW MANY OF THOSE FOUR SHOWED STATISTICALLY
17 SIGNIFICANT DOSE-RESPONSE RELATIONSHIPS OF PANCREATIC
18 CANCER WITH POTATO CONSUMPTION?
19 A WELL, THEY DON'T SHOW PANCREATIC CANCER.
20 THEY SHOW ORO-PHARYNGEAL, BREAST.
21 Q I'M SORRY. HOW MANY OF THEM SHOWED
22 STATISTICALLY SIGNIFICANT DOSE-RESPONSE RELATIONSHIPS
23 WITH THE CANCERS THAT THEY EVALUATED?
24 A THREE.
25 Q SO DID YOU REACH SOME CONCLUSIONS REGARDING
26 THIS BODY OF LITERATURE?
27 A YES.
28 Q NEXT SLIDE.

1 NEXT ONE.
2 WHAT WERE THOSE?
3 A WELL, OF THE 28 STUDIES, 23 REPORTED
4 STATISTICALLY SIGNIFICANT INCREASED RISKS OF CANCER. OF
5 THE 28 STUDIES, NINE REPORT MORE THAN A DOUBLING OF THE
6 CANCER RISK. AND OF THE SAME STUDIES, 13 REPORT
7 STATISTICALLY SIGNIFICANT DOSE-RESPONSE RELATIONSHIPS.
8 Q WHAT DID YOU CONCLUDE AS A RESULT OF THESE
9 STUDIES?
10 A THAT THE CASE-CONTROL STUDIES OF CANCERS AND
11 POTATO CONSUMPTION PROVIDE SUPPORTIVE EVIDENCE FOR THE
12 HUMAN CARCINOGENICITY OF ACRYLAMIDE.
13 MR. SCHURZ: OBJECTION; MOVE TO STRIKE AS LACKS
14 FOUNDATION. THERE IS NO INDICATION THAT ANY OF THESE
15 STUDIES HAD ANYTHING TO DO WITH ACRYLAMIDE. THEY DEAL
16 WITH FRIED POTATO STUDIES.
17 THE COURT: OVERRULED. THE ANSWER WILL STAND.
18 COUNSEL CAN ARGUE IT.
19 Q BY MR. METZGER: DR. INFANTE, WE HAVE
20 DISCUSSED THE OCCUPATIONAL EPIDEMIOLOGY STUDIES OF
21 ACRYLAMIDE PRODUCTION WORKERS AND THE CASE-CONTROL
22 STUDIES OF CANCERS IN RELATION TO POTATO CONSUMPTION.
23 YOU INDICATED, I THINK, THAT THE THIRD TYPE OF
24 EPIDEMIOLOGIC STUDY THAT YOU EVALUATED REGARDING
25 ACRYLAMIDE WAS DIETARY ACRYLAMIDE STUDIES; IS THAT
26 CORRECT?
27 A YES.
28 Q WHAT ARE THOSE STUDIES?

1 A WELL, THESE ARE EPIDEMIOLOGICAL STUDIES OF,
2 YOU KNOW, EVALUATING THE DIETS OF INDIVIDUALS AND IN
3 RELATION TO THEIR CANCERS.
4 Q NOW, IN EVALUATING THIS BODY OF LITERATURE,
5 DID YOU CONSIDER WHETHER THESE STUDIES HAD ADEQUATE
6 STATISTICAL POWER TO DETECT CANCER EFFECTS AT DIETARY
7 EXPOSURE LEVELS?
8 A IN GENERAL, YES.
9 Q WHAT DID YOU CONCLUDE?
10 A THAT THEY LACKED STATISTICAL POWER TO, YOU
11 KNOW, ADEQUATELY EVALUATE THE CANCER RISK FROM DIETARY
12 EXPOSURE TO ACRYLAMIDE.
13 Q ALTHOUGH THEY LACK STATISTICAL POWER, DID
14 SOME OF THE STUDIES NEVERTHELESS YIELD INCREASED RISKS?
15 A YES.
16 Q ALL RIGHT. IF WE CAN GO TO THE NEXT SLIDE.
17 GO AHEAD.
18 ALL RIGHT. AND YOU HAVE PREPARED THE DATA
19 FOR THESE BEGINNING WITH HOGERVORST 2007; IS THAT
20 CORRECT?
21 A YES.
22 Q AND WOULD YOU TELL US WHAT DATA FROM THAT
23 STUDY YOU FOUND SIGNIFICANT?
24 A WELL, THERE ARE -- FOR OVARIAN CANCER IN THE
25 HIGHEST QUINTILE, YOU HAVE A SIGNIFICANT INCREASE. FOR
26 ENDOMETRIAL CANCER AMONG NEVER-SMOKERS AND OVARIAN CANCER
27 IN NEVER-SMOKERS.
28 Q WHY DO YOU FIND THE DATA REGARDING

1 NEVER-SMOKERS TO BE IMPORTANT?
2 A BECAUSE YOU MAY HAVE CONFOUNDING FROM
3 CIGARETTE SMOKING IN SOME OF THESE STUDIES. WHEN YOU
4 EVALUATE THE DATA FOR NON-SMOKERS, YOU DON'T HAVE TO, YOU
5 KNOW, CONSIDER THE CONFOUNDING FROM CIGARETTE SMOKING.
6 Q THE NEXT STUDY THAT YOU LIST IS OLESEN 2008,
7 ESTROGEN-RECEPTOR POSITIVE BREAST CANCER. WHAT DID YOU
8 FIND OF IMPORT FROM THAT STUDY?
9 A THAT DEMONSTRATES A SIGNIFICANT INCREASE.
10 Q HOGERVORST 2008 REGARDING KIDNEY CANCER,
11 WHAT DID YOU FIND IN THAT STUDY OF SIGNIFICANCE?
12 A SAME THING, IT DEMONSTRATED A SIGNIFICANT
13 INCREASE, AS WELL AS THE SCHOUTEN STUDY FOR ORAL CANCER
14 IN NON-SMOKERS, WHICH, AGAIN, IS IMPORTANT BECAUSE
15 CIGARETTES -- THERE IS A RISK OF ORAL CANCER FROM
16 CIGARETTE SMOKING.
17 Q WHAT ABOUT WILSON 2010, WHAT DID YOU FIND OF
18 NOTE IN THAT STUDY?
19 A I FOUND THAT THERE WAS A SIGNIFICANT
20 INCREASE IN ENDOMETRIAL CANCER AND OVARIAN SEROUS CANCER,
21 A TYPE OF OVARIAN CANCER WITH A SIGNIFICANT P-TREND.
22 Q WHAT DID YOU FIND OF SIGNIFICANCE IN THE LIN
23 STUDY FROM 2010?
24 A WELL, THERE IT EVALUATED ESOPHAGEAL CANCER
25 AND YOU SEE THAT IN THE HIGHEST QUARTILE OF CONSUMPTION,
26 YOU HAVE A SIGNIFICANT INCREASE IN ESOPHAGEAL CANCER.
27 THEN ALSO IN THE NON-SMOKERS, YOU HAVE ALMOST A
28 THREE-FOLD RISK, WHICH IS STATISTICALLY SIGNIFICANT.

1 AGAIN, THAT IS IMPORTANT BECAUSE ES --
2 CIGARETTE SMOKING IS ASSOCIATED WITH ESOPHAGEAL CANCER.
3 SO YOU ARE ELIMINATING THE CIGARETTE SMOKING AS PART OF
4 THE CONTRIBUTION OF THIS ELEVATED RISK.
5 Q SO EVEN WHEN SMOKING -- WHEN THE STUDY WAS
6 DONE IN NON-SMOKERS, THEY FOUND AN ALMOST THREE-FOLD RISK
7 OF SQUAMOUS CELL ESOPHAGEAL CANCER?
8 A YES.
9 Q WHAT DID YOU FIND OF NOTE IN THE 2010 STUDY
10 BY HIRVONEN?
11 A THERE IS A SIGNIFICANT INCREASE OF LUNG
12 CANCER IN MALE SMOKERS.
13 Q WHAT DID YOU FIND OF NOTE IN THE 2010 STUDY
14 BY BURLEY?
15 A BORDERLINE SIGNIFICANT INCREASE OF BREAST
16 CANCER IN PRE-MENOPAUSAL WOMEN.
17 Q WHAT DID YOU FIND OF NOTE IN THE 2012 STUDY
18 BY BONGERS?
19 A I FOUND A SIGNIFICANT INCREASE IN THE RISK
20 OF LYMPHOMA AND MULTIPLE MYELOMA.
21 Q AND ALL OF THESE STUDIES ARE OF DIETARY
22 ACRYLAMIDE?
23 A YES.
24 Q WHAT DID YOU FIND OF NOTE IN THE HOGERVORST
25 2014 STUDY?
26 A THE COLORECTAL CANCER THAT HAD A SPECIFIC
27 GENE MUTATION, K-RAS MUTATION, THAT IN THE HIGHEST
28 QUARTILE OF CONSUMPTION IN MEN, THERE WAS A SIGNIFICANT

1 INCREASE.
2 Q WHAT DID YOU FIND OF SIGNIFICANCE IN THE
3 LUJAN-BARROSO STUDY FROM 2014?
4 A YOU HAVE AN INCREASE IN RISK RELATED TO
5 ESOPHAGEAL CANCER, BUT THE HIGHEST RISK WAS FOUND IN
6 NON-SMOKERS.
7 Q LASTLY, WHAT DID YOU FIND OF SIGNIFICANCE IN
8 THE OBON-SANTACANA 2014 STUDY?
9 A A SIGNIFICANT INCREASE IN THE ENDOMETRIAL
10 CANCER, WITH ALSO A SIGNIFICANT DOSE-RESPONSE.
11 Q ALL RIGHT. NOW, WHAT DID YOU CONCLUDE
12 REGARDING THE BODY OF EPIDEMIOLOGIC STUDIES OF VARIOUS
13 CANCERS IN RELATIONSHIP TO DIETARY ACRYLAMIDE EXPOSURE?
14 A WELL, I CONCLUDED THAT ALTHOUGH, AS I
15 MENTIONED AT THE BEGINNING, THE STUDIES LACK ADEQUATE
16 STATISTICAL POWER TO DETECT INCREASED CANCER RISKS AT
17 DIETARY LEVELS OF ACRYLAMIDE EXPOSURE, SIGNIFICANTLY
18 INCREASED RISKS HAVE BEEN REPORTED FOR BREAST CANCER,
19 COLORECTAL CANCER WITH K-RAS MUTATIONS, ENDOMETRIAL
20 CANCER, ESOPHAGEAL CANCER, KIDNEY CANCER, LUNG CANCER,
21 LYMPHOMA, MULTIPLE MYELOMA, ORAL CANCER AND OVARIAN
22 CANCERS.
23 Q DID YOU ASSESS WHETHER THE RESULTS OF THESE
24 STUDIES SHOWED SOME CONSISTENCY AMONG CANCER SITES OR
25 TYPES?
26 A YES.
27 Q WHAT DID YOU FIND?
28 A I FOUND THAT WITH ENDOMETRIAL CANCER, THERE

1 WERE THREE STUDIES.
2 IF YOU GO TO THE NEXT SLIDE.
3 WITH BREAST CANCER, THERE WERE TWO STUDIES;
4 OVARIAN CANCER, THERE WERE TWO STUDIES; AND WITH
5 ESOPHAGEAL CANCER, THERE WERE TWO STUDIES.
6 Q WHAT DID YOU CONCLUDE FROM THIS ANALYSIS?
7 A I CONCLUDED THAT THE DIETARY ACRYLAMIDE
8 STUDIES RELATED TO CANCER PROVIDE SOME EVIDENCE OF A
9 HUMAN CANCER RISK FROM EXPOSURE TO ACRYLAMIDE IN THE
10 DIET.
11 Q ALL RIGHT. NOW, HAVE YOU NOW TOLD THE COURT
12 THE OPINIONS THAT YOU FORMED REGARDING ACRYLAMIDE IN
13 HUMAN CANCER?
14 A YES.
15 Q ALL RIGHT. DID I ASK YOU TO DO ADDITIONAL
16 WORK IN THIS CASE IN ADDITION TO EVALUATING HUMAN CANCER
17 IN RELATIONSHIP TO ACRYLAMIDE EXPOSURE?
18 A YES.
19 Q WHAT DID I ADDITIONALLY ASK YOU TO DO?
20 A YOU ASKED ME TO EVALUATE THE LITERATURE
21 RELATED TO COFFEE CONSUMPTION AND CANCER RISK.
22 Q OKAY. DID YOU HAVE AN UNDERSTANDING AS TO
23 WHY I ASKED YOU TO EVALUATE THAT?
24 THE COURT: SUSTAINED.
25 MR. METZGER: DID YOU SAY SOMETHING, YOUR HONOR?
26 THE COURT: YES, THE OBJECTION IS SUSTAINED.
27 MR. METZGER: I DID NOT HEAR. I'M SORRY. OKAY.
28 THE COURT: YOU ARE ASKING HIM TO SPECULATE AS TO

1 WHY YOU ASKED HIM TO DO SOMETHING?
2 IF YOU TOLD HIM WHY IT IS A DIFFERENT STORY.
3 HOW COULD HE READ YOUR MIND?
4 Q BY MR. METZGER: DID I TELL YOU WHY I WAS
5 ASKING YOU TO EVALUATE COFFEE CONSUMPTION AND CANCER?
6 A YES. WELL, I MEAN, YOU SAID THAT YOU WANTED
7 ME TO EVALUATE THE LITERATURE TO SEE IF THERE WAS AN
8 ELEVATED RISK FROM -- OF CANCER FROM COFFEE CONSUMPTION.
9 Q DID YOU UNDERTAKE THAT EFFORT?
10 A YES, I DID.
11 Q HOW DID YOU GO ABOUT DOING THAT?
12 A WELL, AFTER LOOKING AT THE LITERATURE ON
13 PUB-MED AND TOXLINE, I REALIZED THERE WAS A TREMENDOUS
14 AMOUNT OF LITERATURE ON COFFEE CONSUMPTION AND VARIOUS
15 CANCERS. SO I NEEDED TO TRY TO FOCUS ON, YOU KNOW, SOME
16 OF THE CANCERS, BECAUSE I DID NOT HAVE TIME TO EVALUATE
17 ALL OF THE LITERATURE ON COFFEE CONSUMPTION AND ALL OF
18 THE CANCERS THAT HAVE BEEN EVALUATED TO DATE.
19 Q HOW -- WHAT CANCERS DID YOU DECIDE TO
20 EVALUATE?
21 A I DECIDED TO EVALUATE BLADDER CANCER,
22 PANCREATIC CANCER AND CHILDHOOD LEUKEMIA INITIALLY.
23 Q WHY DID YOU DECIDE TO EVALUATE THE
24 LITERATURE REGARDING COFFEE CONSUMPTION AND BLADDER
25 CANCER?
26 A WELL, THE FIRST THING I DID WAS I SAID,
27 WELL, WHAT DID IARC, THE INTERNATIONAL AGENCY ON RESEARCH
28 ON CANCER HAVE TO SAY ABOUT COFFEE CONSUMPTION AND

1 CANCER.
2 IN THEIR MONOGRAPH THAT WAS PUBLISHED IN
3 1991, THEY STATED THAT THERE WAS WEAK EVIDENCE OF BLADDER
4 CANCER AND PANCREATIC CANCER. SO THAT TOLD ME THAT THEY
5 CONSIDERED THAT THERE WAS SOME EVIDENCE.
6 SO I THOUGHT, WELL, LET ME LOOK, THEN, AT
7 THOSE SITES WHERE THEY CONCLUDED, WHAT 20 -- 1990, A
8 LITTLE OVER 20 YEARS AGO THAT THERE WAS SOME EVIDENCE.
9 THAT IS WHY I PICKED THOSE TWO SITES. I ACTUALLY PICKED
10 LUNG CANCER TOO, BUT I DID NOT REALLY HAVE ENOUGH TIME TO
11 GET THROUGH ALL THE LITERATURE AND I STOPPED ON THAT ONE.
12 Q ARE THERE ANY OTHER SITES OR TYPES OF CANCER
13 THAT YOU CONSIDERED?
14 A YEAH, I CONSIDERED CHILDHOOD LEUKEMIA FROM
15 MATERNAL CONSUMPTION.
16 Q WHY DID YOU CONSIDER THAT LITERATURE?
17 A WELL, I HAVE -- CHILDHOOD LEUKEMIA HAS
18 ALWAYS BEEN AN INTEREST OF MINE. MY BACKGROUND, MY
19 TRAINING AT MICHIGAN WAS FROM THE CENTER FOR HUMAN GROWTH
20 AND DEVELOPMENT, AND I PUBLISHED A LOT OF PAPERS ON
21 LEUKEMIA. IN FACT, THE FIRST PAPER I PUBLISHED IN MY
22 PROFESSIONAL CAREER RELATED TO ENVIRONMENTAL CANCER WAS
23 LOOKING AT LEUKEMIA IN PRESCHOOL CHILDREN. SO I ALWAYS
24 HAD THAT INTEREST.
25 SO I THOUGHT LET ME LOOK AT CHILDHOOD
26 LEUKEMIA. THEN WHILE I WAS DOING THAT I THOUGHT, WELL,
27 YOU KNOW, THERE IS ONLY TWO -- WHAT ARE THE TWO MAIN
28 CAUSES OF CANCER IN CHILDREN? IT IS LEUKEMIA AND BRAIN

1 CANCER. THOSE ARE THE CANCERS THAT SHOW THE TWO HIGHEST
2 RISKS.
3 SO I SAID, WELL, IS THERE ANY EVIDENCE ON
4 BRAIN CANCER ALSO?
5 SO I LOOKED AT THOSE. THERE IS ONLY TWO OR
6 THREE OF THEM, BUT NEVERTHELESS, I LOOKED AT THOSE. THAT
7 IS HOW I GOT THERE.
8 MR. SCHURZ: YOUR HONOR, AT THIS TIME WE WOULD MOVE
9 TO STRIKE AND PRECLUDE ANY TESTIMONY FROM DR. INFANTE
10 WITH RESPECT TO CHILDHOOD BRAIN CANCER. THIS WAS AN
11 ISSUE THAT WAS THE SUBJECT OF OUR IN LIMINE MOTION BEFORE
12 TRIAL. THIS WAS THE VERY CONCERN THAT WE HAD. WE HAVE
13 PROVIDED YOUR HONOR WITH A BRIEF ON THIS ISSUE.
14 WE WOULD ASK TO BE HEARD TO PRECLUDE ANY
15 TESTIMONY FROM DR. INFANTE WITH RESPECT TO CANCER END
16 POINTS THAT WERE NOT THE SUBJECT OF HIS DEPOSITION. HE
17 INDICATED THAT HE LOOKED AT THREE SITES INITIALLY. HE
18 DID NOT LOOK AT BRAIN CANCER. HE DID NOT TESTIFY ABOUT
19 IT. WE GOT VERY CLEAR STATEMENTS IN THE DEPOSITION WITH
20 RESPECT TO THAT, WHICH ARE CITED FOR YOUR HONOR IN THE
21 CONTEXT OF THE BRIEF BEFORE YOU.
22 WE WOULD ALSO NOTE THAT YOU HAVE ALREADY
23 HEARD ABOUT CHILDHOOD BRAIN CANCER FROM DR. MELNICK WHO
24 DID SPEAK ABOUT THIS ISSUE AT HIS DEPOSITION. SO IT IS
25 BOTH DUPLICATIVE AND REDUNDANT OF MATERIAL WE HAVE HEARD.
26 BUT IN THE FIRST INSTANCE, THIS WITNESS WAS VERY CLEAR,
27 "I EVALUATED THESE SITES AND THESE SITES ONLY," AND NOW
28 WE LEARNED FOR THE FIRST TIME YESTERDAY WHEN WE RECEIVED

1 THOSE DEMONSTRATIVES THAT HE HAS ADDED ANOTHER SITE.
2 THE COURT: MR. METZGER, ANY REASON WHY THIS
3 WITNESS'S TESTIMONY SHOULD NOT BE LIMITED TO THE OPINIONS
4 EXPRESSED IN THE DEPOSITION?
5 MR. METZGER: WELL, I AGREE THAT THEY SHOULD BE
6 LIMITED, BUT DR. INFANTE, IN EXHIBIT 222, WHICH WAS NOTES
7 THAT HE PREPARED FOR THE DEPOSITION, PROVIDED HIS
8 ANALYSIS FOR CHILDHOOD BRAIN CANCER.
9 THE COURT: WHATEVER THE NOTES SAY, IF HE DID
10 TESTIFY THAT HE DID NOT REVIEW THE SITE, CERTAIN SITES
11 FOR CANCER, WHY SHOULD HE BE ASKED CERTAIN QUESTIONS NOW
12 ON THAT SAME SUBJECT?
13 MR. METZGER: DR. INFANTE DID NOT TESTIFY THAT HE
14 DID NOT REVIEW CHILDHOOD BRAIN CANCER.
15 THE COURT: I THOUGHT HE LIMITED -- AS I RECALL, I
16 DON'T HAVE IT IN FRONT OF ME RIGHT NOW, BUT AS I RECALL,
17 HE WAS ASKED SPECIFICALLY ABOUT THE SCOPE OF HIS
18 TESTIMONY.
19 MR. METZGER: HE WAS ASKED ABOUT THE SITES THAT HE
20 INTENDED TO TESTIFY ABOUT AND HE MENTIONED THESE SITES.
21 THERE WAS ALSO CHILDHOOD BRAIN CANCER IN HIS NOTES.
22 THE COURT: DO YOU HAVE THE PORTION OF THE
23 DEPOSITION?
24 MR. SCHURZ: YES, YOUR HONOR, WE DO.
25 AND WE DIRECT YOUR HONOR TO -- THERE ARE A
26 COUPLE OF PLACES THAT ARE QUITE CLEAR WITH RESPECT TO
27 THIS ISSUE. IF YOU GO TO -- IT IS EXHIBIT C OF THE
28 MATERIALS THAT PROVIDE THE DEPOSITION OF DR. PETER

1 INFANTE, AND IF YOUR HONOR GOES TO PAGE 21 OF EXHIBIT C,
2 YOU WILL SEE.
3 THE COURT: ALL RIGHT. LET ME LOOK HERE.
4 MR. SCHURZ: BEGINNING AT LINE 18, YOUR HONOR.
5 THE COURT: OKAY, THE QUESTION WAS: "WHAT END
6 POINTS DO YOU INTEND TO OFFER TESTIMONY THAT CONSUMPTION
7 OF COFFEE RESULTS IN AN INCREASE INCIDENCE OF CANCER END
8 POINTS?"
9 THE ANSWER: "PANCREATIC CANCER, BLADDER
10 CANCER AND CHILDHOOD LEUKEMIA."
11 "ANY OTHERS?
12 "THOSE ARE THE THREE FOR NOW THAT I HAVE
13 GOTTEN TO. LOOKS LIKE THERE WAS SOME EVIDENCE WITH LUNG
14 CANCER. I THINK I SENT YOU SOME NOTES I HAD ON THOSE.
15 LOOKS TO ME THAT THE ROLE OF COFFEE IN LUNG CANCER IS
16 LIKE POTENTIATING LUNG CANCER THERE PERHAPS WITH OTHER
17 EXPOSURES."
18 I WILL LOOK A LITTLE FURTHER. JUST ONE
19 SECOND.
20 THEN ON PAGE 22, THE WITNESS IS ASKED:
21 "ANY OTHER SITES YOU INTEND TO OFFER
22 OPINIONS WITH RESPECT TO AN INCREASE INCIDENCE OF CANCER
23 RESULTING FROM CONSUMPTION OF COFFEE?"
24 THE ANSWER: "THAT IS AS FAR AS I HAVE
25 GOTTEN IN THE LITERATURE AT THIS POINT.
26 "HAVE YOU CONCLUDED YOUR WORK IN THIS
27 MATTER?
28 "I DON'T KNOW. I HAVE DONE WHAT I HAVE DONE

1 UP TO THIS POINT IN TIME. IF I AM ASKED TO DO MORE, I
2 WILL."
3 ALL RIGHT. SO BASED UPON THAT TESTIMONY,
4 WHY SHOULDN'T THE WITNESS BE LIMITED TO THE TESTIMONY AT
5 THE DEPOSITION?
6 MR. METZGER: WHY SHOULD HE NOT BE LIMITED?
7 THE COURT: YES.
8 MR. METZGER: WELL, BECAUSE HE PREPARED NOTES WHICH
9 HE PRODUCED AT THE DEPOSITION SETTING FORTH OPINIONS
10 REGARDING CHILDHOOD BRAIN CANCER.
11 THE COURT: SO HE COULD HAVE TAKEN NOTES ON A LOT
12 OF OTHER SUBJECTS.
13 MR. METZGER: I MEAN --
14 THE COURT: YOU BRING A WHOLE TRUCKLOAD OF
15 DOCUMENTS AND HE IS ASKED, "ARE YOU GOING TO TESTIFY
16 ABOUT THIS TRUCKLOAD?"
17 THE WITNESS SAYS, "NO."
18 WHAT GOOD ARE THE DOCUMENTS?
19 MR. METZGER: IF MR. SCHURZ -- THESE NOTES WERE
20 PRODUCED FOR THE DEPOSITION. IF MR. SCHURZ ASKED HIM
21 DIRECTLY, "WELL, I SEE THERE ARE NOTES HERE ABOUT
22 CHILDHOOD BRAIN CANCER. ARE YOU GOING TO TESTIFY ABOUT
23 THAT," THEN WE WOULD KNOW CLEARLY, BUT HE IS ASKING HIM,
24 "WHAT DO YOU RECALL ARE THE THINGS YOU ARE GOING TO
25 TESTIFY ABOUT?"
26 SO HE -- IT IS WITHIN HIS OPINIONS.
27 THE COURT: YOU WERE PRESENT AT THE DEPOSITION;
28 WERE YOU NOT?

1 MR. METZGER: I WAS PRESENT.
2 THE COURT: WHY DIDN'T YOU SAY, "THERE ARE MORE
3 SUBJECTS. HE IS GOING TO TESTIFY ABOUT SOMETHING ELSE."
4 HE COULD BRING A WHOLE BIBLE OF DOCUMENTS
5 ABOUT EBOLA, AND THAT DOESN'T MEAN HE IS GOING TO TESTIFY
6 ABOUT EBOLA.
7 MR. METZGER: I SUPPOSE THAT IS TRUE, YOUR HONOR.
8 THE COURT: ALL RIGHT. LET'S MOVE ON. THANK YOU.
9 THE OBJECTION IS SUSTAINED.
10 MR. METZGER: OKAY.
11 Q SO DR. INFANTE, DID YOU BEGIN YOUR REVIEW OF
12 THE COFFEE/CANCER ISSUE BY REVIEWING THE IARC MONOGRAPH
13 ON COFFEE?
14 A YES.
15 Q AND IS THAT VOLUME 51 OF THE IARC MONOGRAPH
16 THAT WAS OF A 1990 REVIEW PUBLISHED IN 1991?
17 A YES.
18 Q WHAT DID YOU FIND IN REVIEWING THE IARC
19 MONOGRAPH REGARDING COFFEE AND CANCER AT THAT TIME?
20 A WELL, AT THAT TIME, THEY STATED THAT THERE
21 WAS LIMITED EVIDENCE FOR BLADDER CANCER IN HUMANS.
22 Q WHAT DID THAT MEAN TO YOU?
23 A LIMITED EVIDENCE MEANS THERE IS SOME
24 EVIDENCE, BUT THAT, YOU KNOW, THEY COULD NOT RULE OUT
25 CHANCE, BIAS OR CONFOUNDING. SO THERE WAS SOME EVIDENCE,
26 BUT THERE IS NOT SUFFICIENT EVIDENCE.
27 Q IS THE TECHNICAL DEFINITION BY IARC THAT A
28 POSITIVE ASSOCIATION HAS BEEN OBSERVED BETWEEN EXPOSURE

1 TO THE MIXTURE AND CANCER FOR WHICH A CAUSAL
2 INTERPRETATION IS CONSIDERED BY THE WORKING GROUP TO BE
3 CREDIBLE, BUT CHANCE, BIAS OR CONFOUNDING COULD NOT BE
4 RULED OUT WITH REASONABLE CONFIDENCE?
5 MR. SCHURZ: OBJECTION; HEARSAY. ALL MR. METZGER
6 IS DOING NOW IS READING INTO THE RECORD ACTUALLY A
7 PARAPHRASED VERSION OF AN IARC DOCUMENT THAT IS NOT IN
8 EVIDENCE.
9 THE COURT: OVERRULED.
10 MR. METZGER: OKAY.
11 THE COURT: YOU MAY ANSWER THE QUESTION.
12 COULD YOU PLEASE REPEAT THE QUESTION.
13
14 (RECORD READ.)
15
16 THE WITNESS: YES, THAT IS THEIR TECHNICAL
17 DEFINITION, BUT THAT IS WHAT I SAID BEFORE YOU ASKED ME
18 THAT.
19 MR. METZGER: OKAY.
20 Q WERE THERE CERTAIN CONCLUSIONS IN THE
21 MONOGRAPH REGARDING BLADDER CANCER AND PANCREATIC CANCER
22 THAT YOU CONSIDERED OF NOTE?
23 A YES.
24 Q AND WOULD YOU TELL THE COURT WHAT THOSE
25 WERE?
26 A WELL, IN ADDITION TO THE BLADDER CANCER,
27 THEY SAID THAT IN THE DATA TAKEN AS A WHOLE, THERE WAS
28 SUGGESTIVE EVIDENCE OF A WEAK RELATIONSHIP BETWEEN COFFEE

1 CONSUMPTION AND PANCREATIC CANCER.
2 Q OKAY.
3 A BUT, AGAIN, YOU KNOW, THE POSSIBILITY DUE TO
4 CHANCE, BIAS AND CONFOUNDING COULD NOT BE RULED OUT.
5 Q DID YOU CONSIDER IARC'S OVERALL CONCLUSION
6 REGARDING THE CARCINOGENICITY OF COFFEE AS OF 1990/1991?
7 A WELL, ACTUALLY I CONSIDERED -- YES, I
8 CONSIDERED THE EVALUATION AS THEN MY STARTING POINT FOR
9 WHAT LITERATURE I WAS GOING TO SELECT.
10 Q ALL RIGHT. SO HOW DID YOU GO ABOUT
11 ASSESSING THE EPIDEMIOLOGIC LITERATURE REGARDING COFFEE
12 CONSUMPTION AND BLADDER CANCER?
13 A WELL, I LOOKED AT THE -- YOU KNOW, THE
14 EPIDEMIOLOGICAL LITERATURE RELATED TO BLADDER CANCER AND
15 PANCREATIC CANCER.
16 Q I AM ASKING FIRST ABOUT BLADDER CANCER,
17 DR. INFANTE.
18 DID YOU ATTEMPT TO GET YOUR HANDS ON AND
19 READ EVERY STUDY THAT HAD BEEN PUBLISHED REGARDING COFFEE
20 CONSUMPTION AND BLADDER CANCER?
21 A WELL, TO THE BEST OF MY ABILITY, YES.
22 Q SO WAS IT YOUR ATTEMPT TO DO A COMPREHENSIVE
23 REVIEW OF ALL THE STUDIES THAT HAVE BEEN PUBLISHED ON
24 THAT TOPIC?
25 A YES.
26 Q HOW DID YOU GO ABOUT IDENTIFYING THEM?
27 A WELL, THEY ARE IDENTIFIED -- YOU CAN GET
28 ONTO PUB-MED OR TOXLINE AND DO A LITERATURE SEARCH. YOU

1 KNOW, A DIFFERENT LITERATURE SEARCH GIVES YOU DIFFERENT
2 HITS FOR THE STUDIES, BUT BETWEEN THE COMBINATION OF THE
3 TWO, THEN YOU, YOU KNOW, IDENTIFY THE STUDIES. THEN, YOU
4 KNOW, THEN I THINK I ASKED, YOU KNOW, YOUR OFFICE IF YOU
5 COULD PROVIDE ME WITH THOSE -- COPIES OF THOSE ARTICLES
6 SO I DID NOT HAVE TO, YOU KNOW, REQUEST THEM ALL.
7 Q DID YOU ATTEMPT TO REVIEW ALL OF THE
8 EPIDEMIOLOGIC STUDIES THAT -- REGARDING COFFEE
9 CONSUMPTION AND BLADDER CANCER THAT WERE CASE-CONTROL
10 STUDIES?
11 A YES.
12 Q AND COHORT STUDIES?
13 A YES.
14 Q AND META-ANALYSES?
15 A YES.
16 Q DID YOU EXTRACT THE DATA FROM THESE STUDIES
17 INTO TABLES THAT YOU PREPARED AS WRITTEN NOTES?
18 A WHICH I PROVIDED AT MY DEPOSITION, YES.
19 Q SO GO TO SLIDE 97, IF YOU WOULD.
20 ALL RIGHT.
21 IN ANALYZING THE STUDIES, DID YOU LIST THEM
22 BY DIFFERENT STUDY TYPE?
23 A YES. WELL, I HAD THE CASE-CONTROL STUDIES
24 FIRST, YES.
25 Q HERE WE HAVE SOME OF THE CASE-CONTROL
26 STUDIES THAT YOU EVALUATED. WILL YOU TELL US WHAT YOU
27 FOUND OF IMPORT TO YOU IN SOME OF THESE EARLY CASE-
28 CONTROL STUDIES FROM THE 1960S AND 70S?

1 A WELL, THERE ARE STUDIES THAT SHOW LIKE
2 SIGNIFICANT ASSOCIATIONS BETWEEN COFFEE CONSUMPTION AND
3 BLADDER CANCER.
4 Q WOULD YOU IDENTIFY THOSE STUDIES BY AUTHOR
5 AND YEAR?
6 A YES, THE DUNHAM 1968. COLE 1971. FRAUMENI
7 1971. SIMON 1975 IN FEMALES. WYNDER 1977 IN MALES.
8 Q ALL RIGHT. WHILE WE ARE THERE ON THE WYNDER
9 STUDY, WHAT DID YOU FIND OF IMPORT ABOUT THAT STUDY?
10 A I MEAN, IT ALSO DEMONSTRATED A SIGNIFICANT
11 DOSE-RESPONSE.
12 Q CONTINUING ON, PLEASE.
13 A YES. THE HOWE 1980 STUDY FROM CANADA
14 DEMONSTRATED A BORDERLINE STATISTICALLY-SIGNIFICANT
15 INCREASE IN BLADDER CANCER IN MALES. AND THEN WITH
16 INSTANT COFFEE DEMONSTRATED A SIGNIFICANT INCREASE.
17 THE HARTGE STUDY, 1973.
18 Q 1983?
19 A 1983, I AM SORRY. YES, IT DEMONSTRATED A
20 SIGNIFICANT INCREASE IN MEN AND WOMEN.
21 THE MARRETT STUDY, 1983, DEMONSTRATED AN
22 INCREASE IN MALE DRINKERS, BUT IN MALES AND FEMALES
23 COMBINED AMONG NON-SMOKERS, AGAIN, IT DEMONSTRATES A
24 SIGNIFICANT INCREASE. AGAIN, WHICH IS IMPORTANT BECAUSE
25 CIGARETTE SMOKING IS A CONFOUNDER FOR BLADDER CANCER. SO
26 BY FINDING THIS OBSERVATION IN NON-SMOKERS, IT IS A
27 STRONGER FINDING.
28 Q OKAY.

1 A BRAVO 1986 DEMONSTRATED A SIGNIFICANT
2 INCREASE IN MEN AND WOMEN.
3 Q YOU DID NOT MENTION REBEKOLAS, WHAT DID YOU
4 THINK OF THAT STUDY?
5 A THE ONE FROM GREECE?
6 Q YES.
7 A WELL, IT SHOWED IF YOU DRANK TWO OR MORE
8 CUPS A DAY, YOU HAD -- IN MEN AND WOMEN, THERE WAS A
9 SIGNIFICANT INCREASE IN BLADDER CANCER.
10 Q CONTINUE ON, PLEASE.
11 A THE PIPER 1986 STUDY. HERE IS A STUDY THAT
12 USED CUMULATIVE EXPOSURE IN TERMS OF CONSUMING COFFEE.
13 IN FEMALES, THEY FOUND A SIGNIFICANT TREND.
14 Q THAT IS A DOSE-RESPONSE TREND?
15 A YES. THE INDIVIDUAL DATA POINTS ARE NOT
16 STATISTICALLY SIGNIFICANT, BUT THE TREND THAT GOES FROM
17 0.9 -- THAT THE ODDS RATIO THAT GOES FROM 0.9 TO 1.9 TO
18 2.1 IS THE TREND ANALYSIS FOR THOSE ODDS RATIOS BY
19 INCREASING CUMULATIVE CONSUMPTION OF COFFEE IS
20 SIGNIFICANT AT THE 0.004 LEVEL. THAT MEANS THAT
21 OBSERVATION WOULD ONLY OCCUR FOUR TIMES OUT OF 1,000 DUE
22 TO CHANCE.
23 Q PLEASE CONTINUE.
24 A THE ISCOVICH STUDY, ARGENTINA, SHOWS A
25 LITTLE OVER FOUR-FOLD INCREASE AMONG MEN AND WOMEN
26 CONSUMING COFFEE.
27 THE CANTER STUDY DONE IN THE U.S. SHOWS A
28 SIGNIFICANT INCREASE IN ADENOCARCINOMA AND TRANSITIONAL

1 CELL CARCINOMA OF THE BLADDER, AND THE TREND WITH
2 INCREASE IN CONSUMPTION WAS STATISTICALLY SIGNIFICANT.
3 THE RISCH STUDY, 1988, CANADA, FOR THOSE WHO
4 WERE EVER REGULAR USERS OF COFFEE, AND IT DOESN'T SHOW AN
5 INCREASE IN MALES, BUT IN FEMALES THERE IS ALMOST A
6 TWO-FOLD RISK. THAT IS STATISTICALLY SIGNIFICANT.
7 IN THE LA VECCHIA 1989 STUDY, THERE IS AN
8 ODDS RATIO OF 1.8, THAT THEY SAY -- THE AUTHORS SAY WAS
9 STATISTICALLY SIGNIFICANT, BUT THEY DID NOT -- I COULD
10 NOT FIND A CONFIDENCE INTERVAL IN THAT REPORT.
11 Q HAVE YOU NOW DESCRIBED FOR THE COURT THOSE
12 STUDIES PUBLISHED BEFORE THE IARC REVIEW IN 1990 THAT YOU
13 CONSIDERED OF IMPORT?
14 A YES.
15 Q AND DID YOU ALSO CONSIDER THE STUDIES
16 PUBLISHED AFTER IARC?
17 A YES.
18 Q COULD WE HAVE THE NEXT SLIDE THEN.
19 WOULD YOU TELL US WHAT YOU FOUND OF
20 SIGNIFICANCE IN THOSE STUDIES REGARDING BLADDER CANCER?
21 A YES. WELL, THE CLAVEL 1991 STUDY SHOWS A
22 SIGNIFICANT DOSE-RESPONSE WITH MEN AND WOMEN COMBINED IN
23 NON-SMOKERS AS WELL AS SMOKERS. SO THAT IS IMPORTANT
24 SINCE SMOKING IS A CONFOUNDER FOR BLADDER CANCER. I
25 MEAN, IF THEY FIND A DOSE-RESPONSE IN SMOKERS, YOU SAY,
26 "WELL, BUT HOW MUCH IS THAT CONFOUNDED?"
27 THEN THEY COME BACK AND ON THE SAME STUDY
28 THEY SHOW NON-SMOKERS HAVE EVEN A HIGHER TREND, WHICH IS

1 SIGNIFICANT.
2 Q WHAT ELSE?
3 A AND THE KUNZE STUDY OF 1991 FROM GERMANY, IF
4 YOU LOOK AT EXPOSURE BY CUPS PER DAY, THERE IS A
5 SIGNIFICANT TREND IN MEN AS WELL AS WOMEN.
6 IN THE D'AVANZO STUDY FROM ITALY, 1992, IN
7 MEN AND WOMEN, YOU SEE BY NUMBER OF CUPS CONSUMED PER
8 DAY, YOU SEE A -- YOU SEE AN INCREASE. THE AUTHORS
9 REPORTED THERE WAS A SIGNIFICANT DOSE-RESPONSE TREND.
10 Q PLEASE KEEP YOUR VOICE UP, DR. INFANTE.
11 A I'M SORRY, I NEED A DRINK OF WATER.
12 Q GO AHEAD, TAKE A DRINK.
13 A IN THE CHYOU 1991 STUDY OF -- THIS WAS -- IT
14 SAYS U.S.A., BUT IT IS REALLY JAPANESE MALES IN HAWAII.
15 JAPANESE-AMERICAN MALES IN HAWAII.
16 WELL, HERE IT IS INTERESTING, THEY REPORTED
17 THAT TWO TO FOUR CUPS, HIGHLY-ELEVATED RISK, AND FIVE
18 CUPS, THEY DON'T. THEY HAVE A TWO-FOLD RISK, BUT IT IS
19 NOT SIGNIFICANT.
20 THE COURT: IS THERE A QUESTION PENDING OR IS THIS
21 JUST STREAM OF CONSCIOUSNESS TESTIMONY?
22 MR. METZGER: I WILL DO IT QUESTION BY QUESTION.
23 Q LET'S GO ON TO THE NEXT SLIDE.
24 WOULD YOU TELL THE COURT WHAT YOU FOUND OF
25 IMPORT REGARDING THE VENA STUDY FROM 1993?
26 A YES, IT SHOWS A SIGNIFICANT DOSE-RESPONSE
27 WITH THE AMOUNT OF COFFEE CONSUMED IN MALES.
28 Q OKAY.

1 A AND ALSO THE MC GEEHIN 1993 STUDY IN MALES
2 AND FEMALES, THERE IS A SIGNIFICANT INCREASE IN BLADDER
3 CANCER.
4 AND IN THE MOMA 1994 STUDY, IT SHOWS A
5 SIGNIFICANT DOSE-RESPONSE, WHICH MEANS AN INCREASE IN
6 RISK OF BLADDER CANCER WITH AN INCREASE IN COFFEE
7 CONSUMPTION. THIS IS A CUMULATIVE EXPOSURE ANALYSIS.
8 AND THE DONATO 1997 STUDY SHOWS A
9 SIGNIFICANT DOSE-RESPONSE BY AMOUNT OF COFFEE CONSUMED.
10 Q ALL RIGHT. WHAT DID YOU FIND OF
11 SIGNIFICANCE, IF ANYTHING, IN THE GEOFFREY-PEREZ STUDY
12 FROM FRANCE IN 2001?
13 A YES, AMONG NON-SMOKERS, THERE IS A
14 SIGNIFICANT DOSE-RESPONSE TREND.
15 THEN IN THE RADOSAVLJEC 2003 STUDY FROM
16 SERBIA, THEY HAVE A SIGNIFICANTLY INCREASED RISK OF
17 BLADDER CANCER FROM -- BY MILLILITERS OF COFFEE CONSUMED
18 PER DAY.
19 IN THE DE STEFANI 2007 STUDY, THEY REPORT A
20 SIGNIFICANT TREND BY AMOUNT CONSUMED. IN THE
21 NON-SMOKERS, THEY HAVE A TWO-FOLD RISK, BUT IT IS NOT
22 STATISTICALLY SIGNIFICANT.
23 THE COURT: IS THERE A PURPOSE FOR THIS TESTIMONY?
24 MR. METZGER: YES, YOUR HONOR, THERE IS.
25 THE COURT: CAN WE GET TO THE CONCLUSION?
26 HE IS JUST RECITING WHAT IS IN SOMEBODY
27 ELSE'S REPORT. IT IS NOT MEANINGFUL.
28 Q BY MR. METZGER: WELL, DR. INFANTE, WHAT DID

1 YOU CONCLUDE REGARDING THE EPIDEMIOLOGIC STUDIES
2 REGARDING COFFEE CONSUMPTION AND BLADDER CANCER?
3 REGARDING THE CASE-CONTROL STUDIES, THAT IS.
4 A WELL, I CONCLUDED THAT THERE WERE QUITE A
5 LARGE NUMBER OF THEM THAT REPORT STATISTICALLY
6 SIGNIFICANT INCREASED RISKS OF BLADDER CANCER IN RELATION
7 TO COFFEE CONSUMPTION. LIKE THERE ARE 11 CASE-CONTROL
8 STUDIES THAT SHOWS SIGNIFICANT DOSE-RESPONSE
9 RELATIONSHIPS. THERE ARE TWO META-ANALYSES THAT ALSO
10 DEMONSTRATE SIGNIFICANTLY INCREASED DOSE-RESPONSE
11 RELATIONSHIPS AMONG NON-SMOKERS.
12 Q HOLD ON, DR. INFANTE. WE WILL GET TO THE
13 META-ANALYSES.
14 REGARDING THE CASE-CONTROL STUDIES, OF WHAT
15 IMPORT IS TO YOU THAT YOU FOUND NUMEROUS STUDIES
16 REPORTING SIGNIFICANTLY INCREASED RISKS AND SO MANY
17 STUDIES REPORTING STATISTICALLY SIGNIFICANT DOSE-RESPONSE
18 RELATIONSHIPS FOR COFFEE CONSUMPTION AND BLADDER CANCER
19 INCLUDING STUDIES AMONG NON-SMOKERS?
20 MR. SCHURZ: OBJECTION; LEADING. COUNSEL IS
21 TESTIFYING.
22 THE COURT: OVERRULED.
23 THE WITNESS: WELL, TO ME IT INDICATES THAT THERE
24 IS -- THERE IS AN ELEVATED RISK BEING DEMONSTRATED IN
25 THESE STUDIES OF PEOPLE CONSUMING COFFEE, AN INCREASED
26 RISK OF BLADDER CANCER. THEN THAT IS SUPPORTED BY
27 STUDIES THAT ALSO SHOW -- SOME OF THE STUDIES SHOW A
28 DOSE-RESPONSE RELATIONSHIP, WHICH ADDS WEIGHT TO THOSE

1 OBSERVATIONS.
2 Q BY MR. METZGER: OKAY, DID YOU ALSO REVIEW
3 THE COHORT STUDIES REGARDING BLADDER CANCER AND COFFEE
4 CONSUMPTION?
5 A YES, I DID.
6 Q WHAT DID YOU FIND REGARDING THOSE STUDIES?
7 A WELL, I FOUND IN THESE STUDIES, LIKE IN
8 GENERAL, THERE WERE SOME STUDIES THAT SHOWED, YOU KNOW,
9 EVALUATED RISKS, BUT MOST -- BUT MANY OF THEM, THE
10 MAJORITY OF THEM, DO NOT. SO THERE IS A DIFFERENCE
11 BETWEEN THE -- WHAT YOU ARE SEEING IN THE CASE-CONTROL
12 STUDIES VERSUS THE COHORT STUDIES.
13 Q DID YOU REVIEW THE META-ANALYSES THAT HAD
14 BEEN PUBLISHED REGARDING COFFEE CONSUMPTION AND BLADDER
15 CANCER?
16 A YES, I DID.
17 Q WOULD YOU TELL US, FIRST OF ALL, HOW MANY
18 META-ANALYSES YOU FOUND ON THAT TOPIC?
19 A FIVE.
20 Q LET'S BRIEFLY GO OVER EACH OF THEM.
21 WOULD YOU TELL US WHAT YOU FOUND OF
22 SIGNIFICANCE REGARDING THE SALA 2000 META-ANALYSIS OR
23 POOLED ANALYSIS OF 10 CASE-CONTROL STUDIES?
24 A YES, IN NON-SMOKERS IN THE POOLED ANALYSIS,
25 THERE WAS A SIGNIFICANTLY INCREASED RISK OF BLADDER
26 CANCER IN MALES AND FEMALES COMBINED.
27 AND IN THE ZEEGERS 2001 META-ANALYSIS, BASED
28 ON 34 CASE-CONTROL STUDIES, AGAIN WITH MALES AND FEMALES

1 COMBINED, THE STUDY DEMONSTRATES A SIGNIFICANT INCREASED
2 RISK OF BLADDER CANCER.
3 Q OKAY, AND WHAT DID YOU FIND REGARDING THE
4 ZHOU 2012 STUDY?
5 A WELL, IT ALSO -- IF YOU LOOK IN THAT STUDY
6 WITH THE HIGHEST VERSUS THE LOWEST EXPOSURE TO, YOU KNOW,
7 COFFEE CONSUMPTION, YOU FIND A SIGNIFICANTLY INCREASED
8 RISK OF BLADDER CANCER BASED ON A META-ANALYSIS OF 23
9 CASE-CONTROL STUDIES. AND YOU ALSO SEE A, YOU KNOW,
10 SOMEWHAT OF A DOSE-RESPONSE IN THAT STUDY.
11 WHEN YOU LOOK AT THE -- ALSO THE
12 META-ANALYSIS OF NON-SMOKERS, YOU EVEN SEE A MORE
13 PERSUASIVE RISK, CLEAR DOWN ON THE BOTTOM. OF THE
14 NON-SMOKERS FROM THE 23 CASE-CONTROL STUDIES, THE RISK
15 GOES FROM 1.2 TO 1.4 TO 1.6 TO 1.77. SO THERE IS THAT
16 TYPE OF ANALYSIS WHICH WOULD NOT HAVE CONFOUNDING FROM
17 CIGARETTE SMOKING. IT SHOWS A VERY SIGNIFICANT
18 DOSE-RESPONSE.
19 ON THE OTHER HAND, THE META-ANALYSIS OF FIVE
20 COHORT STUDIES, YOU KNOW, DOES NOT SHOW AN ASSOCIATION.
21 Q WHAT DID YOU CONCLUDE REGARDING THE LAST
22 STUDY, THE BAI 2014 STUDY?
23 A IN THAT STUDY, BASED ON 17 CASE-CONTROL
24 STUDIES AND FOUR COHORT STUDIES, IF YOU LOOK AT THE
25 HIGHEST VERSUS THE LOWEST COFFEE CONSUMPTION, YOU SEE
26 ABOUT A 17 PERCENT INCREASE. THAT IS STATISTICALLY
27 SIGNIFICANT FOR BLADDER CANCER.
28 Q AND WAS THERE ANYTHING IN PARTICULAR THAT

1 YOU FOUND IMPORTANT REGARDING THE BAI STUDY?
2 A WELL, YES. I HAVE THAT ON THE NEXT SLIDE
3 THAT IF YOU ARE LOOKING AT FLUID INTAKE, IT WAS EVALUATED
4 IN THE STUDY, THE ONLY ONE, THE ONLY FLUID THAT WAS
5 ASSOCIATED WITH A SIGNIFICANT INCREASE IN BLADDER CANCER
6 WAS COFFEE CONSUMPTION. ALL THE REST OF THEM, THE RISK
7 WAS ABOUT 1.0 OR IT IS BELOW, SLIGHTLY BELOW 1.0.
8 Q SO WHAT DID YOU ULTIMATELY CONCLUDE
9 REGARDING THE EPIDEMIOLOGIC STUDIES CONCERNING COFFEE
10 CONSUMPTION AND BLADDER CANCER?
11 A SPECIFICALLY I IDENTIFIED 28 CASE-CONTROL
12 STUDIES THAT REPORTED SIGNIFICANTLY INCREASED RISKS OF
13 BLADDER CANCER, AND 11 CASE-CONTROL STUDIES, AND TWO
14 COHORT STUDIES REPORTED SIGNIFICANT DOSE-RESPONSE
15 RELATIONSHIPS. AND THREE META-ANALYSES BASED ON
16 CASE-CONTROL STUDIES DEMONSTRATED SIGNIFICANT
17 ASSOCIATIONS. TWO META-ANALYSES BASED ON COHORT STUDIES
18 DID NOT SHOW ANY ASSOCIATION. THEN TWO CASE-CONTROL
19 STUDIES AND TWO META-ANALYSES DEMONSTRATE STATISTICALLY
20 SIGNIFICANT DOSE-RESPONSE RELATIONSHIPS AMONG -- FOR
21 BLADDER CANCER AMONG NON-SMOKERS.
22 Q ALL RIGHT. SO WHAT DID YOU ULTIMATELY
23 CONCLUDE REGARDING THE STATE OF THE EPIDEMIOLOGIC
24 LITERATURE REGARDING COFFEE CONSUMPTION AND BLADDER
25 CANCER THAT POST-DATES IARC'S 1990 REVIEW OF THE ISSUE?
26 A WELL, THE LITERATURE REVIEW CLEARLY
27 INDICATES THAT THERE IS QUITE A BIT OF EVIDENCE RELATED
28 TO COFFEE CONSUMPTION AND BLADDER CANCER SINCE THE IARC

1990 REVIEW.

Q DOES THIS BODY OF LITERATURE, IN YOUR OPINION, EVIDENCE AN ABSENCE OF HUMAN BLADDER CANCER RISK FROM CONSUMPTION OF COFFEE?

A OF COURSE NOT.

Q OKAY. AND WHAT IS YOUR ASSESSMENT OF THE STRENGTH OF THIS ASSOCIATION THAT YOU HAVE OBSERVED BETWEEN COFFEE CONSUMPTION AND BLADDER CANCER?

A IT IS MY OPINION THAT THEY PROVIDE STRONG EVIDENCE OF AN ASSOCIATION BETWEEN COFFEE CONSUMPTION AND BLADDER CANCER.

Q ALL RIGHT. THANK YOU.

HAVE WE NOW COVERED YOUR OPINIONS REGARDING THE COFFEE AND BLADDER CANCER EPIDEMIOLOGY STUDIES?

A YES.

Q SHALL I PROCEED ON TO PANCREATIC CANCER OR DO YOU NEED A MOMENT?

A IS IT POSSIBLE TO GET A SHORT BREAK?

THE COURT: ALL RIGHT. WE WILL TAKE A RECESS AT THIS TIME FOR TEN MINUTES.

MR. METZGER: THANK YOU, YOUR HONOR.

(RECESS TAKEN.)

THE COURT: BACK ON THE RECORD IN THE CASE OF CERT VERSUS STARBUCKS. ALL COUNSEL ARE PRESENT AND SEATED. DR. INFANTE IS ON THE STAND.

DR. INFANTE, YOU UNDERSTAND YOU ARE STILL

1 UNDER OATH?
2 THE WITNESS: YES, SIR.
3 THE COURT: PLEASE RESTATE YOUR NAME FOR THE
4 RECORD.
5 THE WITNESS: PETER FRANCIS INFANTE.
6 THE COURT: AND MR. METZGER WAS INQUIRING.
7 COUNSEL MAY PROCEED.
8 MR. METZGER: THANK YOU, YOUR HONOR.
9 Q DR. INFANTE, HAVE YOU SERVED AS A MEMBER OF
10 THE IARC WORKING GROUPS FOR THE EVALUATION OF
11 CARCINOGENICITY TO HUMANS OF VARIOUS CHEMICALS?
12 A YES, I HAVE.
13 Q ARE YOU -- THROUGH THAT PROCESS, ARE YOU
14 FAMILIAR WITH HOW IARC, THE INTERNATIONAL AGENCY FOR
15 RESEARCH ON CANCER, EVALUATES CHEMICALS OR MIXTURES FOR
16 THEIR CARCINOGENICITY?
17 A YES.
18 Q AND HOW DOES IARC CONSIDER CASE-CONTROL
19 STUDIES IN ITS EVALUATIONS?
20 A WELL, IARC CONSIDERS THAT CASE-CONTROL
21 STUDIES CAN CONTRIBUTE TO THE ASSESSMENT OF
22 CARCINOGENICITY. IN OTHER WORDS, WE EVALUATE THOSE,
23 ALONG WITH COHORT STUDIES.
24 Q HAS IARC EXPRESSED IN ITS PREAMBLE FOR THE
25 MONOGRAPHS THAT CASE-CONTROL STUDIES CONTRIBUTE TO THE
26 ASSESSMENT OF CARCINOGENICITY?
27 A YES, PROBABLY IN EVERY MONOGRAPH -- PREAMBLE
28 TO EVERY MONOGRAPH SHOULD STATE THAT.

1 Q ARE YOU AWARE OF ANY ORGANIZATION THAT
2 DISMISSES CASE-CONTROL STUDIES IN REACHING AN ASSESSMENT
3 OF CARCINOGENICITY OF CHEMICALS?
4 A NO.
5 Q ALL RIGHT. NOW, LET'S TURN TO PANCREATIC
6 CANCER. WHAT APPROACH DID YOU TAKE IN APPRAISING THE
7 EPIDEMIOLOGIC STUDIES REGARDING COFFEE CONSUMPTION AND
8 PANCREATIC CANCER?
9 A WELL, I REVIEWED THE EPIDEMIOLOGICAL
10 STUDIES, THE CASE-CONTROL AND COHORT STUDIES.
11 Q DID YOU EXTRACT DATA FROM THOSE STUDIES AND
12 PUT THAT INTO TABLES?
13 A YES.
14 Q ALL RIGHT. SO WOULD YOU TELL US WHAT YOU
15 FOUND OF SIGNIFICANCE IN THE 1981 STUDY OF BRIAN
16 MAC MAHON OF HARVARD REGARDING COFFEE CONSUMPTION AND
17 BLADDER CANCER?
18 A YES, IT DEMONSTRATES A SIGNIFICANT
19 ASSOCIATION BETWEEN COFFEE CONSUMPTION AND BLADDER
20 CANCER, AND ALSO A -- IN SOME ANALYSES, A DOSE-RESPONSE.
21 Q WHAT OTHER STUDIES DID YOU CONSIDER TO BE
22 IMPORTANT REGARDING COFFEE CONSUMPTION AND BLADDER
23 CANCER?
24 A WELL, I MEAN, I LOOKED AT THE ENTIRE
25 LITERATURE. DO YOU MEAN WHICH ONES DEMONSTRATE A
26 SIGNIFICANT INCREASE BECAUSE THERE COULD BE SOME THAT ARE
27 BORDERLINE SIGNIFICANT, THAT COULD ALSO CONTRIBUTE
28 INFORMATION. YOU DON'T SIMPLY PICK OUT THE ONES THAT ARE

1 STATISTICALLY SIGNIFICANT AND HAVE A BLIND EYE TO ALL THE
2 REMAINING ONES. OTHERWISE A MONKEY COULD DO THIS
3 ANALYSIS.
4 Q WELL, TELL US WHAT YOU CONSIDER TO BE
5 SIGNIFICANT IN YOUR ANALYSIS, PLEASE.
6 A WELL, OTHER THAN MAC MAHON, THE 1986 HSIEH
7 STUDY THAT SHOWED THAT IN MEN, THAT IF THEY CONSUMED OVER
8 FIVE CUPS A DAY COMPARED TO PEOPLE WHO DID NOT CONSUME
9 COFFEE, THERE IS A TWO-FOLD RISK. THAT IS BORDERLINE
10 STATISTICALLY SIGNIFICANT.
11 THE MACK 1986 STUDY IN MEN AND WOMEN
12 COMBINED SHOWS A SIGNIFICANT INCREASE.
13 THE 1986 WYNDER STUDY AMONG NON-SMOKERS FOR
14 DECAFFEINATED COFFEE SHOWS A SIGNIFICANT INCREASE IN
15 WOMEN, BUT NOT MEN.
16 THE 1989 CLAVEL STUDY IN WOMEN DEMONSTRATES
17 A SIGNIFICANT TREND.
18 THE 1991 GHADIRIAN STUDY FROM CANADA --
19 WELL, FOR DECAFFEINATED COFFEE, IT DEMONSTRATES A
20 SIGNIFICANT TREND, BUT IT DOES NOT FOR REGULAR COFFEE.
21 SO I WOULD SAY IT PROVIDES SOME CONFLICTING EVIDENCE.
22 THE LYON 1992 STUDY SHOWS BY CUMULATIVE
23 COFFEE CONSUMPTION A SIGNIFICANT DOSE-RESPONSE AMONG
24 SMOKERS.
25 THE GULLO 1995 STUDY FROM ITALY DEMONSTRATES
26 A SIGNIFICANT DOSE-RESPONSE IN BOTH MEN AND WOMEN. AND
27 FOR THOSE THAT WERE HISTOLOGICALLY CONFIRMED, AND FOR
28 THOSE THAT WERE NEVER-SMOKERS DEMONSTRATES A SIGNIFICANT

1 INCREASE.
2 Q IS THERE ANY SIGNIFICANCE TO YOU OF THEM
3 FINDING A SIGNIFICANT INCREASE IN PANCREATIC CANCER AMONG
4 PANCREATIC CANCER PATIENTS WHO HAD HISTOLOGICAL
5 CONFIRMATION OF THEIR DISEASE?
6 A WELL, IT ADDS TO THE CONFIDENCE IN YOUR
7 ANALYSIS BECAUSE THOSE CANCERS HAVE BEEN HISTOLOGICALLY
8 CONFIRMED. SO YOU KNOW FOR SURE THAT IS WHAT THEY ARE.
9 THAT WOULD BE STRONGER, SAY AN IDENTICAL FINDING, IT
10 WOULD BE STRONGER IN A STUDY THAT HISTOLOGICALLY
11 CONFIRMED THE -- BECAUSE THEN YOU KNOW YOU ARE TALKING
12 ABOUT PANCREATIC CANCER.
13 Q IN THAT STUDY, WHAT WAS THE SIGNIFICANCE TO
14 YOU OF THE SIGNIFICANT INCREASE IN PANCREATIC CANCER
15 AMONG NEVER-SMOKERS CONSUMING MORE THAN THREE CUPS OF
16 COFFEE PER DAY?
17 A IT IS AN IMPORTANT FINDING BECAUSE CIGARETTE
18 SMOKING IS A RISK FACTOR FOR PANCREATIC CANCER. SO WHEN
19 YOU FIND ALMOST A THREE-FOLD INCREASE IN NEVER-SMOKERS,
20 THAT IS AN IMPORTANT OBSERVATION.
21 THE KOKIC STUDY FROM YUGOSLAVIA, OR HOWEVER
22 YOU PRONOUNCE IT, IN MEN AND WOMEN DEMONSTRATES A
23 SIGNIFICANT INCREASE IN PANCREATIC CANCER.
24 THE SILVERMAN STUDY IN THE U.S. ONLY SHOWS A
25 SIGNIFICANT INCREASE WHICH IS BORDERLINE IN BLACKS. IT
26 DOESN'T IN WHITES.
27 THE PORTA 1999 STUDY SHOWS A SIGNIFICANT
28 INCREASE IN PANCREATIC CANCER RELATED TO PANCREATIC

1 CANCER THAT HAS A PARTICULAR KIND OF MUTATION TO IT,
2 CALLED A K-RAS MUTATION, AND THE TREND WAS STATISTICALLY
3 SIGNIFICANT IF YOU LOOK AT THOSE RESULTS.
4 Q LET ME ASK YOU A LITTLE ABOUT THAT STUDY.
5 FIRST, REGARDING THE MAIN RESULTS OF
6 DRINKERS VERSUS NON-DRINKERS FOR PANCREATIC CANCER WITH
7 K-RAS MUTATIONS, WHAT, IF ANYTHING, DID YOU MAKE OF THE
8 FACT THAT THE ODDS RATIO REPORTED FOR THAT WAS GREATER
9 THAN FIVE AND WAS STATISTICALLY SIGNIFICANT?
10 A WELL, IT SHOWS A STRONG ASSOCIATION. THAT
11 MEANS A HIGH ODDS RATIO.
12 Q WHAT, IF ANYTHING, DID YOU CONCLUDE
13 REGARDING THE ODDS RATIO THAT WAS FOUND FOR PANCREATIC
14 CANCER PATIENTS WITH K-RAS MUTATIONS WHO CONSUMED MORE
15 THAN 15 CUPS OF COFFEE PER WEEK?
16 A WELL, I MEAN, IT SHOWS THAT IF YOU GO FROM
17 LESS THAN 15 TO MORE THAN 15, THERE IS QUITE AN INCREASE
18 IN THE RISK. THEY ARE BOTH STATISTICALLY SIGNIFICANT.
19 Q WHAT WAS THE --
20 A IT IS A SIGNIFICANT DOSE-RESPONSE.
21 Q WHAT WAS THE INCREASED RISK FOR CONSUMPTION
22 OF GREATER THAN 15 CUPS OF COFFEE PER WEEK?
23 A TEN-FOLD RISK.
24 Q IS A TEN-FOLD RISK SOMETHING THAT GETS YOUR
25 ATTENTION?
26 A YES, THAT IS VERY HIGH. I MEAN, MOST OF THE
27 STUDIES YOU ARE TALKING ABOUT A 1.5-FOLD INCREASE, A
28 TWO-FOLD RISK. SOMETIMES HIGHER.

1 Q WHAT IS THE SIGNIFICANCE OF A TEN-FOLD
2 INCREASED RISK THAT IS STATISTICALLY SIGNIFICANT
3 REGARDING THE EVALUATION OF CARCINOGENICITY?
4 A WELL, IT IS A VERY STRONG FINDING. THE
5 STRENGTH OF THE ASSOCIATION, THAT IS QUITE A STRONG
6 ASSOCIATION.
7 Q WHAT OTHER STUDIES REGARDING CONSUMPTION OF
8 COFFEE AND PANCREATIC CANCER DID YOU CONSIDER TO BE --
9 A AGAIN, THE MORALES 2007 STUDY AMONG REGULAR
10 DRINKERS WITH K-RAS MUTATION, THEY HAVE A SIGNIFICANT
11 INCREASE. AND IF YOU LOOK AT FROM -- BY DOSE-RESPONSE,
12 THERE IS A SIGNIFICANT TREND. AND THOSE, AGAIN, WHO
13 DRANK MORE THAN 15 CUPS OF COFFEE A WEEK, THEY HAVE GOT
14 AN 11-FOLD RISK. THAT IS STATISTICALLY SIGNIFICANT.
15 Q OKAY.
16 A SO THAT IS, YOU KNOW, IMPORTANT FOR THE
17 REASONS I JUST STATED IN RELATION TO THE PORTA STUDY.
18 IN THE TURATI STUDY FROM ITALY, 2011, THEY
19 DEMONSTRATE A SIGNIFICANT INCREASE IN THE DOSE-RESPONSE
20 FOR PANCREATIC CANCER.
21 Q ALL RIGHT. DID YOU ALSO CONSIDER THE COHORT
22 STUDIES THAT HAVE BEEN PUBLISHED REGARDING COFFEE
23 CONSUMPTION AND PANCREATIC CANCER?
24 A YES, I DID. YES.
25 Q WHAT DID YOU FIND OF NOTE REGARDING THOSE
26 STUDIES?
27 A WELL, THERE WERE SOME STUDIES THAT I
28 THINK MAYBE FIVE OF THEM THAT DEMONSTRATED A SIGNIFICANT

1 ASSOCIATION AND THE OTHERS DID NOT. THEY ARE NOT -- SO
2 THERE ARE SOME COHORT STUDIES AS WELL THAT DEMONSTRATE
3 THE ASSOCIATION. THEY ARE NOT AS MANY AS WITH
4 CASE-CONTROL STUDIES.
5 Q WHAT, IF ANYTHING, DID YOU CONSIDER
6 IMPORTANT ABOUT THE 1989 HIRAYAMA STUDY?
7 A WELL, IF YOU LOOK AT DRINKERS VERSUS
8 NON-DRINKERS, YOU HAVE OVER A FIVE-FOLD RISK. THAT WAS
9 STATISTICALLY SIGNIFICANT.
10 IF YOU LOOK AT THE HARNACK 1997 STUDY, FOR
11 THOSE THAT DRANK MORE THAN 17 AND A HALF CUPS A WEEK,
12 VERSUS THOSE THAT DRANK LESS THAN SEVEN CUPS, YOU HAVE A
13 TWO-FOLD RISK. AND FOR THOSE THAT DRANK EIGHT TO 17
14 CUPS, YOU HAVE A RISK OF 1.9. IT IS NOT SIGNIFICANT, BUT
15 THEN INCREASES WHEN YOU LOOK AT THOSE WITH MORE THAN 17
16 CUPS.
17 SO YOU HAVE A SIGNIFICANT INCREASE IN THE
18 HARNACK STUDY AND ALSO THE DOSE-RESPONSE.
19 Q ARE THERE ANY OTHER COHORT STUDIES THAT YOU
20 FOUND?
21 A WELL, THE LIN STUDY OF 2002 FROM JAPAN, THEY
22 FOUND A SIGNIFICANT INCREASE IN MEN, BUT NOT WOMEN.
23 IN THE STOLZENBERG STUDY IN THE U.S., THE
24 FOURTH QUINTILE DEMONSTRATED A SIGNIFICANT INCREASE, BUT
25 THEN YOU DID NOT FIND ANY INCREASE IN THE FIFTH QUINTILE.
26 I DON'T KNOW WHAT IS GOING ON THERE. I CAN'T -- I HAVE
27 TO LOOK BACK TO SEE WHAT THE NUMBERS WERE IN THOSE
28 DIFFERENT CATEGORIES OF EXPOSURE.

1 THE NILSSON 2010 STUDY, FOR TOTAL COFFEE,
2 THERE IS A 50 PERCENT INCREASE THAT IS NOT SIGNIFICANT,
3 BUT THEN WHEN THEY ANALYZED BY BOILED COFFEE, THEY FIND
4 THAT FROM ONE TO THREE CUPS -- I DON'T THINK IT IS ON THE
5 SLIDE -- THE RISK IS 1.68 AND FOR FOUR OR MORE CUPS, IT
6 GOES UP TO 2.51. THAT IS STATISTICALLY SIGNIFICANT AND
7 ALSO INDICATES A DOSE-RESPONSE.
8 THOSE ARE THE ONES THAT I FOUND HAD SOME
9 EVIDENCE OF AN ASSOCIATION IN THE COHORT STUDIES WITH
10 COFFEE AND PANCREATIC CANCER.
11 Q ALL RIGHT. WOULD YOU TELL US WHAT YOU
12 CONCLUDED ABOUT THE STUDIES REGARDING COFFEE CONSUMPTION
13 AND PANCREATIC CANCER?
14 A YES. AS I INDICATED, I THINK I HAVE IT ON
15 ONE OF THE SLIDES, MAYBE 122, THAT THERE ARE 14
16 CASE-CONTROL STUDIES THAT REPORT SIGNIFICANTLY INCREASED
17 RISKS OF PANCREATIC CANCER IN RELATION TO COFFEE
18 CONSUMPTION, AND 11 OF THESE CASE-CONTROL STUDIES REPORT
19 STATISTICALLY SIGNIFICANT DOSE-RESPONSE RELATIONSHIPS.
20 FOUR CASE-CONTROL STUDIES DEMONSTRATE SIGNIFICANT
21 DOSE-RESPONSE RELATIONSHIPS AMONG NON-SMOKERS.
22 I DON'T THINK WE HAVE DISCUSSED META-
23 ANALYSES YET.
24 Q TELL US WHAT YOU CONCLUDED REGARDING THE
25 META-ANALYSES, PLEASE?
26 A WELL, THERE ARE TWO THAT WERE BASED ON
27 CASE-CONTROL STUDIES, AND TWO BASED ON COHORT STUDIES
28 THAT REPORT INCREASED RISKS THAT ARE NOT STATISTICALLY

1 SIGNIFICANT.
2 Q SO WHAT DID YOU ULTIMATELY CONCLUDE
3 REGARDING THIS BODY OF EPIDEMIOLOGIC LITERATURE
4 CONCERNING COFFEE CONSUMPTION AND PANCREATIC CANCER?
5 A WELL, I CONCLUDED THAT THERE IS SOME
6 EVIDENCE OF AN ASSOCIATION BETWEEN COFFEE CONSUMPTION AND
7 PANCREATIC CANCER.
8 Q DR. INFANTE, IN YOUR OPINION, DOES THE
9 TOTALITY OF THIS LITERATURE DEMONSTRATE AN ABSENCE OF
10 CARCINOGENIC RISK TO HUMANS FOR PANCREATIC CANCER FROM
11 COFFEE CONSUMPTION?
12 A NO.
13 Q OKAY. NOW, DID YOU ALSO, AS PART OF YOUR
14 WORK IN THIS CASE, REVIEW THE META-ANALYSES THAT HAVE
15 BEEN PUBLISHED REGARDING COFFEE CONSUMPTION AND VARIOUS
16 CANCERS?
17 A YES.
18 Q AND DID YOU SET FORTH SOME OF THE FINDINGS
19 THAT YOU CONSIDERED OF NOTE IN YOUR NOTES WHICH ARE
20 EXHIBIT 224?
21 A YES, I DID.
22 Q FOR THE MOMENT, I WOULD LIKE TO SET ASIDE
23 THE CHENG META-ANALYSIS REGARDING CHILDHOOD LEUKEMIA
24 BECAUSE WE WILL BE DISCUSSING THAT AT LENGTH, BUT WOULD
25 YOU TELL US WHAT YOU CONCLUDED FROM YOUR REVIEW OF THE
26 OTHER META-ANALYSES REGARDING COFFEE CONSUMPTION AND
27 VARIOUS TYPES OF HUMAN CANCER?
28 A YES, THERE ARE THREE --

1 MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT,
2 OBVIOUSLY, WITH RESPECT FOR THE SAME REASONS THAT WE HAVE
3 DISCUSSED. ANY OPINIONS THAT DR. INFANTE WOULD NOW LIKE
4 TO OFFER THAT ARE UNDISCLOSED WITH RESPECT TO OTHER
5 CANCER SITES OTHER THAN THE THREE THAT HAVE BEEN
6 IDENTIFIED ARE NEW UNDISCLOSED OPINIONS THAT SHOULD BE
7 BARRED FOR THE SAME REASONING THAT WE DISCUSSED --
8 THE COURT: OBJECTION SUSTAINED.
9 MR. METZGER: YOUR HONOR, THESE ARE IN
10 DR. INFANTE'S REPORT IN THIS CASE.
11 THE COURT: SO?
12 MR. METZGER: HE TESTIFIED TO THESE AT HIS
13 DEPOSITION.
14 THE COURT: THAT IS THE QUESTION, WHETHER HE
15 TESTIFIED. THE EXCERPT I WAS SHOWN INDICATES THAT HE WAS
16 NOT PREPARED TO TESTIFY ABOUT IT.
17 MR. METZGER: DR. INFANTE TESTIFIED THAT HE HAD
18 WRITTEN OUT HIS OPINIONS AND THOSE WERE HIS OPINIONS FOR
19 THE CASE. IF MR. SCHURZ CHOOSES NOT TO ASK HIM ABOUT
20 THOSE OPINIONS WHEN HE TESTIFIED THAT HE HAS WRITTEN OUT
21 ALL HIS OPINIONS AND HERE THEY ARE, THEN THAT -- THEY ARE
22 OPINIONS THAT HE HAS IN THE CASE.
23 THE COURT: THAT MAY BE, BUT THE TESTIMONY I SAW
24 INDICATED THAT HE WAS NOT PREPARED, THAT HE DID NOT DO
25 ANY REVIEW, THAT HE DID NOT EVEN READ THE ARTICLES IN
26 CONNECTION WITH THOSE OTHER CANCER SITES.
27 THE WITNESS: YOUR HONOR, MAY I SHOW THE COURT?
28 THE COURT: WELL, LET'S REVIEW THE TESTIMONY AGAIN.

1 MR. METZGER: THIS IS IN THE CONTEXT OF HIS
2 CRITIQUE OF DR. BOFFETTA'S TESTIMONY. HE DID CRITIQUE
3 DR. BOFFETTA IN HIS DEPOSITION.
4 THE COURT: THAT MAY BE, BUT THE TESTIMONY THAT WAS
5 PREVIOUSLY CITED -- IF THERE WAS SOMETHING ELSE LATER IN
6 THE DEPOSITION WHERE HE DID EXPRESS THE OPINION
7 PREVIOUSLY -- LET'S SEE WHAT PAGE IT WAS.
8 MR. METZGER: I THINK PAGE 148 IS WHERE THE
9 TESTIMONY OCCURS, YOUR HONOR.
10 THE COURT: 148?
11 MR. SCHURZ: YOUR HONOR, WELL, WHEN YOU ARE -- WHEN
12 IT IS APPROPRIATE, WE DIRECT THE COURT TO --
13 THE COURT: SHOW ME PAGE 148.
14 MR. METZGER: ON PAGE 148, AT LINE 16 THROUGH 18,
15 DR. INFANTE --
16 THE COURT: WHERE IS THE TRANSCRIPT FOR 148?
17 DO WE HAVE A TRANSCRIPT?
18 MR. METZGER: YES. SORRY, YOUR HONOR. I THOUGHT
19 YOU HAD IT.
20 THE COURT: ALL RIGHT. PAGE?
21 MR. METZGER: SO HE DISCUSSES THE GENKINGER STUDY
22 ON PAGE 148.
23 MR. SCHURZ: FOR THE COURT'S ANALYSIS, GENKINGER WE
24 ALREADY DISCUSSED. IT IS RELATING TO PANCREATIC CANCER.
25 THE COURT: PAGE AND LINE NUMBER?
26 MR. METZGER: PAGE 148, LINES 16 THROUGH 19.
27 THE COURT: OKAY.
28 SO THE ANSWER IS PANCREATIC CANCER AND THE

1 OBJECTION IS SUSTAINED.
2 ANYTHING ELSE?
3 MR. METZGER: YES, YOUR HONOR. IT WILL TAKE ME A
4 MOMENT TO FIND IT, BUT DR. INFANTE TESTIFIED THAT HE HAD
5 REVIEWED THE META-ANALYSES AND THAT HE HAD PREPARED THESE
6 NOTES REGARDING THEM.
7 HE ALSO TESTIFIED THAT -- IF YOU LOOK AT
8 PARAGRAPH 52 OF HIS REPORT, HE PROVIDES HIS OPINION THERE
9 REGARDING THESE META-ANALYSES. IT IS RIGHT IN HIS
10 REPORT. HE TESTIFIED THAT HIS REPORT SET FORTH HIS
11 OPINIONS FOR THE CASE.
12 THE COURT: ALL RIGHT. OKAY. THAT IN ITSELF IS
13 IMPORTANT, BUT DEPENDS WHAT HE WAS ASKED AT THE
14 DEPOSITION.
15 MR. SCHURZ, YOU WANTED TO SHOW ME SOMETHING?
16 MR. SCHURZ: FIRST, WELL, BINKINGER, AS YOUR HONOR
17 CAN SEE, IS RELATED TO PANCREATIC CANCER. WE HAVE
18 ALREADY DISCUSSED IT AT SOME LENGTH. WE GOT THE SALA
19 STUDY RELATING TO BLADDER CANCER. ZEEGERS RELATING TO
20 URINARY TRACT CANCER, ALSO DISCUSSED, RELATING TO
21 BLADDER. WE HAVE GOT THE GINZINGER, TURATI AND ZHOU ALL
22 RELATING TO BLADDER OR PANCREAS THAT WE DISCUSSED.
23 WE WOULD DIRECT YOUR HONOR TO THOSE PORTIONS
24 OF THE TRANSCRIPT WHERE WE SPECIFICALLY ASK WHAT CANCER
25 END POINTS ARE YOU GOING TO TESTIFY TO. WE DISCUSSED
26 EARLIER AT PAGES 21 AND 22, WE FURTHER DIRECT YOUR HONOR
27 TO THE INTERCHANGE BETWEEN COUNSEL THAT BEGINS AT
28 PAGE 23, LINE 17.

1 THE COURT: OKAY.
2 MR. SCHURZ: IF YOU CAN SEE THAT IT PRECEDES, YOUR
3 HONOR, IF -- DR. INFANTE INDICATES:
4 "IF I AM ASKED TO DO SOME OTHER THINGS, BUT
5 THESE ARE THE ONLY ONES I COULD GET TO AND I CHOSE THOSE
6 BASED ON THE FACTORS THAT I GAVE YOU EARLIER."
7 MR. METZGER: YOUR HONOR, I WOULD DIRECT --
8 MR. SCHURZ: TO WHICH I ASKED:
9 "SO, IF DR. INFANTE INTENDS TO OFFER
10 TESTIMONY WITH RESPECT TO ANY OTHER CANCER END POINTS
11 OTHER THAN THE FOUR HE HAS JUST IDENTIFIED, WE WOULD LIKE
12 TO -- WE WILL INSIST UPON HAVING A FURTHER DEPOSITION
13 WITH RESPECT TO THOSE THINGS."
14 MR. METZGER RESPONDS:
15 "IF HE IS GOING TO DO THAT, I WILL, OF
16 COURSE, PRODUCE HIM FOR ANOTHER DEPOSITION. I DON'T KNOW
17 THAT IS GOING TO BE NECESSARY, BUT I HAVE NOT REALLY
18 THOUGHT ABOUT IT YET. I ASSURE YOU THAT YOU ARE NOT
19 GOING TO -- THAT WE ARE NOT GOING TO TRY TO SURPRISE YOU
20 AT TRIAL. IF HE FORMS OTHER OPINIONS ON OTHER CANCER
21 SITES, I WILL PRODUCE HIM FOR ANOTHER DEPOSITION.
22 MR. METZGER: YOUR HONOR --
23 MR. SCHURZ: FURTHER -- WE HAD FURTHER DISCUSSION
24 WITH RESPECT TO THE COMPLETENESS OF THE TESTIMONY THAT
25 DR. INFANTE OFFERED AT THE CONCLUSION OF HIS DEPOSITION,
26 WHERE WE ASKED:
27 "IS IT CLEAR THAT WE HAVE DISCUSSED ALL OF
28 THE OPINIONS THAT YOU INTEND TO OFFER IN THIS CASE?"

1 AT WHICH POINT DR. INFANTE CONFIRMED THAT
2 YES, IN FACT, HE HAD.
3 WHAT WE HAVE SEEN TODAY IS THAT THE OPINIONS
4 THAT HE HAS OFFERED WITH RESPECT TO LUNG CANCER IN THE
5 CONTEXT OF HIS DEPOSITION, HE IS NO LONGER ADVANCING IN
6 THIS ACTION.
7 THE COURT: ALL RIGHT. WELL, LET ME HEAR FROM
8 MR. METZGER.
9 THE TESTIMONY GOING BACK TO 21, THE WITNESS
10 INDICATED HE INTENDED TO OFFER TESTIMONY WITH RESPECT TO
11 PANCREATIC CANCER, BLADDER CANCER, CHILDHOOD LEUKEMIA AND
12 LUNG CANCER. THEN AS MR. SCHURZ QUOTED THE TRANSCRIPT,
13 IF HE INTENDS TO OFFER ANY ADDITIONAL TESTIMONY ON OTHER
14 SITES, AND YOU SAID YOU WOULD LET MR. SCHURZ KNOW AND
15 PRODUCE DR. INFANTE FOR ANOTHER DEPOSITION.
16 WHERE ARE WE IN THIS?
17 MR. METZGER: HERE IS WHERE WE ARE, YOUR HONOR: IF
18 YOU WOULD KINDLY LOOK AT PAGE 134 OF THE TRANSCRIPT.
19 THE COURT: 134?
20 MR. METZGER: YES, LINE 13.
21 THE COURT: ONE SECOND. 134, LINE 13.
22 MR. METZGER: THE WITNESS IDENTIFIES DEPOSITION
23 EXHIBIT 16 AS HIS OPINIONS FOR THE CASE.
24 MR. SCHURZ ASKED HIM:
25 "YOU PREPARED EXHIBIT 16?"
26 "ANSWER: YES.
27 "QUESTION: WHAT IS EXHIBIT 16?
28 "ANSWER: THESE ARE MY OPINIONS IN THIS CASE

1 RELATED TO ACRYLAMIDE AND CANCER AND COFFEE CONSUMPTION
2 AND CANCER."
3 MR. SCHURZ ASKED: "DOES IT SET FORTH A
4 COMPREHENSIVE LIST OF ALL THE OPINIONS YOU INTEND TO
5 OFFER IN THIS MATTER?
6 "ANSWER: YES."
7 WELL, EXHIBIT 16 HAS PARAGRAPH 52 IN IT IN
8 WHICH DR. INFANTE RENDERS AN OPINION REGARDING THESE
9 META-ANALYSES. SO IT IS PART OF HIS OPINIONS, IT WAS
10 STATED SUCH AT THE DEPOSITION
11 THE COURT: WHERE IS EXHIBIT 16?
12 ALL RIGHT. I HAVE THAT. I AM LOOKING AT
13 EXHIBIT 16 AND PARAGRAPH 52.
14 ALL RIGHT, SO?
15 MR. METZGER: SO IN PARAGRAPH 52, DR. INFANTE
16 RENDERS AN OPINION REGARDING THE META-ANALYSES REGARDING
17 COFFEE CONSUMPTION AND CANCER WHICH HE INDICATES THAT
18 DR. BOFFETTA FAILED TO CONSIDER WHICH META-ANALYSES
19 REPORT INCREASED RISKS FOR CANCER. HE IDENTIFIES THEM
20 HERE, AND THOSE ARE DESCRIBED WITH THE DATA IN THE NOTES
21 THAT HE PRODUCED FOR HIS DEPOSITION, WHICH ARE
22 EXHIBIT 224.
23 SO HE WROTE OUT HIS OPINIONS, HE SAID AT HIS
24 DEPOSITION, "THESE ARE MY OPINIONS," AND MR. SCHURZ IS
25 NOW TRYING TO PERSUADE THE COURT THAT THESE ARE NOT HIS
26 OPINIONS THAT HE RENDERED AT HIS DEPOSITION.
27 THE COURT: WHERE IS HIS OPINION?
28 PARAGRAPH 52 IS A CRITICISM OF DR. BOFFETTA.

1 WHERE DOES IT GO FROM THERE?
2 HE DOES NOT LIKE DR. BOFFETTA'S WORK.
3 MR. METZGER: IT IS MORE THAN THAT. HE SAYS THAT
4 THESE META-ANALYSES FOR COFFEE CONSUMPTION AND CANCER
5 REPORTED INCREASED RISKS. THAT IS THE OPINION.
6 THE COURT: ALL RIGHT.
7 MR. METZGER: DR. BOFFETTA SAID ALL THE
8 META-ANALYSES DEMONSTRATED AN ABSENCE OF RISK. SO THAT
9 IS -- THAT IS HIS OPINION THAT THESE META-ANALYSES SHOW
10 INCREASED RISK, CONTRARY TO WHAT DR. BOFFETTA CONCLUDED.
11 THESE ARE OPINIONS HE PREPARED FOR THIS CASE, AND AT HIS
12 DEPOSITION HE TESTIFIED THAT THESE ARE MY OPINIONS.
13 SO FOR MR. SCHURZ TO SAY THAT THEY ARE NOT
14 OPINIONS THAT HE RENDERED AT HIS DEPOSITION IS SIMPLY
15 WRONG. CLEARLY WHAT DR. INFANTE -- THE QUESTION THAT
16 MR. SCHURZ WAS ASKING AND WHAT DR. INFANTE WAS ANSWERING
17 WAS CONCERNING THOSE SITES OF CANCER WHERE HE HAD
18 REVIEWED ALL OF THE STUDIES. THIS IS SOMETHING ELSE
19 REGARDING THE META-ANALYSES. HE SAID THAT THESE ARE HIS
20 OPINIONS AT HIS DEPOSITION.
21 THE COURT: WELL -- YES, GO AHEAD.
22 MR. SCHURZ: THERE ARE A SERIES OF
23 MISREPRESENTATIONS, YOUR HONOR.
24 FIRST, DR. INFANTE DID NOT TESTIFY AT HIS
25 DEPOSITION THAT HE HAD REVIEWED ALL OF THE STUDIES WITH
26 RESPECT TO BLADDER AND PANCREAS. THAT WAS SOMETHING HE
27 DID AFTER HIS DEPOSITION. IT IS QUITE CLEAR THAT HE HAD
28 NOT CONCLUDED. HE READ ONLY THREE COHORT STUDIES. SO

1 THAT REPRESENTATION IS FALSE.
2 SECOND, WE HAVE NOW HEARD THAT WE ARE
3 SUPPOSED TO BE LOOKING AT THE NOTES. THE NOTES INCLUDE
4 STUDIES THAT ARE NOT REFLECTED IN PARAGRAPH 52. THE
5 NOTES WERE NOT INDICATED AS "HERE IS MY REPORT." THE
6 NOTES ARE WHAT THEY PURPORT TO BE, THEY ARE NOTES.
7 THE COURT: FORGET ABOUT THE NOTES. THE NOTES ARE
8 NOTES. WE ARE TALKING ABOUT THE OPINIONS. THIS DOCUMENT
9 WAS PRODUCED PURPORTING TO STATE DR. INFANTE'S OPINIONS.
10 LET'S GO TO THE OPINIONS.
11 MR. SCHURZ: AND WHAT HE HAS IDENTIFIED AS A SERIES
12 OF STUDIES RELATING TO PANCREATIC CANCER AND BLADDER
13 CANCER, WHICH WE HAVE DISCUSSED A TOTAL OF SIX OF THOSE
14 STUDIES HERE, WHAT IS NOW AT ISSUE IS WITH RESPECT TO
15 WHETHER THIS WITNESS MAY TESTIFY WITH RESPECT TO OTHER
16 CANCER SITES, NAMELY OVARIAN CANCER, GASTRIC CANCER, LUNG
17 CANCER, WHICH HE HAS NOW DISOWNED, AND GASTRIC CANCER.
18 THE POINT IS HE CANNOT.
19 IN THE ABSENCE OF AN EXPRESSION THAT -- AND
20 A REQUEST, "WHAT ARE THE CANCER SITES YOU INTEND TO
21 ADDRESS," HE ANSWERED, "I HAVE LOOKED AT THESE AND THESE
22 ALONE."
23 AS YOUR HONOR KNOWS, DR. BOFFETTA LOOKED AT
24 17 SITES AND WE WERE VERY CAREFUL ABOUT WHAT EXACTLY WAS
25 -- WERE THE CANCER END POINTS THAT WERE GOING TO BE
26 RAISED. WHAT WERE THE ISSUES THAT WERE IN PLAY, SO TO
27 SPEAK, WITH RESPECT TO THE FOCUS OF DR. INFANTE'S
28 TESTIMONY.

1 SO WE WENT OVER THIS IN SOME DETAIL. IT IS
2 REFERENCED REPEATEDLY IN THE TEXT AT PAGES 21, 22 AND 23.
3 WE DID IT RIGHT AT THE OUTSET BECAUSE WE WANTED TO KNOW
4 WHAT ARE THE PARAMETERS OF THE OPINIONS THAT THIS WITNESS
5 IS GOING TO OFFER.
6 MR. METZGER: DR. -- EXCUSE ME.
7 THE COURT: YES.
8 MR. METZGER: ON PAGE 114 OF HIS DEPOSITION, AT
9 LINE 23, MR. SCHURZ ASKED DR. INFANTE:
10 "CAN YOU IDENTIFY EXHIBIT 10 FOR US."
11 HE ANSWERED: "YES, THESE ARE MY NOTES
12 SUMMING UP THE META-ANALYSES THAT SHOW INCREASED CANCER
13 RISKS."
14 MR. SCHURZ ASKS: "AND SPECIFICALLY FOR ALL
15 SITES?"
16 DR. INFANTE ANSWERS: "FOR ALL SITES."
17 SO MR. SCHURZ THEN ASKS: "YOU DID PERFORM A
18 REVIEW BEYOND THE FOUR SITES THAT WE HAVE BEEN DISCUSSING
19 THIS MORNING, BLADDER, PANCREAS, CHILDHOOD LEUKEMIA AND
20 LUNG?
21 "ANSWER: IN TERMS OF META-ANALYSES, YES."
22 THE COURT: ALL RIGHT. THE COURT IS GOING TO
23 ALLOW, TO SOME EXTENT, SOME FURTHER QUESTIONS, BUT IT IS
24 LIMITED -- IT IS LIMITED TO THE OPINION EXPRESSED IN
25 PARAGRAPH 52, AND THAT IS AS SET FORTH IN THIS EXHIBIT 16
26 TO THE DEPOSITION, CRITICISM BY DR. INFANTE OF
27 DR. BOFFETTA'S OPINION WITH REGARD TO DR. BOFFETTA'S
28 ALLEGED FAILURE TO CONSIDER OTHER META-ANALYSES REPORTING

1 INCREASED RISK OF COFFEE CONSUMPTION AND CANCER. ONLY
2 THE SPECIFIC ITEMS IN THE SPECIFIC REPORTS, NOT TO GO
3 BEYOND THAT. WE ARE NOT GOING TO OPEN IT UP FOR JUST
4 GENERAL DISCUSSION OF OTHER SITES OF CANCER, BUT LIMIT IT
5 TO THE OPINIONS EXPRESSED AS TO THE CRITICISM OF
6 DR. BOFFETTA.
7 MR. METZGER: OKAY. VERY WELL. SHALL I PROCEED,
8 YOUR HONOR?
9 THE COURT: YES.
10 Q BY MR. METZGER: DR. INFANTE, DID YOU REVIEW
11 THE META-ANALYSES REGARDING COFFEE CONSUMPTION AND
12 CANCERS TO DETERMINE WHETHER THE META-ANALYSES ALL
13 DEMONSTRATED AN ABSENCE OF RISK AS DR. BOFFETTA CLAIMED?
14 MR. SCHURZ: OBJECTION. IT LACKS FOUNDATION. THAT
15 IS NOT WHAT DR. BOFFETTA HAS TESTIFIED.
16 THE COURT: THE OBJECTION SUSTAINED.
17 LIMIT IT TO WHAT IS SAID IN PARAGRAPH 52.
18 MR. METZGER: ALL RIGHT.
19 THE COURT: NOT ANY OTHER ARTICLES, JUST WHAT IS
20 REFERRED TO IN PARAGRAPH 52.
21 MR. METZGER: ALL RIGHT.
22 Q WELL, THEN LET'S TAKE -- DO THAT.
23 DR. INFANTE, DID YOU CONSIDER THE SALA 2000
24 META-ANALYSIS IN YOUR EVALUATION OF DR. BOFFETTA'S
25 OPINION OF ABSENCE OF RISK FROM COFFEE/CANCER
26 META-ANALYSIS?
27 A YES.
28 Q WHAT DID YOU CONCLUDE REGARDING THE SALA

1 META-ANALYSIS?
2 A IT SHOWS A BORDERLINE STATISTICALLY
3 SIGNIFICANT INCREASE FOR BLADDER CANCER.
4 Q DID YOU CONSIDER THE ZEEGERS 2001
5 META-ANALYSIS IN THE SAME CONTEXT?
6 A YES.
7 Q WHAT DID YOU CONCLUDE REGARDING THAT
8 META-ANALYSIS?
9 A IT DEMONSTRATES A SIGNIFICANT INCREASE OF
10 BLADDER CANCER.
11 Q DID YOU ALSO CONSIDER THE BOTELHO,
12 B-O-T-E-L-H-O, 2006 META-ANALYSIS REGARDING GASTRIC
13 CANCER FROM COFFEE CONSUMPTION?
14 A YES.
15 Q AND WHAT DID YOU CONCLUDE REGARDING THAT
16 META-ANALYSIS?
17 MR. SCHURZ: YOUR HONOR, WE WOULD FURTHER OBJECT AS
18 LACKS FOUNDATION. WHAT HAS NOT OCCURRED HERE WITH
19 RESPECT TO ANY OF THIS IS THE PREDICATE WHICH IS
20 DR. INFANTE'S OPINION THAT DR. BOFFETTA FAILED TO
21 CONSIDER THESE META-ANALYSES. THAT HAS NOT BEEN
22 ESTABLISHED. IN FACT, ALL OF THESE META-ANALYSES WERE
23 PART OF DR. BOFFETTA'S MATERIALS AND WERE CONSIDERED.
24 THE COURT: WELL, IF THE WITNESS FAILED TO SUPPORT
25 THE CRITICISM, SO BE IT.
26 GO AHEAD.
27 Q BY MR. METZGER: WHAT DID YOU CONCLUDE
28 REGARDING THE BOTELHO 2006 META-ANALYSIS OF COFFEE

1 CONSUMPTION AND GASTRIC CANCER?
2 A IT DEMONSTRATED A SIGNIFICANT INCREASED RISK
3 FOR GASTRIC CANCER.
4 Q AND WHAT DID YOU CONCLUDE REGARDING THE
5 STEVENS 2007 META-ANALYSIS REGARDING COFFEE CONSUMPTION
6 AND OVARIAN CANCER?
7 A IT DEMONSTRATED AN INCREASE IN RISK OF
8 OVARIAN CANCER THAT MISSED BY 100 BEING STATISTICALLY
9 SIGNIFICANT.
10 Q MISSED BY WHAT?
11 A ONE ONE HUNDREDTH. IN OTHER WORDS, THE
12 LOWER BOUNDS OF THE CONFIDENCE INTERVAL WAS .99, SO IT
13 PROVIDES SOME EVIDENCE.
14 Q IS THAT WHAT ONE CALLS A BORDERLINE
15 SIGNIFICANCE?
16 A YES.
17 Q WHAT DID YOU CONCLUDE REGARDING THE PARK
18 2010 META-ANALYSIS OF COFFEE CONSUMPTION AND PROSTATE
19 CANCER?
20 A THAT IT DEMONSTRATES A SIGNIFICANTLY
21 INCREASED RISK OF PROSTATE CANCER.
22 Q WHAT DID YOU CONCLUDE REGARDING THE TANG
23 2010 META-ANALYSIS OF COFFEE CONSUMPTION AND LUNG CANCER?
24 A THAT IT DEMONSTRATED A SIGNIFICANTLY
25 INCREASED RISK OF LUNG CANCER.
26 Q WHAT DID YOU CONCLUDE REGARDING THE
27 GENKINGER 2012 META-ANALYSIS OF COFFEE CONSUMPTION AND
28 PANCREATIC CANCER?

1 A WELL, IT SHOWS AN INCREASED RISK, BUT THE
2 TREND WAS NOT SIGNIFICANT AT THE .05 LEVEL.
3 Q WHAT DID YOU CONCLUDE REGARDING THE TURATI
4 2012 META-ANALYSIS OF COFFEE CONSUMPTION AND PANCREATIC
5 CANCER?
6 A THAT IT INDICATED AN INCREASE THAT WAS VERY
7 CLOSE TO BEING STATISTICALLY SIGNIFICANT.
8 Q LASTLY, WHAT DID YOU CONCLUDE REGARDING THE
9 ZHOU 2012 META-ANALYSIS OF COFFEE CONSUMPTION AND BLADDER
10 CANCER?
11 A THAT IT DEMONSTRATED A SIGNIFICANTLY
12 INCREASED RISK OF BLADDER CANCER.
13 Q BASED UPON YOUR REVIEW OF THESE
14 META-ANALYSES OF COFFEE CONSUMPTION AND VARIOUS CANCERS,
15 DID YOU REACH AN OPINION AS TO WHETHER THE META-ANALYSES
16 OF COFFEE CONSUMPTION AND HUMAN CANCER DEMONSTRATED AN
17 ABSENCE OF RISK OF HUMAN CANCER?
18 A YES.
19 Q WHAT WAS YOUR CONCLUSION?
20 A THEY DO NOT DEMONSTRATE AN ABSENCE OF RISK.
21 MR. SCHURZ: YOUR HONOR, WE WOULD MOVE TO STRIKE AS
22 NEW OPINIONS OUTSIDE THE SCOPE NOT PREVIOUSLY DISCLOSED
23 WITH RESPECT TO ALL SITES OTHER THAN THE SALA, ZEEGERS,
24 TURATI, GENKINGER, ZHOU, WHICH WERE PART OF THE MATERIALS
25 THAT HE STUDIED, AND THEY WERE PART OF HIS PRIOR
26 TESTIMONY.
27 THE COURT: OVERRULED. THE ANSWER WILL STAND.
28 NEXT QUESTION.

1 Q BY MR. METZGER: DR. INFANTE, I THINK WE ARE
2 NOW READY TO TALK ABOUT CHILDHOOD LEUKEMIA IF THAT IS
3 OKAY?
4 A OKAY.
5 Q BEFORE WE GET INTO THOSE STUDIES, WILL YOU
6 TELL THE COURT WHETHER YOU HAVE PUBLISHED ARTICLES IN THE
7 PEER-REVIEWED LITERATURE REGARDING EPIDEMIOLOGY STUDIES
8 FOR LEUKEMIA?
9 A YES, QUITE A FEW OF THEM I HAVE PUBLISHED.
10 Q HAS THAT BEEN A MAJOR AREA OF YOUR RESEARCH?
11 A YES. THE MAJOR AREA.
12 Q YOU MENTIONED EARLIER A STUDY REGARDING
13 BENZENE. WAS THAT KNOWN AS THE PLIOFILM STUDY?
14 A YES.
15 Q IS THAT THE STUDY IN WHICH YOU REPORTED FOR
16 THE FIRST TIME IN AN EPIDEMIOLOGIC STUDY SIGNIFICANTLY
17 INCREASED RISKS OF LEUKEMIA AMONG BENZENE-EXPOSED
18 WORKERS?
19 A IT WAS THE FIRST TIME IT WAS REPORTED IN A
20 COHORT STUDY.
21 Q ALL RIGHT. HAVE YOU ALSO PUBLISHED STUDIES
22 REGARDING CHILDHOOD LEUKEMIA?
23 A YES.
24 Q WOULD YOU TELL US ABOUT SOME OF THOSE
25 STUDIES?
26 A WELL, THE -- I MEAN, IN 1974, I THINK THE
27 FIRST PAPER THAT I PUBLISHED IN "ENVIRONMENTAL HEALTH"
28 WAS EVALUATING SECULAR CHANGES IN CHILDHOOD LEUKEMIA

1 MORTALITY TO -- I CAN GO INTO MORE DETAIL IF YOU WANT.
2 THAT WAS THE FIRST PUBLICATION THAT I HAD. I HAVE
3 PUBLISHED OTHER PAPERS RELATED TO ALSO CHILDHOOD
4 LEUKEMIA, PARTICULARLY RELATED TO BENZENE AND OTHER
5 PETROLEUM SOLVENTS.
6 Q NOW, HOW DID YOU GO ABOUT ASSESSING THE
7 EPIDEMIOLOGIC STUDIES REGARDING MATERNAL CONSUMPTION OF
8 COFFEE DURING PREGNANCY AND THE DEVELOPMENT OF CHILDHOOD
9 LEUKEMIA?
10 A I EVALUATED ALL OF THE -- I IDENTIFIED ALL
11 OF THE STUDIES AND EVALUATED THE DATA IN ALL OF THOSE
12 STUDIES.
13 Q WOULD YOU TELL US BY AUTHOR AND YEAR WHICH
14 STUDIES YOU IDENTIFIED THAT EXPLORED RELATIONSHIPS
15 BETWEEN MATERNAL CONSUMPTION OF COFFEE DURING PREGNANCY
16 AND THE DEVELOPMENT OF CHILDHOOD LEUKEMIA?
17 A ROSS 19 -- I'M SORRY, 1996. PETRIDOU 1997.
18 CLAVEL 2005. MENEGAUX 2005. BONAVENTURE 2011. THE
19 CHENG META-ANALYSIS, 2014.
20 Q DID YOU REVIEW THE MENEGAUX 2007?
21 A I'M SORRY, YES, I DID. I MISSED THAT.
22 Q AND THE MILNE 2011 STUDY?
23 A YES.
24 Q NOW, ARE THESE ALL OF THE PUBLISHED STUDIES
25 THAT ASSESS RISK OF CHILDHOOD LEUKEMIA IN RELATIONSHIP TO
26 MATERNAL CONSUMPTION OF COFFEE DURING PREGNANCY?
27 A YES.
28 Q YOU DID NOT LEAVE OUT ANY STUDIES?

1 A WELL, UNLESS I MISSED ONE, THEY ARE ALL I
2 COULD FIND.
3 Q NOW, THERE WAS A MENTION MADE EARLIER IN
4 THIS TRIAL REGARDING A STUDY BY PETERS AND CHILDHOOD
5 LEUKEMIA. ARE YOU FAMILIAR WITH THAT STUDY?
6 A YEAH, JOHN PETERS FROM U.S.C.
7 Q DID THAT STUDY EVALUATE THE RISK OF
8 CHILDHOOD LEUKEMIA IN RELATIONSHIP TO MATERNAL
9 CONSUMPTION OF COFFEE DURING PREGNANCY?
10 A NO.
11 Q WHAT DID THAT STUDY DO?
12 A WELL, IT LOOKED AT -- IT WAS POSTNATAL
13 EXPOSURE.
14 Q ALL RIGHT. SO DID YOU ABSTRACT THE
15 ESSENTIAL DATA FROM THE STUDIES THAT YOU IDENTIFIED?
16 MR. SCHURZ: OBJECTION; LEADING.
17 THE COURT: OVERRULED.
18 THE WITNESS: YES, I DID.
19 Q BY MR. METZGER: DID YOU PREPARE THOSE IN
20 WRITTEN NOTES THAT WERE PRODUCED AS ONE OF THE EXHIBITS
21 TO YOUR DEPOSITION?
22 A YES, I DID.
23 Q HAVE YOU INCLUDED THOSE DATA IN THE
24 POWERPOINT SLIDES SO THAT WE COULD SEE THEM?
25 A YES.
26 Q IS THIS SLIDE HERE REGARDING MATERNAL
27 CONSUMPTION DURING PREGNANCY AND CHILDHOOD ACUTE
28 LEUKEMIA, IS THAT THE FIRST PRESENTATION OF THESE?

1 A YES.
2 Q SO WOULD YOU TELL US REGARDING THE ROSS 1996
3 STUDY WHAT YOU FOUND OF NOTE IN YOUR REVIEW OF THAT
4 STUDY?
5 A YES, THIS IS THE STUDY OF INFANT LEUKEMIAS,
6 WHICH MEANS CHILDREN THAT DEVELOP LEUKEMIA BY THE AGE OF
7 ONE, NOT AFTER ONE YEAR OF AGE. AND THE STUDY SHOWS
8 THE -- BY COFFEE CONSUMPTION OF THE MOTHER -- SHOWS AN
9 INCREASED RISK OF INFANT LEUKEMIA. AND THERE, IN FACT,
10 IS A SIGNIFICANT DOSE-RESPONSE, WHICH IS NOT INDICATED
11 THERE. I THINK THE P-VALUE IS .04.
12 Q SO WHEN YOU SAY THERE WAS A SIGNIFICANT
13 ELEVATION, WAS THAT FOR WOMEN WHO CONSUMED GREATER THAN
14 OR EQUAL TO FOUR CUPS OF COFFEE PER WEEK?
15 A YES, AND ALSO THE DOSE-RESPONSE IS
16 SIGNIFICANT.
17 Q OKAY, AND WHY DID YOU CONSIDER THAT STUDY
18 WITH THE SIGNIFICANT ELEVATION AND THE SIGNIFICANT
19 DOSE-RESPONSE TO BE IMPORTANT?
20 A BECAUSE IT IS SHOWING AS THE MOTHER CONSUMES
21 AN INCREASED AMOUNT OF COFFEE, THERE IS AN INCREASED RISK
22 OF HER GIVING BIRTH TO A CHILD WITH LEUKEMIA.
23 Q OKAY, AND WAS THERE ANYTHING ELSE ABOUT THIS
24 STUDY THAT YOU FOUND OF SIGNIFICANCE?
25 A WELL, THOSE ARE THE MAIN FINDINGS, BUT I
26 MEAN, I HAVE THE DATA THERE BY -- THE MAJOR FORMS OF
27 LEUKEMIA IN CHILDREN, THERE ARE TWO. THE MAJORITY IS
28 ACUTE LYMPHATIC LEUKEMIA AND ACUTE MYELOID LEUKEMIA.

1 MAYBE YOU HAVE ONE ACUTE MYELOID LEUKEMIA FOR EVERY EIGHT
2 ACUTE LYMPHATIC LEUKEMIAS. SO ACUTE LYMPHATIC LEUKEMIA
3 REALLY IS A DISEASE OF CHILDREN.
4 SO THE DATA SHOWS WHEN I HAVE "INFANT
5 LEUKEMIAS," THAT IS COMBINING THE RESULTS OF A.L.L. AND
6 A.M.L., AND THEN THEY ARE SPLIT OUT BELOW.
7 Q ALL RIGHT. WHAT WAS THE NEXT STUDY THAT
8 EVALUATED MATERNAL CONSUMPTION OF COFFEE AND CHILDHOOD
9 LEUKEMIA THAT YOU CONSIDERED?
10 A THE PETRIDOU STUDY FROM GREECE.
11 Q WHAT WAS THE RESULT OF THAT STUDY?
12 A THAT STUDY DID NOT INDICATE ANY ELEVATED
13 RISK OF CHILDHOOD LEUKEMIA.
14 Q WHAT WAS THE NEXT STUDY THAT YOU CONSIDERED?
15 A THE CLAVEL 2005.
16 Q WHAT DID YOU FIND OF NOTE OR IMPORTANCE IN
17 THAT STUDY?
18 A WELL, IN THIS STUDY, THERE IS -- THEY HAVE A
19 SIGNIFICANT INCREASE AT THE HIGHEST AMOUNT OF MATERNAL
20 CONSUMPTION. YOU HAVE A RISK OF 4.1. THERE IS ALSO A
21 SIGNIFICANT DOSE-RESPONSE IN THIS STUDY.
22 SO, IN OTHER WORDS, IF YOU COMPARED MOTHERS
23 WHO DRANK LESS THAN THREE CUPS, YOU SEE WHAT THE RISK IS.
24 AND FOR THOSE WHO DRANK MORE THAN THREE CUPS, THE RISK
25 GOES UP TO 4.1. SO THAT INDICATED A SIGNIFICANT INCREASE
26 IN CHILDHOOD LEUKEMIA AND A SIGNIFICANT DOSE-RESPONSE,
27 WHICH IS A POWERFUL OBSERVATION.
28 Q THERE WAS ALSO A 2005 STUDY BY MENEGAUX, IS

1 THAT RELATED TO THIS 2005 STUDY BY CLAVEL?
2 A YES. SOME OF THE CASES, QUITE A NUMBER OF
3 THE CASES OVERLAP. IT IS ESSENTIALLY ABOUT THE SAME
4 POPULATION, BUT IN ONE OF THEM, THEY PULLED OUT SOME OF
5 THE CASES.
6 Q IN THE MENEGAUX STUDY, DID THEY LOOK AT THE
7 SUBTYPES OF CHILDHOOD LEUKEMIA?
8 A YES.
9 Q WHAT, IF ANYTHING, DID YOU CONSIDER OF
10 SIGNIFICANCE IN THE MENEGAUX 2005 STUDY?
11 A WELL, FOR CHILDHOOD LEUKEMIA, WHICH IN THIS
12 STUDY WAS DEFINED AS CHILDREN 15 YEARS OF AGE OR YOUNGER,
13 YOU SEE THAT THERE IS A DOSE-RESPONSE BY AMOUNT OF COFFEE
14 CONSUMED BY THE MOTHER. IT GOES FROM 1.0 FOR LESS THAN
15 THREE CUPS A DAY, TO 2.1 FOR FOUR TO EIGHT CUPS A DAY, TO
16 2.8 FOR MOTHERS THAT CONSUMED MORE THAN EIGHT CUPS A DAY.
17 THE RESULT OF THAT ANALYSIS, THE TREND
18 ANALYSIS IS STATISTICALLY SIGNIFICANT.
19 Q WHAT DID YOU CONCLUDE REGARDING THE RESULT
20 OF THAT STUDY CONCERNING ACUTE LYMPHOID LEUKEMIA OR
21 LYMPHATIC LEUKEMIA?
22 A WELL, I MEAN, YOU ESSENTIALLY SEE THE SAME
23 TREND FOR ACUTE LYMPHATIC LEUKEMIA AND ACUTE MYELOID
24 LEUKEMIA, BUT I DON'T RECALL IF THE TREND IS SIGNIFICANT
25 OR NOT BECAUSE YOU HAVE GOT FEWER CASES. YOU ARE
26 SPLITTING UP THE TOP ANALYSIS INTO FEWER CASES. BUT YOU
27 ARE SEEING, ESSENTIALLY, A TREND OF AN INCREASED RISK
28 WITH AN INCREASE OF BOTH A.L.L. AND A.M.L.

1 Q HOW INCREASED WAS THE RISK OF A.L.L. FOR THE
2 MOTHERS WHO CONSUMED LARGE AMOUNTS OF COFFEE DURING
3 PREGNANCY IN THE MENEGAUX 2005 STUDY?
4 A 3.1.
5 Q A THREE-FOLD RISK?
6 A INCREASE, YES.
7 Q WAS THAT STATISTICALLY SIGNIFICANT?
8 A WELL, THAT DATA POINT IS BORDERLINE
9 STATISTICALLY SIGNIFICANT, BUT THE DOSE-RESPONSE TREND
10 FOR COMBINING BOTH IS STATISTICALLY SIGNIFICANT, WHICH IS
11 ABOVE THAT. BUT IT IS CONSISTENT WITH BOTH SUBTYPES OF
12 LEUKEMIA IN CHILDREN DATA.
13 Q THE NEXT STUDY THAT YOU MENTIONED WAS THE
14 MENEGAUX 2007 STUDY, AND WHAT DID YOU CONCLUDE FROM THIS
15 STUDY?
16 A WELL, I CONCLUDED FROM THIS STUDY THAT IT
17 ALSO PROVIDED EVIDENCE FOR AN ASSOCIATION BETWEEN
18 MATERNAL CONSUMPTION OF COFFEE AND LEUKEMIA. AND ALSO,
19 WHEN YOU LOOK AT NON-SMOKERS, YOU ACTUALLY HAVE THE
20 HIGHEST RISK.
21 Q WHY WAS THAT OF SIGNIFICANCE TO YOU?
22 A WELL, BECAUSE OF ANY POTENTIAL CONFOUNDING
23 FROM SMOKING WOULD BE ELIMINATED WHEN YOU ARE ANALYZING
24 THE DATA. SO I THINK THAT IS IMPORTANT IN THAT STUDY.
25 Q ALL RIGHT. THE NEXT STUDY WAS BY MILNE FROM
26 AUSTRALIA IN 2011. DID THAT STUDY PROVIDE INDEPENDENT
27 DATA REGARDING THIS ISSUE?
28 A YES.

1 Q DID THOSE AUTHORS ALSO INCLUDE IN THAT
2 PUBLICATION A META-ANALYSIS?
3 A YES.
4 Q LET'S FIRST TALK ABOUT THE DATA THAT THEY
5 COLLECTED.
6 WOULD YOU TELL THE COURT WHAT YOU FOUND OF
7 NOTE IN THEIR DATA?
8 A IN THE MILNE ANALYSIS?
9 Q NOT IN THE META-ANALYSIS, BUT IN THE MILNE
10 STUDY, THE CASE-CONTROL STUDY.
11 A IN THE STUDY?
12 Q YES.
13 A WELL, FOR ACUTE LEUKEMIA IN CHILDREN,
14 THEY -- NONE OF THE RESULTS ARE STATISTICALLY SIGNIFICANT
15 EVEN THOUGH THERE IS, YOU KNOW, A SLIGHT -- THERE IS
16 SOMEWHAT OF A DOSE-RESPONSE. I GUESS THERE IS REALLY
17 LIKE A 45 PERCENT DOSE-RESPONSE BETWEEN LESS THAN TWO
18 CUPS A DAY TO MORE THAN TWO CUPS A DAY. THOSE INDIVIDUAL
19 RESULTS AREN'T STATISTICALLY SIGNIFICANT.
20 BUT THEN WHEN YOU LOOK AT ACUTE LEUKEMIA IN
21 NON-SMOKERS, YOU SEE A HIGHER RISK. THEN WHEN THEY
22 ANALYZE THEIR DATA BY CHILDREN WITH LEUKEMIA WHO HAD
23 SPECIFIC TRANSLOCATIONS --
24 Q STOP RIGHT THERE. WHAT IS A TRANSLOCATION?
25 A THESE ARE CHILDREN THAT ARE BORN WITH A
26 LEUKEMIA THAT HAS GOT LIKE A GENETIC TRANSFORMATION TO
27 IT. LIKE WHEN YOU -- CERTAINLY I KNOW LIKE IN ADULT, IT
28 IS RELATED TO HOW YOU TREAT THE LEUKEMIA. WHAT THE

1 PROGNOSIS IS, HOW MANY CHROMOSOMAL TRANSLOCATIONS AND THE
2 TYPES YOU MAY HAVE.
3 Q SO THESE ARE TRANSLOCATIONS OF CHROMOSOMES?
4 A YES.
5 Q I SEE. OKAY. ALL RIGHT. AND WHAT DID YOU
6 CONSIDER TO BE IMPORTANT ABOUT THE FINDINGS REGARDING THE
7 CHILDREN WHO WERE BORN, OR DEVELOPED, I SHOULD NOT SAY
8 BORN, BUT DEVELOPED CHILDHOOD LEUKEMIA WITH TRANCE --
9 CHROMOSOME TRANSLOCATIONS?
10 A THEY HAD THE HIGHEST RISK RELATED TO
11 CIGARETTE SMOKING. AS YOU CAN SEE FROM -- IF THE MOTHER
12 CONSUMED LESS THAN TWO CUPS A DAY, THE RISK IS 1.2. IF
13 SHE CONSUMED MORE THAN TWO CUPS A DAY, THE RISK IS 2.5.
14 Q DID YOU SAY RELATED TO CIGARETTE SMOKING?
15 A IF I DID, I DID NOT MEAN TO SAY THAT. I AM
16 TALKING ABOUT COFFEE CONSUMPTION. PARDON ME.
17 Q SO JUST SO WE ARE CLEAR, THE WOMEN WHO
18 CONSUMED COFFEE DURING PREGNANCY MORE THAN TWO CUPS PER
19 DAY WHO WERE NON-SMOKERS, THEY HAD -- THEIR CHILDREN HAD
20 A TWO-AND-A-HALF-FOLD INCREASED RISK OF DEVELOPING
21 CHILDHOOD LEUKEMIA WITH THESE CHROMOSOME TRANSLOCATIONS?
22 IS THAT --
23 A NO, THE MOTHER HAS A TWO-AND-A-HALF-FOLD
24 INCREASED RISK OF HAVING HER CHILD THAT SHE BEARS DEVELOP
25 LEUKEMIA WITH THESE TRANSLOCATIONS.
26 Q GOT IT. THANK YOU.
27 WHAT IS THE SIGNIFICANCE TO YOU THAT -- OF
28 THAT, THAT THESE CHILDREN WERE BORN WITH A LEUKEMIA, I

1 SHOULD NOT SAY WERE BORN WITH, BUT THEY DEVELOPED
2 LEUKEMIA WITH THESE CHROMOSOME TRANSLOCATIONS?
3 A WELL, I MEAN, IT IS -- YOU KNOW, IT IS
4 ANOTHER TYPE OF ANALYSIS THAT IS DONE. IT IS SAYING,
5 HEY, THERE IS THIS SEGMENT OF CHILDHOOD LEUKEMIA WHERE
6 CHILDREN HAVE THESE TRANSLOCATIONS. IN THIS STUDY, YOU
7 ARE SEEING, YOU KNOW, A HIGH RISK FROM, AND A
8 DOSE-RESPONSE IN THE DATA FROM COFFEE CONSUMPTION.
9 Q GOT IT. THANK YOU.
10 NOW, WOULD YOU TELL US WHAT YOU GLEANED FROM
11 THE MILNE AUTHORS' META-ANALYSIS THAT THEY ALSO REPORTED
12 IN THIS PUBLICATION?
13 A YES, IN THEIR META-ANALYSIS, THEY
14 DEMONSTRATE A SIGNIFICANT INCREASE IN CHILDHOOD ACUTE
15 LEUKEMIA. THAT IS 1.67 FOR THOSE THAT CONSUME MORE THAN
16 THREE CUPS A DAY. THEN WHEN YOU LOOK AT THE ACUTE
17 LEUKEMIA IN NON-SMOKERS CONSUMING THE SAME AMOUNT, IT IS
18 EVEN HIGHER. IT IS 2.3. THAT IS ALSO HIGHLY
19 SIGNIFICANT.
20 Q ALL RIGHT. WHAT WAS THE NEXT STUDY THAT YOU
21 CONSIDERED?
22 A THE BONAVENTURE 2013 STUDY.
23 Q OKAY. WOULD YOU TELL US, FIRST OF ALL,
24 ABOUT THAT STUDY. WHAT YOU THOUGHT ABOUT THE QUALITY OF
25 THAT STUDY.
26 A I MEAN, THIS IS A VERY WELL-CONTROLLED
27 STUDY. IT WAS DONE -- IT ALSO HAS -- I THINK THERE WERE
28 OVER 700 CHILDHOOD LEUKEMIA CASES INVOLVED IN IT. THE

1 STRONG ASPECTS OF THIS STUDY ARE THAT THERE WAS A HIGH
2 PARTICIPATION RATE. IT WAS OVER 90 PERCENT FOR THE
3 CASES, AND FOR THE CONTROLS, IT WAS OVER 70 PERCENT.
4 THAT IS A PRETTY HIGH PARTICIPATION RATE FOR CONTROLS
5 BECAUSE IT IS OFTEN DIFFICULT TO GET THEM TO PARTICIPATE.
6 THEY INSURED THAT THE CONTROLS WERE
7 COMPARABLE TO THE FRENCH POPULATION IN TERMS OF REGION,
8 BIRTH ORDER AND MATERNAL EDUCATION BY THE WAY THAT THEY
9 SELECTED THE CONTROLS TO PUT INTO THEIR DATABASE. SO
10 THAT WOULD, YOU KNOW, IN MY OPINION, INDICATE THAT
11 SELECTION BIAS IS UNLIKELY FOR THE CONTROLS BECAUSE THEY
12 ARE REPRESENTING THE FRENCH GENERAL POPULATION IN TERMS
13 OF THE FACTORS THAT THEY EVALUATED FOR.
14 THE STUDY USED A STANDARD QUESTIONNAIRE AND
15 THEY USED IDENTICAL INTERVIEW CONDITIONS. SO THAT SHOULD
16 REDUCE THE RISK OF DIFFERENTIAL RECALL BIAS.
17 THEN THEY -- THEN ALSO, IF YOU LOOK AT IT,
18 YOU COULD SAY, WELL, MAYBE WOMEN -- YOU KNOW, THIS CAN GO
19 BOTH WAYS. YOU CAN TAKE THE ONE HAND AND SAY, WELL,
20 MAYBE WOMEN THAT HAVE A CHILD WITH LEUKEMIA FEEL GUILTY
21 AND THEY UNDER-REPORT THEIR COFFEE CONSUMPTION BECAUSE
22 THEY ARE FEELING GUILTY THAT -- YOU KNOW, IF THEY KNEW
23 THAT COFFEE CONSUMPTION WAS RELATED TO THE LEUKEMIA OR
24 ADVERSE HEALTH EFFECTS, BUT I DON'T THINK THEY KNEW THAT.
25 SO THEN YOU CAN ALSO ENTERTAIN THE OPPOSITE
26 AND SAY, WELL, MAYBE IF THEY FELT GUILTY BECAUSE THEIR
27 CHILD, YOU KNOW, DEVELOPED LEUKEMIA, THEN THEY MIGHT
28 REPORT MORE COFFEE CONSUMPTION.

1 BUT YOU KNOW -- BUT THAT SEEMS UNLIKELY IN
2 THE STUDY BECAUSE WHEN YOU LOOK AT THE ANALYSIS BY
3 ALCOHOL INTAKE, WHICH MOTHERS AND PREGNANT MOTHERS KNOW
4 SHE SHOULD NOT CONSUME, IF OUT OF GUILT THEY
5 OVER-REPORTED FACTORS THAT THEY THOUGHT MIGHT BE RELATED
6 TO CHILDHOOD LEUKEMIA, ONE WOULD THINK THEY CERTAINLY
7 WOULD HAVE REPORTED ALCOHOL INTAKE, YET THERE IS NO
8 ASSOCIATION BETWEEN CHILDHOOD LEUKEMIA AND ALCOHOL INTAKE
9 IN THIS STUDY OR IN ANY OF THE STUDIES THAT THEY DID.
10 THEN FURTHER ANALYSIS THAT THEY DID, AND
11 THEY INDICATED THERE WAS NO MODIFYING EFFECTS ON THE RISK
12 OF LEUKEMIA WHEN THE DATA WERE ANALYZED OR ADJUSTED FOR
13 BIRTH ORDER, BREAST FEEDING, MATERNAL EDUCATION,
14 SOCIO-PROFESSIONAL CATEGORY OF THE HOUSEHOLD. SO THEY
15 HAVE, IN ESSENCE, ADJUSTED THE DATA FOR OTHER FACTORS
16 THAT COULD POSSIBLY BE RELATED TO AN ELEVATED RISK OF
17 LEUKEMIA. AND WHEN THEY DID THAT, IT DID NOT MODIFY
18 THEIR FINDINGS.
19 SO, IN MY OPINION, THIS IS A VERY STRONG
20 STUDY.
21 Q I WANT TO ASK YOU A QUESTION. NOW, DID YOU
22 MAKE ANY EFFORTS TO DETERMINE WHETHER THE CASES IN THIS
23 BONAVENTURE 2013 STUDY HAD BEEN INCLUDED IN ANY OF THE
24 EARLIER FRENCH CASE-CONTROL STUDIES?
25 A WELL, YOU CAN SEE FROM THE DATE OF WHEN THEY
26 WERE DIAGNOSED THAT THERE IS NO OVERLAP.
27 Q IS THAT IMPORTANT?
28 A WELL, YOU WOULD NOT WANT TO BE -- WELL, IF

1 YOU ARE GOING TO INCLUDE THIS STUDY AND THEN INCLUDE
2 ANOTHER STUDY, IF THERE IS SOME OVERLAP, THEN IT IS NOT
3 REALLY TWO INDEPENDENT STUDIES. BUT IN THIS, THERE IS NO
4 OVERLAP BETWEEN THIS AND THE EARLIER STUDIES IN THE
5 CASES.
6 Q WAS THERE ANYTHING ELSE ABOUT THE WAY THAT
7 THE BONAVENTURE STUDY WAS CONDUCTED OR ITS NATURE THAT
8 YOU CONSIDERED IMPORTANT?
9 A WELL, I JUST WENT THROUGH QUITE A FEW.
10 NOTHING THAT COMES TO MY HEAD. I GUESS IF I TOOK A LOOK
11 AT THE STUDY RIGHT NOW, I MIGHT BE ABLE TO POINT SOME
12 OTHER THINGS OUT TO YOU.
13 Q WELL, LET'S LOOK AT THE RESULTS AND TELL US
14 WHAT YOU CONSIDERED TO BE IMPORTANT.
15 LET'S START WITH THE TOTAL CATEGORY OF ACUTE
16 CHILDHOOD LEUKEMIA AND TELL US WHAT YOU FOUND TO BE
17 IMPORTANT REGARDING THE RESULTS THAT THEY REPORTED IN
18 BONAVENTURE 2013.
19 A WELL, YOU SEE A SIGNIFICANT DOSE-RESPONSE --
20 YOU SEE A SIGNIFICANT TREND WITH AN INCREASE IN THE
21 AMOUNT OF COFFEE CONSUMED PER DAY AND THE RISK OF
22 CHILDHOOD LEUKEMIA. THEN WHEN THEY SEPARATED IT OUT, AND
23 SAID, WELL, LET'S SEPARATE IT OUT INTO ACUTE
24 LYMPHATIC --
25 Q LET ME INTERRUPT YOU JUST A MINUTE BEFORE WE
26 GET TO THE SUBTYPES, I WOULD LIKE TO GO OVER THIS WITH
27 YOU. WHEN YOU SAID THERE WAS A SIGNIFICANT TREND, ARE
28 YOU REFERRING TO THE ODDS RATIO INCREASING FROM 1.0 TO

1 1.3 TO 1.6?
2 A YES, AND THE -- THAT TREND PIECE HAS LESS
3 THAN .001.
4 Q WHICH MEANS?
5 A THAT WOULD ONLY OCCUR ONE TIME IN 1,000 DUE
6 TO CHANCE ALONE.
7 Q DO YOU CONSIDER THAT TYPE OF A P-VALUE TO BE
8 ROBUST?
9 A YES.
10 Q ALL RIGHT. I SEE THAT ON THE POWERPOINT THE
11 ODDS RATIOS OF 1.3 AND 1.6 ARE BOLDED. WHY IS THAT?
12 A WELL, BECAUSE -- WELL, THE 1.3 IS BORDERLINE
13 SIGNIFICANT AND THE 1.6, BY ITSELF, IS STATISTICALLY
14 SIGNIFICANT, BUT I WOULD PUT MORE WEIGHT INTO THIS
15 MONOTONIC DOSE-RESPONSE AND THE P-TREND THAT IS
16 STATISTICALLY SIGNIFICANT BECAUSE IN THAT ANALYSIS, YOU
17 ARE INCLUDING DATA FROM ALL THREE. YOU ARE COMBINING THE
18 THREE DATA POINTS TO FACTOR IT INTO: IS THE RESULT
19 SIGNIFICANT OR IS THERE A DOSE-RESPONSE OR NOT.
20 TO ME, THAT IS A MORE POWERFUL OBSERVATION
21 THAN THE INDIVIDUAL DATA POINTS.
22 Q I UNDERSTAND. WOULD YOU NOW PROCEED TO THE
23 DATA REGARDING THE ACUTE LYMPHATIC LEUKEMIA IN CHILDREN
24 AND TELL US WHAT YOU FOUND TO BE NOTEWORTHY OF THAT DATA?
25 A YES. WELL, YOU CAN SEE THE ODDS RATIO THERE
26 IS INCREASED WITH AN INCREASE IN MATERNAL CONSUMPTION.
27 AGAIN, THE P-TREND IS HIGHLY SIGNIFICANT, .002.
28 Q AND THOSE WOMEN WHO CONSUMED GREATER THAN

1 TWO CUPS PER DAY HAD AN INCREASED RISK FOR THEIR CHILDREN
2 TO DEVELOP ACUTE LYMPHOID LEUKEMIA OF A 2.4-FOLD
3 INCREASED RISK?
4 MR. SCHURZ: OBJECTION; HEARSAY.
5 THE WITNESS: YES. WELL, IT IS 2.4 TO BE EXACT.
6 THE COURT: OVERRULED.
7 Q BY MR. METZGER: ALL RIGHT. AND WHAT
8 SIGNIFICANCE DID YOU ATTRIBUTE TO THE DATA REGARDING
9 ACUTE MYELOID LEUKEMIA IN THE CHILDREN?
10 A THAT IT SHOWS A SIGNIFICANT DOSE-RESPONSE IN
11 RELATION TO MATERNAL COFFEE CONSUMPTION DURING PREGNANCY.
12 Q OKAY. AND WOULD YOU TELL US WHAT THE STUDY
13 INDICATED TO YOU REGARDING THE RISK OF CHILDHOOD LEUKEMIA
14 AMONG MOTHERS WHO WERE NON-SMOKERS BUT CONSUMED COFFEE
15 DURING PREGNANCY?
16 A YES, YOU SEE THAT -- WELL, YOU SEE A
17 MONOTONIC DOSE-RESPONSE FOR NONSMOKING MOTHERS ALSO,
18 WHICH I THINK IS, YOU KNOW, EVEN A VERY POWERFUL
19 OBSERVATION IN AND OF ITSELF BECAUSE NOW YOU -- YOU KNOW,
20 THERE IS NO CONFOUNDING FROM CIGARETTE SMOKING.
21 Q WELL, HAS CIGARETTE SMOKING BEEN ASSOCIATED
22 WITH LEUKEMIA?
23 A WITH MYELOGENOUS LEUKEMIA IN ADULTS. SO,
24 YOU KNOW, I WOULD -- WELL, I WOULD NOT WANT A PREGNANT
25 MOTHER SMOKING CIGARETTES. I WOULD HOPE THEY WOULD NOT.
26 Q WELL, FOR THE NONSMOKING MOTHERS WHOSE
27 CHILDREN DEVELOPED ACUTE MYELOGENOUS -- THAT IS THE SAME
28 THING, MYELOID AND MYELOGENOUS LEUKEMIA?

1 A YES.
2 Q FOR THOSE WOMEN, THEIR CHILDREN HAD -- WAS
3 IT A GREATER THAN THREE-FOLD EXCESS RISK OF DEVELOPING
4 THAT SUBTYPE OF LEUKEMIA?
5 A YES.
6 Q WAS THAT STATISTICALLY SIGNIFICANT?
7 A YES, IT IS.
8 Q ALL RIGHT. SO WHAT DID YOU CONCLUDE
9 REGARDING THE BONAVENTURE 2013 STUDY?
10 A I THINK IT IS A VERY WELL CONDUCTED STUDY OF
11 A LARGE NUMBER OF CASES OF CHILDHOOD LEUKEMIA. IT
12 DEMONSTRATES A SIGNIFICANT DOSE-RESPONSE BETWEEN MATERNAL
13 ALCOHOL -- I MEAN MATERNAL COFFEE CONSUMPTION DURING
14 PREGNANCY AND THE RISK OF HAVING A CHILD WITH LEUKEMIA.
15 Q OKAY. GIVE ME ONE MOMENT.
16 NOW, IN YOUR OPINION, IS IT FEASIBLE TO
17 STUDY THE QUESTION OF WHETHER MATERNAL CONSUMPTION OF
18 COFFEE DURING PREGNANCY INCREASES THE RISK OF CHILDHOOD
19 LEUKEMIA IN A COHORT STUDY?
20 A I THINK I HAD MENTIONED EARLIER THAT IT
21 WOULD BE VIRTUALLY IMPOSSIBLE TO DO BECAUSE YOU WOULD
22 NEED TO ENROLL TOO MANY PEOPLE IN THE STUDY. YOU COULD
23 NOT POSSIBLY EVER GET ENOUGH CASES FROM WHAT I THINK I
24 ESTIMATED 1,500,000 JUST TO LIKE PRODUCE ONE CASE OF
25 CHILDHOOD LEUKEMIA. YOU KNOW, IN THESE STUDIES, THIS ONE
26 HAD OVER 700 CASES. SO THE CASE-CONTROL STUDIES ARE MORE
27 POWERFUL.
28 Q OKAY. WHEN YOU SAY "MORE POWERFUL," DO YOU

1 MEAN IN TERMS OF STATISTICAL --
2 A STATISTICAL POWER, YES.
3 Q GO IT.
4 A IT IS THE ONLY WAY I KNOW THAT YOU COULD
5 STUDY CHILDHOOD LEUKEMIA.
6 Q NOW, WE HAVE HEARD ABOUT CASE-CONTROL
7 STUDIES HAVING THE POTENTIAL FOR RECALL BIAS. I THINK
8 YOU MENTIONED THAT. WHAT EFFORTS DID THE INVESTIGATORS
9 IN THE BONAVENTURE STUDY UNDERTAKE OR WHAT DATA IS THERE
10 THAT BEARS UPON THE ISSUE OF WHETHER THIS STUDY IS
11 CONFOUNDED BY RECALL BIAS?
12 A WELL, YOU KNOW, THERE IS A POTENTIAL FOR
13 RECALL BIAS IN ANY RETROSPECTIVE STUDY THAT YOU DO, BUT I
14 DON'T SEE EVIDENCE OF ANY RECALL BIAS IN THIS STUDY. I
15 MEAN, IT IS POSSIBLE THAT MOTHERS, AS I MENTIONED
16 EARLIER, THAT HAVE A CHILD WITH LEUKEMIA, YOU KNOW, OUT
17 OF GUILT MIGHT OVER-REPORT HAZARDOUS THINGS THEY PUT INTO
18 THEIR BODY DURING PREGNANCY. AS I SAID, THERE IS SOME
19 INDIRECT EVIDENCE THAT WOULD CONTRADICT THAT BASED ON
20 THAT THERE IS NO INCREASED RISK RELATED TO ALCOHOL
21 CONSUMPTION DURING PREGNANCY.
22 ON THE OTHER HAND, IT COULD BE THAT OUT OF
23 GUILT, YOU KNOW, THEY UNDER-REPORT IT. SO MAYBE THE RISK
24 COULD BE HIGHER AND YOU JUST DON'T KNOW.
25 Q WHAT DID THE DATA SHOW REGARDING ALCOHOL
26 CONSUMPTION IN THIS STUDY?
27 A WELL, THERE IS NO ASSOCIATION. WITH AN
28 INCREASE OF ALCOHOL CONSUMPTION DURING PREGNANCY, THERE

1 WAS NO RISK OF AN INCREASE OF CHILDHOOD LEUKEMIA.
2 Q DID THEY ALSO REPORT DATA IN THIS STUDY
3 REGARDING SMOKING?
4 A YES.
5 Q WHAT DID THAT SHOW?
6 A WELL, THE NON-SMOKER DATA, IT GOT A
7 MONOTONIC DOSE-RESPONSE BETWEEN -- I'M SORRY, THEY HAVE
8 AN OVERALL FINDING HERE FOR NON-SMOKERS. THERE IS A
9 SIGNIFICANT INCREASE OF ACUTE LEUKEMIA IN CHILDHOOD,
10 SIGNIFICANT INCREASE IN A.L.L., AND SIGNIFICANT INCREASE
11 IN A.M.L.
12 Q OKAY. WHAT DOES THAT INDICATE TO YOU ABOUT
13 THE EFFECT OF SMOKING ON THESE RESULTS FOR COFFEE?
14 A WELL, THAT SMOKING CERTAINLY DID NOT
15 CONFOUND THE FINDINGS.
16 Q NOW, YOU ALSO MENTIONED THE CHENG
17 META-ANALYSIS, I BELIEVE; IS THAT CORRECT?
18 A YES.
19 Q AND WHAT DID THAT META-ANALYSIS ATTEMPT TO
20 DO?
21 A WELL, THIS META-ANALYSIS INCLUDED THE
22 STUDIES ON CHILDHOOD LEUKEMIA THAT HAD BEEN DONE THAT
23 THEY IDENTIFIED, YOU KNOW, PRIOR TO 2014. THEY ARE
24 ESSENTIALLY THE SAME STUDIES THAT I EVALUATED. SO THEY
25 DID A META-ANALYSIS.
26 Q WAS THIS META-ANALYSIS ALL OF CASE-CONTROL
27 STUDIES THAT EVALUATED THE MATERNAL CONSUMPTION OF COFFEE
28 DURING PREGNANCY AND CHILDHOOD LEUKEMIA?

A YES.

Q ALL RIGHT. IN DOING A META-ANALYSIS, IS IT IMPORTANT TO MAKE SURE THAT THE STUDIES THAT YOU ARE INCLUDING IN THE META-ANALYSIS ARE NOT DOUBLE COUNTED?

A OF COURSE. YES.

Q WHY IS THAT?

A BECAUSE YOU DON'T -- YOU WOULD NOT HAVE INDEPENDENCE IN TERMS OF YOUR ANALYSIS IF YOU ARE COUNTING SAY TWO DIFFERENT STUDIES THAT HAVE THE SAME CASES AND RESULTS.

Q WHY IS IT IMPORTANT TO HAVE INDEPENDENCE IN A META-ANALYSIS?

A WELL, IF YOU ARE REPORTING WHAT THE SUMMARY RISK IS, YOU DON'T WANT TO BE COUNTING -- YOU DON'T WANT TO BE COUNTING, YOU KNOW, TWO POPULATIONS RATHER THAN IF IT IS JUST ONE.

Q GOT IT. ALL RIGHT.

NOW, WOULD YOU TELL US WHICH STUDIES WERE INCLUDED IN THE CHENG META-ANALYSIS?

PERHAPS WE CAN --

A YES, WELL, I HAVE A -- I THINK I TOOK SOME COPIES RIGHT OUT OF -- WELL, HERE THEY ARE. YES. THERE IS THE ROSS STUDY.

Q SO THERE IS TABLE 1, REPRODUCED FROM THE CHENG META-ANALYSIS?

A YES.

Q WHICH OF THE STUDIES THAT YOU JUST IDENTIFIED ARE INCLUDED?

1 A THE SAME ONES THAT I JUST IDENTIFIED.
2 Q TO YOUR KNOWLEDGE, ARE THESE ALL OF THE
3 STUDIES THAT SPECIFICALLY ADDRESS THE RISK OF CHILDHOOD
4 LEUKEMIA IN RELATIONSHIP TO MATERNAL CONSUMPTION OF
5 COFFEE DURING PREGNANCY?
6 A THEY ARE ALL THAT ARE IN THE LITERATURE TO
7 MY KNOWLEDGE.
8 Q ALTHOUGH THE PETRIDOU STUDY DID NOT REPORT
9 AN INCREASED RISK, WAS THAT STILL INCLUDED IN THE
10 CALCULATION OF THE META-RISK?
11 A I WOULD HOPE SO, YES.
12 Q WAS IT?
13 A YES.
14 MR. SCHURZ: I WILL OBJECT THAT IT MISSTATES THE
15 DOCUMENT. IT IS QUITE CLEAR AS REFLECTED IN TABLE NO. 1
16 THAT NOT ONLY DID PETRIDOU NOT INDICATE AN INCREASED
17 RISK, NEITHER DID MENEGAUX 2007, NOR DID MILNE IN 2011
18 INDICATE ANY INCREASED RISK, CONTRARY TO THE PRIOR
19 TESTIMONY.
20 THE COURT: ALL RIGHT. YOU WILL ARGUE ABOUT THAT
21 LATER.
22 Q BY MR. METZGER: SO IS THERE ANYTHING ELSE
23 THAT YOU FEEL IS SIGNIFICANT FOR WHAT WAS INCLUDED IN
24 THIS TABLE 1 OF THE CHENG META-ANALYSIS?
25 A WELL, THIS WAS THE UNIVERSE OF STUDIES THAT
26 WAS INCLUDED IN THE META-ANALYSIS. HOWEVER, IN SOME
27 META-ANALYSES, THERE MIGHT BE SAY ONE STUDY THAT IS
28 EXCLUDED BECAUSE OF THE TYPE OF ANALYSIS THEY DID SO THAT

1 THEY DID NOT DOUBLE COUNT. SO IT DEPENDS ON THE TYPE OF
2 ANALYSIS THAT THEY ARE DOING.
3 Q NOW, IF WE TAKE A LOOK AT THE CLAVEL 2004 --
4 I THINK YOU IDENTIFIED IT AS 2005?
5 A RIGHT.
6 Q AND THE MENEGAUX 2005, I SEE THAT FOR THE
7 CLAVEL, THERE ARE RESULTS FOR ACUTE LEUKEMIA AND FOR
8 MENEGAUX, THEY HAVE THE RESULTS FOR THE TWO SUBTYPES. IS
9 THIS THE SAME STUDY WHERE THEY JUST DID DIFFERENT
10 ANALYSES?
11 A IT IS THE SAME POPULATION. THE CLAVEL, WHAT
12 THEY HAVE IS 2004 AND I INDICATE AS 2005, IT IS THE SAME,
13 THAT STUDY AND THE MENEGAUX STUDY ARE THE -- THEY ARE
14 IDENTICAL POPULATIONS. BUT IN THE CLAVEL STUDY, THEY ARE
15 ONLY LOOKING AT 219 OF THE ACUTE CHILDHOOD LEUKEMIAS OUT
16 OF 280 THAT ARE IN THAT POPULATION, BECAUSE THEY ARE
17 DOING A DIFFERENT KIND OF ANALYSIS.
18 SO WHEN THIS META-ANALYSIS IS DONE BY CHENG,
19 HE IS NOT DOUBLE COUNTING.
20 Q HOW DO YOU KNOW THERE IS NOT DOUBLE
21 COUNTING?
22 A YOU CAN LOOK IN THE FIGURES AND SEE WHICH
23 STUDIES ARE INCLUDED.
24 Q OKAY. ALL RIGHT.
25 NOW, WOULD YOU TELL THE COURT WHAT A FOREST
26 PLOT IS?
27 A WHAT A FOREST PLOT IS?
28 Q MAYBE I AM USING THE WRONG TERM. TELL THE

1 COURT WHAT FIGURE 2 IN THE MENEGAUX -- I AM SORRY, WOULD
2 YOU PLEASE TELL THE COURT WHAT FIGURE 2 IN THE CHENG
3 META-ANALYSIS DESCRIBES?
4 A YES. THIS WAS, AS IT INDICATES, IT IS A
5 SUMMARY OF THE ODDS RATIOS FOR TOTAL ACUTE LEUKEMIA FOR
6 YOU KNOW, EVER, LOW TO MODERATE, AND HIGH LEVEL DRINKERS
7 VERSUS NEVER AND LOWEST DRINKERS.
8 SO IN THIS FIRST ANALYSIS, BECAUSE THEY ARE
9 LOOKING AT -- THIS IS TOTAL LEUKEMIA, WHICH MEANS IT IS
10 COMBINING THE A.M.L.S AND THE A.L.L.S IN CHILDHOOD.
11 Q SO ALL CHILDHOOD LEUKEMIA?
12 A ALL CHILDHOOD LEUKEMIAS, YES.
13 Q I SEE IN THIS FIGURE THERE IS A LINE, A
14 VERTICAL LINE IN THE MIDDLE WITH A 1.0 BELOW IT. WHAT IS
15 THAT SIGNIFYING?
16 A WELL, THAT WOULD BE A RELATIVE -- THAT WOULD
17 BE AN ODDS RATIO OF 1.0, WHICH MEANS THAT THAT LINE,
18 THERE IS NO INCREASED RISK. SO ANYTHING TO THE LEFT OF
19 THAT LINE WOULD SHOW A DECREASED RISK. ANYTHING TO THE
20 RIGHT WOULD SHOW AN INCREASED RISK OF WHERE THE DOTS ARE.
21 THEN THE LINES ARE THE 95 PERCENT CONFIDENCE INTERVALS.
22 Q SO WAS THERE ANY STUDY THAT REPORTED A
23 DECREASED RISK?
24 A WELL, YES, THE PETRIDOU STUDY.
25 Q DID ALL OF THE OTHER STUDIES REPORT
26 INCREASED RISKS?
27 A YES.
28 Q IS THAT GRAPHICALLY SHOWN ON FIGURE 2?

1 A YES. THEN HE HAS THE SUMMARY FROM THAT
2 FIRST ANALYSIS WHICH IS THE, YOU KNOW, HIGH CONSUMPTION
3 VERSUS EVER.
4 Q WOULD YOU TELL US WHAT THE RESULTS WERE FOR
5 THAT?
6 A I'M SORRY, VERSUS THE LOWEST.
7 Q SO HIGHEST CONSUMPTION VERSUS LOWEST FOR
8 TOTAL LEUKEMIA, CHILDHOOD LEUKEMIA; IS THAT CORRECT?
9 A WELL, IT IS ACTUALLY NEVER/LOWEST. SO IN
10 THE STUDY, IF THERE WAS NO EXPOSURE, THEY USED THAT. IF
11 IN THE STUDY THEY DID NOT HAVE NO EXPOSURE, BUT HAD THE
12 LOWEST EXPOSURE, THEN THEY USED THAT.
13 SO IN THIS FIRST ANALYSIS FOR TOTAL
14 CHILDHOOD LEUKEMIA, THEY ARE LOOKING AT, IT LOOKS LIKE,
15 EVER EXPOSED VERSUS NEVER IN THE LOWEST EXPOSURE.
16 Q WHAT WAS THE META-RISK FOR THAT ANALYSIS?
17 A 1.22.
18 Q WAS THAT STATISTICALLY SIGNIFICANT?
19 A YES.
20 Q WHAT IS -- WHAT WERE THE RESULTS FOR THE LOW
21 TO MODERATE CONSUMPTION VERSUS NEVER OR LOWEST EXPOSURE?
22 A THE META-RISK IS 1.16.
23 Q IS THAT STATISTICALLY SIGNIFICANT?
24 A YES, IT IS.
25 Q WHAT WAS THE RESULT FOR THE HIGHEST
26 CONSUMPTION VERSUS NEVER AND LOWEST FOR THE META-RISK OF
27 ALL THESE STUDIES?
28 A 1.72.

1 Q WAS THAT STATISTICALLY SIGNIFICANT?
2 A YES.
3 Q ALL RIGHT. NOW, I HAVE BEEN USING THE TERM
4 "META-RISK." I DON'T KNOW THAT WE HAVE ACTUALLY DEFINED
5 THAT. WOULD YOU TELL THE COURT WHAT THAT MEANS?
6 A JUST SIMPLY THE OVERALL RISK FROM YOUR
7 META-ANALYSIS.
8 Q HOW IS THAT DETERMINED?
9 A IT IS DETERMINED FROM POOLING THE DATA IN
10 ALL OF THE STUDIES THAT YOU HAVE, INCLUDING IN YOUR META-
11 ANALYSIS.
12 Q SO ALL THE DATA IS POOLED AND ESSENTIALLY
13 THE RISK IS CALCULATED FROM THE POOLED DATA?
14 A YES.
15 Q ALL RIGHT. WHAT ARE THE ADVANTAGES OF DOING
16 THAT?
17 A WELL, IF YOU HAVE, YOU KNOW, A NUMBER OF
18 STUDIES THAT HAVE -- THAT ARE SMALL, YOU CAN INCREASE THE
19 STATISTICAL POWER BY INCREASING THE NUMBER OF CASES.
20 THAT IS A GOOD REASON TO DO IT. IF YOU JUST WANT TO LOOK
21 AT AN OVERALL SUMMARY RISK OF LEUKEMIA RELATED TO, YOU
22 KNOW, THE LITERATURE ON MATERNAL COFFEE CONSUMPTION, JUST
23 POOLING ALL THE DATA, YOU CAN DO IT THAT WAY. THEY WOULD
24 CALL THAT THE META-RISK.
25 Q DOES THAT HELP ASSESS WHETHER A STUDY THAT
26 IS AN OUTLIER IS AFFECTING THE RESULT?
27 A WELL, I DON'T KNOW THAT IT INDICATES THE
28 STUDY IS AFFECTING THE RESULTS. I MEAN, IF THERE IS A

1 STUDY THAT IS LOW OR HIGH IN THERE, THERE COULD BE AN
2 OUTLIER, IT WOULD BE INCLUDED IN THE RESULTS. SO IT IS
3 GOING TO LIKE PULL YOU BACK TOWARD THE MEAN.
4 Q OKAY. SO THE DATA -- THE RESULTS FROM ALL
5 THE STUDIES END UP BEING INCLUDED IN THE CALCULATION OF
6 THE META-RISK; IS THAT IT?
7 A YES.
8 Q EVEN THE NEGATIVE STUDY, THE PETRIDOU STUDY?
9 A YES.
10 Q DID THE CHENG -- AUTHORS OF THE CHENG
11 META-ANALYSIS ALSO DO META-RISK CALCULATIONS FOR THE
12 MAJOR CHILDHOOD LEUKEMIA SUBTYPE, ACUTE LYMPHATIC
13 LEUKEMIA?
14 A YES, THAT IS IN FIGURE 4.
15 Q WHAT DID YOU NOTE FROM THIS ANALYSIS?
16 A WELL, IN THIS ANALYSIS, YOU LOOK AT THE
17 FIRST RESULT, THE ODDS RATIO FROM THE POOLED DATA IS
18 1.26. THAT IS FOR EVER VERSUS NEVER OR LOWEST DRINKERS.
19 SO EVER IS LIKE MORE THAN LOWEST AND IT COULD BE THE
20 HIGHEST. SO THAT IS THE COMBINED GROUP IN THIS ONE.
21 SO WHEN YOU LOOK AT IF YOU EVER CONSUMED
22 COFFEE DURING PREGNANCY, COMPARED TO THE LOWEST, OR
23 NEVER, YOU HAVE AN ODDS RATIO OF 1.26 THAT IS
24 STATISTICALLY SIGNIFICANT.
25 NOW, THERE IS ONE THING, SINCE THIS IS ACUTE
26 LYMPHATIC LEUKEMIA, YOU DON'T SEE THE GREEK STUDY IN HERE
27 BECAUSE THE GREEK STUDY DID NOT PRESENT DATA BY ACUTE
28 LYMPHATIC LEUKEMIA. IT JUST SAID "ACUTE LEUKEMIA." SO

1 YOU COULD INCLUDE IT IN THE FIRST ANALYSIS, BUT YOU CAN'T
2 INCLUDE IT IN THE SECOND ANALYSIS.
3 Q I UNDERSTAND. WHAT ABOUT THE DATA THAT THEY
4 CONCLUDED FOR LOW TO MODERATE CONSUMPTION OF COFFEE
5 VERSUS NEVER OR LOWEST CONSUMPTION?
6 A FOR LOW EXPOSURE, THE RISK IS 1.09 AND THAT
7 IS NOT -- THAT IS NOT STATISTICALLY SIGNIFICANT.
8 Q WHAT ABOUT THE HIGHEST CONSUMPTION OF COFFEE
9 VERSUS NEVER OR LOWEST CONSUMPTION IN RELATIONSHIP TO
10 CHILDHOOD ACUTE LYMPHATIC LEUKEMIA?
11 A THAT RISK IS 1.6 AND THAT IS HIGHLY
12 SIGNIFICANT.
13 Q WHAT DO YOU MEAN BY "HIGHLY SIGNIFICANT"?
14 A WELL, THE LOWER BOUND OF THE CONFIDENCE
15 INTERVAL IS 1.28 AND THE UPPER BOUND IS 2.12. SO, YOU
16 KNOW, THAT IS A PRETTY ROBUST FINDING.
17 Q IS THERE ANYTHING ELSE OF SIGNIFICANCE TO
18 YOU IN THIS ANALYSIS OF THE META-RISK FOR A.L.L.?
19 A WELL, I DON'T KNOW. IF YOU HAD ANOTHER
20 QUESTION TO ASK ME ABOUT IT, I DON'T KNOW WHAT YOU ARE
21 THINKING, BUT IT SHOWS THAT WHEN YOU POOL ALL OF THE DATA
22 FROM THESE -- ALL OF THE STUDIES THAT HAD BEEN DONE TO
23 DATE, YOU FIND THAT, YOU KNOW, FROM THE HIGHEST MATERNAL
24 CONSUMPTION OF COFFEE, YOU HAVE THE HIGHEST ODDS RATIO
25 FOR ACUTE LYMPHATIC LEUKEMIA AMONG MOTHERS OF THE HIGHEST
26 COFFEE CONSUMERS.
27 Q VERY GOOD. DID YOU ALSO DO A REVIEW OF THE
28 ANALYSIS FOR CHILDHOOD ACUTE MYELOGENOUS LEUKEMIA?

1 A YES.
2 Q IS THAT CONTAINED IN FIGURE 5?
3 A YES.
4 Q WOULD YOU TELL US WHAT YOU FOUND SIGNIFICANT
5 ABOUT THAT ANALYSIS OR CALCULATION?
6 A WELL, AGAIN, WHEN YOU LOOK AT THE EVER
7 CONSUMING COFFEE VERSUS NEVER OR LOWEST DRINKERS IN THE
8 STUDY, THE ODDS RATIO IS 1.35, AND THAT IS STATISTICALLY
9 SIGNIFICANT. AND IN THE SECOND GROUPING, WHEN YOU LOOK
10 AT -- I THINK IT IS -- MY COPY IS BLURRED, I THINK IT IS
11 LOW TO MODERATE EXPOSURE VERSUS NEVER TO LOWEST, THE RISK
12 IS 1.18. THAT IS STATISTICALLY SIGNIFICANT.
13 THEN WHEN YOU GO TO THE HIGH COFFEE
14 CONSUMERS VERSUS NEVER OR LOWEST COFFEE CONSUMERS, THE
15 RISK IS -- IT LOOKS LIKE 1.68 ON MY COPY AND THAT RESULT
16 IS STATISTICALLY SIGNIFICANT.
17 SO YOU HAVE A SIGNIFICANT INCREASE IN RISK
18 IN THE META-ANALYSIS, WHETHER IT IS TOTAL CHILDHOOD
19 LEUKEMIA, A.L.L. OR A.M.L. SEPARATELY.
20 Q OKAY. SO WHAT DO YOU CONCLUDE REGARDING THE
21 CHENG META-ANALYSIS OF THE CASE-CONTROL STUDIES OF
22 MATERNAL CONSUMPTION OF COFFEE DURING PREGNANCY AND THE
23 DEVELOPMENT OF CHILDHOOD LEUKEMIA?
24 A I THINK IT PROVIDES VERY STRONG EVIDENCE
25 THAT THERE IS A SIGNIFICANT ASSOCIATION BETWEEN MATERNAL
26 COFFEE CONSUMPTION DURING PREGNANCY AND CHILDHOOD
27 LEUKEMIA.
28 Q NOW, I THINK WE HAVE HEARD ABOUT PUBLICATION

1 BIAS. DID YOU ASSESS THAT ISSUE WITH REGARD TO THIS
2 META-ANALYSIS?
3 A WELL, I DON'T THINK THERE IS ANY PUBLICATION
4 BIAS IN THE ANALYSIS BECAUSE HE HAS INCLUDED EVERY -- HE
5 DID NOT EXCLUDE ANY STUDIES FOR, YOU KNOW, FOR WHATEVER
6 REASON. LIKE HE COULD, IN A META-ANALYSIS, EXCLUDE
7 STUDY X OR STUDY Y BECAUSE OF DEFICIENCIES IN IT OR IF
8 THE EXPOSURE WASN'T -- YOU HAD PROBLEMS WITH THE
9 EXPOSURE. BUT IN THIS ANALYSIS, HE INCLUDED EVERY STUDY
10 IN THE LITERATURE.
11 Q WERE THERE ANY OTHER FEATURES OF THIS STUDY
12 THAT YOU CONSIDERED TO BE IMPORTANT?
13 A WELL, HE SAYS THAT THEY EVALUATED
14 PUBLICATION BIAS AND THEY DID NOT FIND THAT THAT AFFECTED
15 THE RESULTS. SO, I MEAN, I THINK IT IS A VERY SOLID
16 STUDY. IT IS A VERY GOOD STUDY. A VERY STRONG STUDY.
17 Q HAVE YOU SEEN ANY PUBLISHED CRITICISMS IN
18 THE PEER-REVIEWED LITERATURE OF THE CHENG META-ANALYSIS?
19 A I HAVE NOT.
20 Q HAVE YOU SEEN ANY PUBLISHED CRITICISMS IN
21 THE PEER-REVIEWED LITERATURE OF THE BONAVENTURE
22 CASE-CONTROL STUDY FROM 2013?
23 A I HAVE NOT.
24 Q OKAY. NOW, THERE HAS BEEN A CLAIM MADE
25 THAT -- OR I WOULD LIKE YOU TO ASSUME THAT A CLAIM HAS
26 BEEN MADE THAT COFFEE CONSUMPTION DURING PREGNANCY IS NOT
27 A RISK FACTOR FOR CHILDHOOD LEUKEMIA BECAUSE WEBSITES OF
28 ORGANIZATIONS LIKE THE AMERICAN CANCER SOCIETY AND OTHER

1 ORGANIZATIONS HAVE NOT PUT IT UP AS A RISK FACTOR.
2 DO YOU AGREE WITH THAT CONTENTION?
3 MR. SCHURZ: OBJECTION; MISSTATES EVIDENCE AND IS
4 ARGUMENTATIVE.
5 THE COURT: THE OBJECTION IS SUSTAINED.
6 ARGUMENTATIVE. NO FOUNDATION.
7 MR. METZGER: I WILL ASK IT THIS WAY:
8 Q ASSUMING, DR. INFANTE, THAT ORGANIZATIONS
9 LIKE THE AMERICAN CANCER SOCIETY, THE NATIONAL CANCER
10 INSTITUTE AND OTHERS HAVE NOT LISTED CHILDHOOD -- HAVE
11 NOT LISTED MATERNAL CONSUMPTION OF COFFEE DURING
12 PREGNANCY AS A RISK FACTOR FOR CHILDHOOD LEUKEMIA. WHAT
13 SIGNIFICANCE WOULD YOU ATTRIBUTE TO THAT?
14 A WELL, I WOULD NOT ATTRIBUTE ANY SIGNIFICANCE
15 TO IT. I MEAN, THERE IS USUALLY A LONG LAG TIME BETWEEN
16 WHEN KNOWLEDGE BECOMES AVAILABLE AND WHEN INSTITUTIONS
17 MAKE, YOU KNOW, PRONOUNCEMENTS ABOUT THOSE ASSOCIATIONS.
18 PEOPLE DON'T SIT ON THE EDGE OF THEIR CHAIRS AND WAIT FOR
19 A NEW STUDY, AND THEN ALL OF A SUDDEN INCORPORATE IT INTO
20 SOME EVALUATION. EVERYBODY IS BUSY DOING THEIR OWN
21 THING. BUT -- SO I DON'T -- I MEAN, THIS IS A FAIRLY NEW
22 META-ANALYSIS. THE BONAVENTURE STUDY HAS JUST BEEN DONE
23 IN 2013, WHICH IS A VERY STRONG STUDY. AND
24 ORGANIZATIONS, AMERICAN CANCER SOCIETY, WHOEVER, JUST
25 DOESN'T ACT THAT FAST.
26 THE COURT: WE ARE GOING TO RECESS AT THIS TIME.
27 HOW MUCH LONGER ARE YOU GOING TO BE WITH
28 THIS WITNESS, MR. METZGER?

1 MR. METZGER: I THINK I AM CLOSE TO BEING DONE.
2 JUST A FEW MORE MINUTES TOMORROW. I SHOULD WRAP IT UP.
3 THE COURT: ALL RIGHT. MR. SCHURZ, HOW MUCH TIME
4 ON CROSS?
5 MR. SCHURZ: I WILL BE CONCLUDED TOMORROW FOR SURE,
6 YOUR HONOR.
7 THE COURT: ALL RIGHT. WE WILL BE IN RECESS UNTIL
8 TOMORROW AT 9:00 O'CLOCK A.M.
9 MR. METZGER: THANK YOU.
10
11 (THE MATTER WAS ADJOURNED AT 4:24 P.M.)
12
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SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT 323 HON. ELIHU M. BERLE, JUDGE

COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS, A CALIFORNIA CORPORATION, PLAINTIFF, VS. STARBUCKS CORPORATION, A CALIFORNIA CORPORATION, ET AL., DEFENDANTS. AND CONSOLIDATED ACTION.	CASE NO. BC435759

I, KAREN VILICICH, CSR NO. 7634, OFFICIAL COURT REPORTER OF THE SUPERIOR COURT OF THE STATE OF CALIFORNIA, FOR THE COUNTY OF LOS ANGELES, DO HEREBY CERTIFY THAT THE FOREGOING PAGES 151 THROUGH 237 COMPRISE A FULL, TRUE AND CORRECT TRANSCRIPT OF THE TESTIMONY AND PROCEEDINGS HELD IN THE ABOVE-ENTITLED MATTER ON MONDAY, OCTOBER 20, 2014.

DATED THIS 20TH DAY OF OCTOBER, 2014.

KAREN VILICICH, CSR NO. 7634
OFFICIAL REPORTER PRO TEMPORE

EXHIBIT “E”

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT NO. 323 HON. ELIHU M. BERLE, JUDGE

COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS,

PLAINTIFF,

VS. NO. BC435759

STARBUCKS CORPORATION, ET AL.,

DEFENDANTS.

AND CONSOLIDATED ACTION.

REPORTER'S TRANSCRIPT OF TRIAL PROCEEDINGS

TUESDAY, OCTOBER 21, 2014

MORNING SESSION

APPEARANCES:

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DANA L. SHELLEY, RPR, CSR #10177
OFFICIAL REPORTER PRO TEM

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MORNING SESSION

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1 CASE NUMBER: BC435759
2 CASE NAME: CERT VS. STARBUCKS
3 DEPARTMENT: 323 HON. ELIHU M. BERLE
4 REPORTER: DANA SHELLEY, RPR, CSR #10177
5 LOS ANGELES, CALIFORNIA TUESDAY, OCTOBER 21, 2014
6 TIME: 9:21 A.M.
7 APPEARANCES: (AS HERETOFORE NOTED.)
8
9 THE COURT: ON THE TRIAL, CERT VS. STARBUCKS, ALL
10 COUNSEL ARE PRESENT. DR. INFANTE IS ON THE STAND. AND
11 MR. METZGER SAID THERE ARE ONLY A FEW QUESTIONS LEFT.
12
13 PETER FRANCIS INFANTE,
14 CALLED AS A WITNESS BY THE PLAINTIFF, HAVING BEEN
15 PREVIOUSLY SWORN, TESTIFIED FURTHER AS FOLLOWS:
16 THE COURT: DR. INFANTE, YOU UNDERSTAND YOU'RE
17 STILL UNDER OATH?
18 THE WITNESS: YES, SIR.
19 THE COURT: PLEASE RESTATE YOUR NAME FOR THE
20 RECORD.
21 THE WITNESS: PETER FRANCIS INFANTE.
22 THE COURT: MR. METZGER, DO YOU HAVE ANY
23 QUESTIONS?
24 MR. METZGER: YES, YOUR HONOR.
25 THE COURT: OKAY.
26 MR. METZGER: THANK YOU.
27
28

1 DIRECT EXAMINATION (RESUMED)
2 BY MR. METZGER:
3 Q DR. INFANTE, YESTERDAY YOU DISCUSSED THREE
4 TYPES OF EPIDEMIOLOGIC STUDIES THAT BEAR ON THE HUMAN
5 CARCINOGENICITY OF ACRYLAMIDE. THE FIRST TYPE OF STUDY
6 THAT YOU DISCUSSED WERE THE OCCUPATIONAL EPIDEMIOLOGY
7 STUDIES OF ACRYLAMIDE PRODUCTION WORKERS EXPOSED TO
8 ACRYLAMIDE.
9 WHAT DO YOU CONCLUDE REGARDING THE HUMAN
10 CARCINOGENICITY OF ACRYLAMIDE, BASED UPON THAT BODY OF
11 EPIDEMIOLOGIC LITERATURE?
12 MR. SCHURZ: ASKED AND ANSWERED.
13 THE COURT: OVERRULED.
14 THE WITNESS: MY CONCLUSION ABOUT THE OCCUPATIONAL
15 STUDIES RELATED TO ACRYLAMIDE EXPOSURE IS THAT THEY
16 DEMONSTRATE A SIGNIFICANT INCREASE IN MORTALITY FROM
17 PANCREATIC CANCER AND THAT THE -- THERE ARE TWO STUDIES
18 THAT DEMONSTRATE DOSE RESPONSE BY FOUR MODES OF EXPOSURE
19 TO ACRYLAMIDE, SHOWING AN INCREASED RISK OF PANCREATIC
20 CANCER.
21 SO BASED UPON THAT INFORMATION, IT'S MY
22 OPINION THAT THE OCCUPATIONAL STUDIES DEMONSTRATE A
23 SIGNIFICANT INCREASED RISK OF PANCREATIC CANCER.
24 Q BY MR. METZGER: OKAY. THE SECOND TYPE OF
25 STUDY THAT YOU DISCUSSED WERE CASE-CONTROL STUDIES OF
26 VARIOUS CANCERS IN RELATIONSHIP TO CONSUMPTION OF COOKED
27 POTATOES. WHAT DO YOU CONCLUDE REGARDING THE HUMAN
28 CARCINOGENICITY OF ACRYLAMIDE BASED UPON THAT BODY OF

1 EPIDEMIOLOGIC LITERATURE?
2 A WELL, THE POTATO STUDIES DEMONSTRATE
3 SIGNIFICANTLY ELEVATED RISKS OF VARIOUS TYPES OF CANCERS
4 AT A NUMBER OF SITES. AND THE STUDIES ALSO --
5 SEVERAL -- OR MORE THAN SEVERAL OF THESE STUDIES ALSO
6 DEMONSTRATED DOSE-RESPONSE RELATIONSHIP.
7 SO IN MY OPINION, THERE'S SOME EVIDENCE
8 RELATED TO POTATO CONSUMPTION AND CANCER.
9 Q OKAY. AND LASTLY, REGARDING THE ACRYLAMIDE
10 STUDIES, THE THIRD TYPE OF STUDY THAT YOU DISCUSSED WERE
11 THE EPIDEMIOLOGIC STUDIES OF DIETARY ACRYLAMIDE
12 EXPOSURE. AND WHAT DO YOU CONCLUDE REGARDING THE HUMAN
13 CARCINOGENICITY OF ACRYLAMIDE BASED UPON THAT BODY OF
14 EPIDEMIOLOGIC LITERATURE?
15 A WELL, THE DIETARY ACRYLAMIDE STUDIES
16 DEMONSTRATE THAT THERE ARE SOME CANCERS THAT SHOW
17 SIGNIFICANTLY ELEVATED RISKS.
18 AND I NOTE THAT PARTICULARLY THE OVARIAN AND
19 THE BREAST CANCER FINDINGS ARE, I THINK, IMPORTANT
20 BECAUSE OF THE EXPERIMENTAL STUDIES DEMONSTRATING A HIGH
21 FREQUENCY OF THESE TUMORS IN EXPERIMENTAL ANIMALS.
22 SO MY CONCLUSION ABOUT IT ALL IS THAT, YOU
23 KNOW, THERE'S SOME EVIDENCE.
24 Q ALL RIGHT. WELL, NOW TAKING ALL OF THE
25 EPIDEMIOLOGIC STUDIES FOR THE THREE BODIES OF
26 EPIDEMIOLOGIC LITERATURE THAT YOU'VE ASSESSED REGARDING
27 THE HUMAN CARCINOGENICITY OF ACRYLAMIDE, WHAT IS YOUR
28 OVERALL CONCLUSION REGARDING THE HUMAN CARCINOGENICITY

1 OF ACRYLAMIDE, BASED UPON THESE EPIDEMIOLOGIC STUDIES?
2 A WELL, THERE'S CERTAINLY SOME -- I THINK THE
3 STRONGEST EVIDENCE IS IN THE OCCUPATIONAL SETTING
4 BECAUSE THAT DEMONSTRATES A MONOTONIC DOSE RESPONSE.
5 AND THE OTHER DATA SETS, I THINK THEY CONTRIBUTE SOME
6 EVIDENCE.
7 Q ALL RIGHT. YESTERDAY YOU ALSO DISCUSSED
8 EPIDEMIOLOGIC STUDIES THAT EVALUATED CONSUMPTION OF
9 COFFEE IN RELATION TO THREE TYPES OF HUMAN CANCER.
10 THE FIRST BODY OF EPIDEMIOLOGIC LITERATURE
11 THAT YOU DISCUSSED CONCERNED CONSUMPTION OF COFFEE AND
12 BLADDER CANCER. WHAT DO YOU CONCLUDE REGARDING THE RISK
13 OF BLADDER CANCER FROM CONSUMPTION OF COFFEE BASED UPON
14 YOUR REVIEW OF THOSE EPIDEMIOLOGIC STUDIES?
15 A THERE ARE A LARGE NUMBER OF STUDIES THAT
16 DEMONSTRATE A SIGNIFICANTLY INCREASED RISK OF BLADDER
17 CANCER IN RELATION TO COFFEE CONSUMPTION. AND A NUMBER
18 OF THEM DEMONSTRATE SIGNIFICANT DOSE RESPONSES.
19 AND WHEN YOU ADD THIS INFORMATION TO WHAT
20 IARC HAD CONCLUDED IN 1990, THAT THERE WAS LIMITED
21 EVIDENCE FOR THE CARCINOGEN RELATED TO -- LIMITED
22 EVIDENCE FOR BLADDER CANCER, I THINK THIS ADDS TO THAT
23 EVIDENCE.
24 Q OKAY. AND YOU ALSO DISCUSSED THE
25 EPIDEMIOLOGIC STUDIES REGARDING COFFEE CONSUMPTION AND
26 PANCREATIC CANCER. WHAT DO YOU CONCLUDE REGARDING THE
27 RISK OF PANCREATIC CANCER FROM CONSUMPTION OF COFFEE,
28 BASED UPON THOSE EPIDEMIOLOGIC STUDIES?

1 A WELL, THAT THERE ARE A LARGE NUMBER OF
2 STUDIES THAT DEMONSTRATE SIGNIFICANTLY INCREASED RISKS
3 OF PANCREATIC CANCER, INCLUDING SOME THAT DEMONSTRATED
4 DOSE RESPONSE. AND --
5 MR. SCHURZ: YOUR HONOR, WE WOULD OBJECT. IT
6 APPEARS AS THOUGH DR. INFANTE IS JUST READING FROM A
7 TABLET IN FRONT OF HIM AS OPPOSED TO ANSWERING
8 QUESTIONS. WE'VE BEEN NOT PROVIDED THE NOTES THAT HE'S
9 READING FROM.
10 AND WE WOULD MOVE TO STRIKE THE PRIOR
11 ANSWERS THAT HE'S BEEN READING FROM HIS TABLET AND ASK
12 TO SEE IT.
13 THE COURT: HAVE YOU BEEN READING FROM A TABLET,
14 DR. INFANTE?
15 THE WITNESS: YES. I'M MAKING NOTES AS WE SPEAK,
16 LIKE -- IF YOU'D LIKE -- YOUR HONOR, IF YOU'D LIKE TO
17 SEE IT?
18 THE COURT: ALL RIGHT. WELL, LET'S --
19 THE WITNESS: THIS IS MY SUMMARY.
20 THE COURT: ALL RIGHT. SO DURING THE BREAK, ANY
21 PROBLEM PRODUCING THAT FOR COUNSEL FOR THE DEFENDANT?
22 MR. METZGER: NO, YOUR HONOR.
23 THE COURT: OKAY. DO THAT DURING THE BREAK.
24 SO LET'S TRY TO WRAP UP HIS TESTIMONY. THIS
25 IS JUST RETREADING THE SAME GROUND.
26 Q BY MR. METZGER: DR. INFANTE, TURN OVER YOUR
27 TABLET, PLEASE.
28 A OKAY.

1 Q SO WE WERE ON THE -- I THINK YOU JUST
2 QUITE -- I DON'T KNOW IF YOU QUITE FINISHED YOUR ANSWER
3 REGARDING PANCREATIC CANCER.
4 WHAT IS YOUR CONCLUSION REGARDING THE --
5 YOU'RE REVIEW OF THE EPIDEMIOLOGIC STUDIES REGARDING
6 COFFEE CONSUMPTION AND PANCREATIC CANCER?
7 A MY CONCLUSION IS, THERE ARE A LARGE NUMBER
8 OF STUDIES THAT DEMONSTRATE A SIGNIFICANTLY INCREASED
9 RISK OF PANCREATIC CANCER, AND SEVERAL OF WHICH
10 DEMONSTRATE A DOSE RESPONSE.
11 AND IN MY OPINION, THAT ADDS TO THE IARC
12 EVALUATION IN THE EARLY '90S. SO IN MY OPINION, THEY
13 CONTRIBUTE SOME EVIDENCE TO THE CARCINOGENICITY OF
14 COFFEE IN HUMANS.
15 Q THE LAST BODY OF LITERATURE THAT YOU
16 DISCUSSED WAS THE EPIDEMIOLOGIC STUDIES REGARDING
17 MATERNAL CONSUMPTION OF COFFEE AND CHILDHOOD LEUKEMIA.
18 WHAT DO YOU CONCLUDE REGARDING THE HUMAN CARCINOGENICITY
19 OF COFFEE, BASED UPON THAT BODY OF EPIDEMIOLOGIC
20 LITERATURE?
21 A THE LITERATURE RELATED TO MATERNAL COFFEE
22 CONSUMPTION AND LEUKEMIA IN THEIR CHILDREN, I THINK, IS
23 VERY STRONG EVIDENCE OF A CARCINOGENIC EFFECT FROM
24 COFFEE CONSUMPTION TO PREGNANT WOMEN AND THE RISK TO
25 THEIR CHILDREN.
26 AND THE STUDIES DEMONSTRATE A DOSE RESPONSE
27 FOR TOTAL LEUKEMIA, FOR ACUTE LYMPHATIC LEUKEMIA, AND
28 ALSO FOR ACUTE MYELOGENOUS LEUKEMIA.

1 Q OKAY. SO REGARDING THESE THREE TYPES OF
2 CANCER FOR WHICH YOU HAVE ASSESSED THE BODY OF
3 EPIDEMIOLOGIC LITERATURE -- NAMELY, BLADDER CANCER,
4 PANCREATIC CANCER, AND CHILDHOOD LEUKEMIA -- WHAT IS
5 YOUR OVERALL CONCLUSION REGARDING THE CARCINOGENICITY OF
6 COFFEE, BASED UPON THOSE DATA SETS?
7 A THAT CONSUMPTION OF COFFEE CARRIES WITH IT
8 A -- THERE'S EVIDENCE OF AN INCREASED RISK OF CANCER IN
9 HUMANS, WITH THE STRONGEST DATA BEING FOR CHILDHOOD
10 LEUKEMIA.
11 Q OKAY. NOW, DO ANY OF THE EPIDEMIOLOGIC
12 STUDIES REGARDING CONSUMPTION OF COFFEE AND CANCER THAT
13 YOU READ ASSESS THE IMPACT OF ACRYLAMIDE IN COFFEE ON
14 HUMAN CANCER?
15 A IN NONE OF THE STUDIES THAT I READ DID
16 ANYONE MEASURE THE AMOUNT OF THE ACRYLAMIDE IN THE
17 COFFEE.
18 Q HAVE YOU FORMED ANY CONCLUSION REGARDING THE
19 RISK OF CANCER SPECIFICALLY FROM ACRYLAMIDE IN COFFEE?
20 A I DON'T THINK IT'S POSSIBLE TO DRAW ANY
21 CONCLUSION FROM THE EPIDEMIOLOGICAL DATA BECAUSE THE
22 ACRYLAMIDE WASN'T MEASURED IN THE COFFEE.
23 Q OKAY. HOW COULD ONE ASSESS THE HUMAN
24 CARCINOGENICITY OF ACRYLAMIDE IN COFFEE IF NOT FROM THE
25 EPIDEMIOLOGIC LITERATURE?
26 MR. SCHURZ: OBJECTION; LACKS FOUNDATION, CALLS
27 FOR SPECULATION FROM THIS WITNESS.
28 THE COURT: OVERRULED.

1 THE WITNESS: WELL, YOU WOULD HAVE TO DO A
2 QUANTITATIVE RISK ASSESSMENT BASED ON EXPERIMENTAL DATA.
3 MR. METZGER: OKAY. THANK YOU VERY MUCH, DR.
4 INFANTE. I HAVE NO FURTHER QUESTIONS.
5 THE COURT: ALL RIGHT. MR. SCHURZ?
6 MR. SCHURZ: THANK YOU, YOUR HONOR.
7
8 CROSS-EXAMINATION
9 BY MR. SCHURZ:
10 Q GOOD MORNING, DR. INFANTE.
11 A GOOD MORNING.
12 Q I SEE YOU'VE GOT SOME NOTES THERE. DO YOU
13 HAVE ANY NOTES THAT YOU'RE USING TO RESPOND TO QUESTIONS
14 THAT I'LL BE ASKING?
15 A NO, BUT I'M GOING TO MAKE NOTES AS YOU ASK
16 ME QUESTIONS. I USUALLY DO THAT.
17 Q LET'S BEGIN WITH SOME OF THE OPINIONS YOU
18 DISCUSSED WITH MR. METZGER RELATING TO THE COFFEE
19 EPIDEMIOLOGY. AND I'D LIKE TO START WITH THE OPINIONS
20 YOU'VE OFFERED, DR. INFANTE, WITH RESPECT TO PANCREATIC
21 CANCER.
22 SHOWING YOU THE PAGE 121 OF YOUR
23 DEMONSTRATIVE -- AND YOU WILL SEE THIS ON YOUR SCREEN --
24 YOU IDENTIFY FIVE META-ANALYSES ON COFFEE AND PANCREATIC
25 CANCER; IS THAT CORRECT?
26 A 121 -- LET ME GET IT.
27 META-ANALYSES, PANCREATIC CANCER. YES.
28 Q AND INCLUDED AMONG THOSE FIVE IS THE NISHI

1 META-ANALYSIS, WHICH WAS SIX CASE CONTROLS, PUBLISHED IN
2 1996; CORRECT?
3 A YES.
4 Q AND ALL OF THOSE CASE CONTROLS WERE INCLUDED
5 IN THE SUBSEQUENT TURATI 2011 META-ANALYSIS; CORRECT?
6 A I WOULD HAVE TO -- I'M NOT SURE, AS I SIT
7 HERE. I DON'T RECALL. I'D HAVE TO LOOK BACK AND
8 COMPARE THE TWO STUDIES.
9 Q ALL RIGHT. SO I'D LIKE TO FOCUS OUR
10 ATTENTION ON THE FOUR MORE RECENT ONES.
11 NOW, SPECIFICALLY WITH RESPECT TO THE
12 PANCREATIC CANCER META-ANALYSES THAT YOU HAVE IDENTIFIED
13 AND THE VALUES THAT YOU HAVE SET FORTH, NONE OF THE
14 META-ANALYSES REPORT A STATISTICALLY SIGNIFICANT
15 POSITIVE ASSOCIATION BETWEEN COFFEE AND PANCREATIC
16 CANCER, DO THEY?
17 A THAT'S CORRECT, YES. AND THEY --
18 Q AND THE META-ANALYSES --
19 MR. METZGER: EXCUSE ME. I DON'T THINK DR.
20 INFANTE HAD FINISHED.
21 THE COURT: DO YOU WISH TO COMPLETE YOUR ANSWER?
22 THE WITNESS: WELL, THERE ARE SOME THAT SHOW THE P
23 TREND, BUT IT'S NOT SIGNIFICANT AT THE 05 LEVEL. IT'S
24 SIGNIFICANT AT THE .11 LEVEL.
25 THE COURT: CAN YOU SPEAK UP LOUDER, PLEASE.
26 THE WITNESS: YES. SO THAT DOES NOT MEET THE 05
27 LEVEL OF STATISTICAL SIGNIFICANCE. I THINK THAT'S
28 INDICATED IN THE SLIDE.

1 Q BY MR. SCHURZ: OKAY. NOW, THE
2 META-ANALYSES SUMMARIZED HERE REFLECT THE COMBINED
3 ANALYSIS OF SOME 34 CASE-CONTROL STUDIES AND A TOTAL OF
4 15 COHORT STUDIES; CORRECT?
5 A 34 CASE-CONTROL STUDIES AND 15 COHORT
6 STUDIES, YES.
7 Q AND AMONG THOSE COHORT STUDIES ARE A NUMBER
8 OF LARGE, PUBLICLY FINANCED STUDIES, INCLUDING THE
9 HARVARD NURSES STUDY, THE EPIC STUDY, AND OTHERS;
10 CORRECT?
11 A YOU KNOW, I DON'T KNOW THEM BY THOSE NAMES.
12 ARE YOU REFERRING TO SOME OF THE STUDIES THAT ARE ON
13 THIS SLIDE?
14 Q I'M REFERRING TO THE COHORT STUDIES THAT
15 WERE PART OF YOUR REVIEW.
16 A OKAY. I'M ONLY SAYING, I DON'T RECALL THEM
17 BY WHO FUNDED THEM BUT BY THE AUTHORS. SO MAYBE IF YOU
18 COULD REFER TO THEM, I'LL KNOW WHICH ONES YOU'RE
19 SPEAKING ABOUT.
20 Q OKAY. WELL, WE'LL TALK ABOUT THEM
21 INDIVIDUALLY.
22 WOULD YOU AGREE WITH ME, DR. INFANTE, THAT
23 THE RANGE OF STUDIES THAT ARE ENCOMPASSED WITHIN THE
24 META-ANALYSES FOR COFFEE AND PANCREATIC CANCER
25 CONSTITUTE A LARGE BODY OF EPIDEMIOLOGIC LITERATURE?
26 A THE META-ANALYSES? YES.
27 Q AND THE STUDIES INVOLVE A BROAD RANGE OF
28 DIFFERENT POPULATIONS, DO THEY NOT?

1 A YES.
2 Q IN FACT, POPULATIONS FROM THREE DIFFERENT
3 CONTINENTS; ISN'T THAT CORRECT?
4 A WELL, YOU KNOW, I DIDN'T -- I GUESS I
5 LOOKED -- I INDICATED WHERE THEY WERE FROM. I DON'T
6 KNOW HOW MANY CONTINENTS THAT COULD BE.
7 Q OKAY. DOES IT SOUND ACCURATE TO SAY THAT
8 THERE ARE STUDIES EVALUATING COFFEE CONSUMPTION AND
9 PANCREATIC CANCER INVOLVING POPULATIONS FROM EUROPE,
10 ASIA, AND THE UNITED STATES, NORTH AMERICA?
11 A YOU LEFT OUT -- I DON'T KNOW IF THERE WERE
12 SOUTH AMERICA IN THOSE OR NOT, SOME OF THE STUDIES I
13 REVIEWED FROM SOUTH AMERICA.
14 BUT WHATEVER THEY ARE, I WOULDN'T ARGUE WITH
15 THAT, BECAUSE I HAVE THEM BY INDIVIDUAL COUNTRY, I
16 THINK, ON SOME OF THE OTHER SLIDES.
17 Q ALL RIGHT. AND THE PUBLICATIONS RELATING TO
18 COFFEE CONSUMPTION AND PANCREATIC CANCER COVER AN
19 EXTENDED PERIOD OF TIME, MORE THAN 30 YEARS OF
20 PUBLICATIONS FROM 1980 THROUGH 2013; CORRECT?
21 A WHATEVER IS ON THE SLIDES, I WOULDN'T ARGUE
22 WITH YOU ABOUT THAT. TO GIVE YOU THE CORRECT ANSWER,
23 I'D HAVE TO GO BACK AT THE SLIDES AND SEE WHEN THEY
24 STARTED, BUT THAT COULD BE CORRECT.
25 Q OKAY. AS YOU SIT HERE TODAY, YOU DON'T
26 KNOW?
27 A WELL, NO, I CAN -- WELL, I'M SAYING I WOULD
28 HAVE TO REFER TO MY SLIDES TO ANSWER YOUR QUESTION

1 ACCURATELY.
2 Q OKAY. SO LET'S TALK ABOUT SOME OF THE
3 INDIVIDUAL META-ANALYSES YOU IDENTIFIED AND REVIEWED AS
4 PART OF YOUR WORK IN THIS CASE. AND LET ME START WITH
5 THE TURATI 2011 META-ANALYSES, WHICH IS EXHIBIT 2083.
6 AND YOU'LL SEE IT ON YOUR SCREEN, AND WE'LL GET YOU A
7 HARD COPY, AS WELL.
8 AND DO YOU RECOGNIZE THIS TURATI
9 META-ANALYSIS OF COFFEE CONSUMPTION AND PANCREATIC
10 CANCER, DR. INFANTE?
11 A YES.
12 (EXHIBIT 2083 MARKED FOR
13 IDENTIFICATION.)
14 Q BY MR. SCHURZ: AND YOU REVIEWED THIS AS
15 PART OF YOUR WORK IN THIS CASE; CORRECT?
16 A I'M LOOKING AT MY -- I MADE NOTES ON ALL OF
17 THEM THAT I REVIEWED. SO I'M JUST GOING TO REFER TO MY
18 NOTES, TO FAMILIARIZE MYSELF WITH IT, IF YOU DON'T MIND.
19 Q ARE THESE NOTES THAT HAVE BEEN PROVIDED TO
20 US, DR. INFANTE?
21 A YES. THEY'RE EXHIBIT 222.
22 Q ALL RIGHT.
23 A (REVIEWS DOCUMENT.)
24 WHOOPS, SORRY. THAT'S BLADDER CANCER. I
25 PULLED THE WRONG ONES. IT'S EXHIBIT 227.
26 (REVIEWS DOCUMENT.)
27 Q AND DR. INFANTE, THE QUESTION THAT I ASKED
28 IS: DID YOU RELY ON THIS STUDY IN FORMING YOUR

1 OPINIONS?
2 A YES. I MEAN, I RELIED ON ALL OF THE
3 INFORMATION THAT I READ --
4 Q ALL RIGHT.
5 A -- IN THE LITERATURE. AND SOME SHOWED MORE
6 POSITIVE EFFECTS THAN OTHERS.
7 Q AND LET'S DISCUSS THE OPINIONS -- OR EXCUSE
8 ME. LET'S DISCUSS THE FINDINGS OF THE TURATI
9 META-ANALYSIS THAT ARE SET FORTH IN EXHIBIT 2083.
10 NOW, AS REFLECTED IN THE ABSTRACT, THIS
11 META-ANALYSIS COVERS 37 CASE CONTROLS AND 17 COHORTS;
12 CORRECT?
13 A NO -- WELL, I THINK, 34 CASE-CONTROL STUDIES
14 AND 17 COHORT STUDIES.
15 Q AND INVOLVED OVER 10,000 CASES OF PANCREATIC
16 CANCER; CORRECT?
17 A YES.
18 Q ALL RIGHT. AND LET ME FOCUS YOUR ATTENTION
19 TO PAGE 1 OF THE EXHIBIT 2083, WHERE THE AUTHORS OFFER
20 THEIR CONCLUSIONS IN THE ABSTRACT. AND THE TURATI
21 AUTHORS CONCLUDE:
22 "THIS META-ANALYSIS PROVIDES
23 QUANTITATIVE EVIDENCE THAT COFFEE CONSUMPTION
24 IS NOT APPRECIABLY RELATED TO PANCREATIC
25 CANCER RISK, EVEN AT HIGH INTAKES."
26 CORRECT?
27 A YES. WELL, YOU'LL NOTE IT SAYS
28 "APPRECIABLY," BECAUSE THE LOWER BOUND OF THE CONFIDENCE

1 INTERVAL IS .99. IF THAT WERE 1.01, TWO HUNDREDTHS
2 MORE, THE RESULT WOULD BE STATISTICALLY SIGNIFICANT. SO
3 I THINK THAT'S WHY THEY USED THE WORDS "APPRECIABLY
4 RELATED."
5 Q LET'S TAKE A LOOK AT FIGURE NO. 2 AT PAGE
6 003 OF THE TURATI PAPER, WHICH SETS FORTH --
7 DO YOU HAVE THAT IN FRONT OF YOU?
8 A I'M SORRY. WHAT PAGE ARE YOU ON?
9 Q IT'S PAGE 3.
10 A OKAY.
11 Q AND THIS FIGURE SETS OUT THE RELATIVE RISKS
12 AND CONFIDENCE INTERVALS OF THE PANCREATIC CANCER FOR
13 HIGH -- HIGHEST VERSUS LOWEST COFFEE-DRINKING
14 CATEGORIES; CORRECT?
15 A ARE YOU TALKING ABOUT THE TOP ENTRY? IT
16 SAYS "CASE-CONTROL STUDIES WITHOUT SMOKING ADJUSTMENT."
17 Q YES.
18 A IS THAT THE SECTION YOU'RE SPEAKING OF?
19 Q YES -- WELL, I'M LOOKING AT THE ENTIRE
20 FIGURE, WHICH YOU CAN SEE AT THE BOTTOM OF PAGE 3 IS
21 IDENTIFIED AS FIGURE 2. DO YOU SEE THAT?
22 A NO. I THINK WE'RE ON THE SAME PAGE, BUT I
23 JUST DON'T KNOW WHICH YOU'RE REFERRING TO.
24 Q SURE, I APPRECIATE THAT. IF YOU LOOK AT THE
25 BOTTOM OF THE PAGE, YOU CAN SEE WHERE IT READS "FIGURE
26 NO. 2, RELATIVE RISKS." DO YOU SEE THAT? AND 95
27 PERCENTAGE CONFIDENCE INTERVALS.
28 DO YOU SEE THAT?

1 A YES.
2 Q ALL RIGHT. THIS IS ALL JUST BY WAY OF
3 ORIENTATION.
4 NOW LET'S LOOK AT THE VALUES THAT THE TURATI
5 AUTHORS CAPTURED HERE. AND YOU CAN SEE THAT THEY'VE
6 SEGREGATED THOSE STUDIES THAT ADDRESS THE RISK OF
7 PANCREATIC CANCER WHERE THERE WAS AN ADJUSTMENT FOR
8 SMOKING AND WHERE THERE WAS NO ADJUSTMENT FOR SMOKING;
9 CORRECT?
10 A YES.
11 Q AND LOOKING AT THE TOP ONE, AND DIRECTING
12 YOUR ATTENTION TO THE TOP OF FIGURE 2, THEY REPORT A
13 VALUE FOR ALL STUDIES WITHOUT SMOKING ADJUSTMENT. AND
14 THEY INCLUDE A RELATIVE RISK VALUE OF 1.25, WITH A
15 CONFIDENCE -- 95TH PERCENT CONFIDENCE INTERVAL OF 0.96
16 TO 1.63; CORRECT?
17 A YES.
18 Q SO THIS IS NOT STATISTICALLY SIGNIFICANT;
19 CORRECT?
20 A CORRECT. BUT I MEAN, IT'S CLOSE TO BEING.
21 Q YEAH.
22 A IT PROVIDES SOME EVIDENCE OF AN ELEVATED
23 RISK.
24 Q AND THESE ARE STUDIES THAT SHOW THAT THERE
25 WAS NO ADJUSTMENT FOR SMOKING; CORRECT?
26 A CORRECT.
27 Q AND YESTERDAY YOU TESTIFIED THAT SMOKING IS
28 A RISK FACTOR FOR PANCREATIC CANCER; CORRECT?

1 A YES.
2 Q SO THESE STUDIES DO NOT CONTROL FOR THE
3 POTENTIAL CONFOUNDING THAT WOULD RESULT FROM CIGARETTE
4 SMOKING; CORRECT?
5 A YOU MEAN, THAT ANALYSIS?
6 Q YES.
7 A CORRECT.
8 Q ALL RIGHT. SO IF WE CONTINUE ON --
9 A BUT SOME OF THE STUDIES THAT ARE -- I'LL
10 JUST MAKE A POINT. SOME OF THE STUDIES INCLUDED IN THIS
11 META-ANALYSIS HAVE VERY POOR METHODOLOGY. LIKE JUST FOR
12 EXAMPLE, THE FIRST ONE, JICK. I MEAN THAT WAS TERRIBLE
13 METHODOLOGY IN THAT.
14 SO I DON'T KNOW THAT THEY SEPARATED THESE
15 STUDIES THAT THEY'RE INCLUDING IN THEIR META-ANALYSIS --
16 THAT THEY DID ANY CRITICAL EVALUATION OF THEM. LOOKS TO
17 ME LIKE THEY JUST THREW EVERYTHING IN.
18 Q ALL RIGHT. AND WE'LL DISCUSS A NUMBER OF
19 THESE INDIVIDUAL STUDIES THAT YOU'VE INCLUDED ON YOUR
20 TABLES.
21 BUT LET'S STAY HERE FOR THE MOMENT WITH
22 FIGURE NO. 2. AND WOULD YOU AGREE THAT AS WE LOOK AT
23 STUDIES WITH THE SMOKING ADJUSTMENT -- AND WE'RE NOW
24 MOVING DOWN IN FIGURE 2 TO THE NEXT CATEGORY OF DATA.
25 AND WE SEE A SEPARATE CALCULATION FOR
26 STUDIES WITH SMOKING. AND WE SEE A -- FOR THE
27 CASE-CONTROL STUDIES, WE SEE A VALUE OF 1.10 AND A
28 RELATIVE -- WITH A CONFIDENCE INTERVAL OF 0.92 TO 1.31;

1 CORRECT?
2 A I'M TRYING TO SEE WHICH ONE FROM THE CHART.
3 I'VE REDONE THIS, AND I'M TRYING TO SEE WHICH ONE THIS
4 IS FROM THE ACTUAL PUBLICATION.
5 WHAT'S THE -- ARE YOU TALKING ABOUT ALL
6 STUDIES WITHOUT ADJUSTMENT NOW? WHICH ONES?
7 Q I'M LOOKING AT STUDIES WITH ADJUSTMENT FOR
8 SMOKING. STUDIES WITH SMOKING ADJUSTMENT, CASE-CONTROL
9 STUDIES. THE QUESTION --
10 A WELL, THEY HAVE TWO SETS OF STUDIES WITH
11 SMOKING ADJUSTMENT. THAT'S WHY I'M WONDERING WHICH
12 ONE -- WHICH GROUP YOU'RE SPEAKING OF.
13 Q AND AS REFLECTED HERE ON THE SCREEN, DR.
14 INFANTE, WE'RE LOOKING AT THE CASE-CONTROL STUDIES. AND
15 DO YOU SEE THAT?
16 A YES.
17 Q OKAY. AND HERE, AGAIN, THE TURATI AUTHORS
18 OBSERVED THAT THERE IS A NON-STATISTICALLY SIGNIFICANT
19 RISK ASSOCIATED WITH THE CASE-CONTROL STUDIES FOR
20 PANCREATIC CANCER WHERE THERE HAS BEEN AN ADJUSTMENT FOR
21 SMOKING; CORRECT?
22 A CORRECT.
23 Q AND AS WE CAN SEE HERE, WHEN WE COMPARE IT,
24 THE VALUES GO DOWN. THERE'S A DIFFERENCE BETWEEN
25 STUDIES WITHOUT THE SMOKING ADJUSTMENT AND THOSE WITH
26 IT; CORRECT?
27 A YES.
28 Q ALL RIGHT. NOW, WOULD YOU AGREE, DR.

1 INFANTE, THAT IN EVALUATING THE INCIDENCE OF PANCREATIC
2 CANCER AND COFFEE CONSUMPTION, ADJUSTING FOR TOBACCO USE
3 IS IMPORTANT?
4 A YES.
5 Q ALL RIGHT. SO LET'S TALK A LITTLE BIT ABOUT
6 THE CONCLUSIONS THAT THE TURATI AUTHORS REPORT. AND IF
7 I COULD DIRECT YOUR ATTENTION TO PAGE 6 OF EXHIBIT 2083.
8 LET ME KNOW WHEN YOU'RE THERE.
9 A 6. OKAY.
10 I'M THERE.
11 Q OKAY. AND YOU RECALL -- AND DIRECTING YOUR
12 ATTENTION TO THE LEFT-HAND COLUMN AT THE TOP. AND THE
13 TURATI AUTHORS OBSERVE:
14 "BESIDES THE ORIGINAL HYPOTHESIS-
15 GENERATING ARTICLE, AMONG THE 37 SMOKING-
16 ADJUSTING STUDIES, ONLY 5 FOUND SIGNIFICANT
17 INCREASED RISKS."
18 DO YOU SEE THAT?
19 A YES.
20 Q NOW, YOU -- IN YOUR SLIDES THAT YOU PROVIDED
21 TO US YESTERDAY, YOU IDENTIFIED 14 CASE-CONTROL STUDIES
22 THAT REPORT SIGNIFICANTLY INCREASED RISKS OF PANCREATIC
23 CANCER; CORRECT?
24 A YES.
25 Q ALL RIGHT. NOW, LET'S TAKE A LOOK AT PAGE
26 NO. 5 OF THE TURATI ARTICLE. AND I'M RIGHT NOW AT THE
27 SECTION RIGHT UNDER THE HEADER "DISCUSSION." DO YOU SEE
28 THAT?

1 A OKAY.
2 Q AND THE TURATI AUTHORS BEGIN THEIR
3 DISCUSSION WITH THE STATEMENT:
4 "THE PRESENT META-ANALYSES, CARRIED OUT
5 ON 54 STUDIES AND 10,594 CASES, FOUND NO
6 APPRECIABLE OVERALL ASSOCIATION BETWEEN COFFEE
7 CONSUMPTION AND PANCREATIC CANCER RISK.
8 RESULTS WERE CONSISTENT FOR CASE-CONTROL AND
9 COHORT STUDIES THAT INCLUDED ADJUSTMENT FOR
10 SMOKING CONSUMPTION IN MULTIPLE REGRESSION
11 MODELS."
12 DO YOU SEE THAT?
13 A YES.
14 Q WOULD YOU AGREE, DR. INFANTE, THAT THE CASE
15 CONTROLS AND COHORT STUDIES THAT ARE ADJUSTED FOR
16 SMOKING ARE CONSISTENT?
17 A IN THEIR META-ANALYSES, THAT'S WHAT THEY'RE
18 SAYING.
19 Q ALL RIGHT. AND THE AUTHORS CONCLUDE -- THE
20 AUTHORS CONTINUE TO OBSERVE:
21 "WE OBSERVED A WEAK ASSOCIATION IN
22 CASE-CONTROL STUDIES NOT ADJUSTED FOR TOBACCO,
23 WHICH CAN BE ATTRIBUTED TO RESIDUAL
24 CONFOUNDING BY SMOKING."
25 DO YOU SEE THAT, DR. INFANTE?
26 A YES.
27 Q AND WOULD YOU AGREE THAT THE WEAK
28 ASSOCIATION THAT IS FOUND IN SOME OF THE CASE-CONTROL

1 STUDIES THAT ARE NOT ADJUSTED FOR TOBACCO CAN BE
2 ATTRIBUTED TO RESIDUAL CONFOUNDING BY SMOKING?
3 A WELL, THAT'S WHAT THEY'RE SAYING HERE.
4 Q AND MY QUESTION TO YOU, DR. INFANTE, IS:
5 WOULD YOU AGREE THAT THE OBSERVED WEAK ASSOCIATION IN
6 THE CASE-CONTROL STUDIES THAT YOU REVIEWED THAT ARE NOT
7 ADJUSTED FOR TOBACCO CAN BE ATTRIBUTED TO RESIDUAL
8 CONFOUNDING BY SMOKING?
9 A CAN BE, BUT YOU DON'T KNOW THAT THEY WERE.
10 Q OKAY. NOW, YOU INCLUDED A RANGE OF
11 CASE-CONTROL STUDIES THAT WERE NOT ADJUSTED FOR SMOKING;
12 IS THAT CORRECT?
13 A YES. I PRESENTED THE RESULTS THAT THE
14 AUTHORS PRESENTED.
15 Q AND HOW MANY OF THE CASE-CONTROL STUDIES
16 THAT YOU PRESENTED IN YOUR TABLES RELATING TO PANCREATIC
17 CANCER WERE NOT ADJUSTED FOR SMOKING?
18 A I DON'T KNOW THAT NUMBER OFFHAND. I
19 REVIEWED --
20 Q OKAY. LET'S TALK, IF I MAY -- IF I COULD
21 DIRECT YOUR ATTENTION TO PAGE 4 OF EXHIBIT 2083, IT'S
22 FIGURE NO. 4. AND IT APPEARS JUST ABOVE THE MATERIAL
23 THAT WE WERE LOOKING AT TOGETHER.
24 A WAIT A MINUTE. IS THIS A DIFFERENT -- ARE
25 WE ON THE SAME -- WHAT PAGE, PLEASE?
26 Q SAME PAGE, PAGE 4.
27 MR. METZGER: PAGE 5, I THINK.
28 THE WITNESS: PAGE 4?

1 Q BY MR. SCHURZ: EXCUSE ME, PAGE 5 -- THANK
2 YOU -- OF EXHIBIT 2083. AND YOU SEE A FIGURE NO. 4?
3 A YES.
4 Q OKAY. NOW, THIS GRAPH SHOWS THE CUMULATIVE
5 RELATIVE RISKS FOR ALL OF THE STUDIES WITH SMOKING
6 ADJUSTED; IS THAT CORRECT?
7 A YES.
8 Q AND WHAT THIS GRAPH SHOWS OVER TIME IS THAT
9 THE NUMBER OF STUDIES THAT HAVE BEEN PUBLISHED PROVIDING
10 INFORMATION WITH RESPECT TO HIGHEST VERSUS LOWEST
11 COFFEE-DRINKING IN THE SMOKING-ADJUSTED STUDIES FOR
12 PANCREATIC CANCER; CORRECT?
13 A YES.
14 Q AND IF WE TAKE A LOOK AT THE LEFT-HAND SIDE
15 OF THE CHART THAT WE'RE LOOKING AT HERE, WE SEE A SINGLE
16 STUDY -- OR A PAIR OF STUDIES FROM 1981 THAT WERE THE
17 FIRST STUDIES RELATING TO PANCREATIC CANCER AND COFFEE
18 CONSUMPTION; CORRECT?
19 A YES.
20 Q AND THAT STUDY THAT INCLUDES THE MC MAHON
21 STUDY, DOES IT NOT?
22 A YES.
23 Q AND THAT STUDY SHOWS A RELATIVE RISK OF
24 ROUGHLY 2.7; CORRECT?
25 A YES.
26 Q WITH VERY WIDE CONFIDENCE INTERVALS;
27 CORRECT?
28 A YES.

1 Q AND THEN OVER TIME WHAT WE SEE IS THE
2 ADDITION OF ADDITIONAL STUDIES THAT ARE PUBLISHED IN THE
3 PEER-REVIEWED ARTICLE, ANALYZING PANCREATIC CANCER AND
4 COFFEE CONSUMPTION; CORRECT?
5 A YES.
6 Q SO IF WE LOOK AT THE BOTTOM OF THE GRAPH, WE
7 SEE ON THE -- WHAT I GUESS IS THE X AXIS, WE SEE A YEAR
8 AND NUMBER OF STUDIES; CORRECT?
9 A YES.
10 Q AND WHAT THE AUTHORS ARE REFLECTING HERE IS
11 THE CUMULATIVE GROWTH OF STUDIES OVER TIME AND THE
12 CORRESPONDING RELATIVE RISK ASSOCIATED WITH COFFEE
13 CONSUMPTION AT THE HIGHEST VERSUS LOWEST LEVELS;
14 CORRECT?
15 A YES.
16 Q ALL RIGHT. NOW, AND WHAT WE SEE, AS THIS
17 GRAPH INDICATES, IS THAT OVER TIME THE RELATIVE RISK
18 VALUES DROP; CORRECT?
19 A YES, EXCEPT FOR THE LAST INTERVAL, WHERE
20 THEY RISE AGAIN.
21 Q AND WHAT WE SEE IN THE CONTEXT OF THE DROP
22 IN THE GRAPH IS THAT BEGINNING IN 1984 -- STRIKE THAT --
23 BEGINNING IN 1983, THE VALUES THAT ARE BEING REPORTED
24 FOR PANCREATIC CANCER AND COFFEE CONSUMPTION ARE NO
25 LONGER STATISTICALLY SIGNIFICANT; CORRECT?
26 A WELL, EXCEPT THE 1990 -- IT'S HARD TO SEE
27 WITH THAT BAR, AS TO HOW -- IF THAT'S ABOVE OR WHERE --
28 IT LOOKS LIKE IT'S EITHER ON THE LINE OR SOMEWHERE. SO

1 THAT ONE COULD BE STATISTICALLY SIGNIFICANT.
2 Q AND CERTAINLY, BY 1995, WE ARE -- WHEN WE
3 HIT THE RANGE OF 25 STUDIES EVALUATING THE HIGHEST
4 VERSUS LOWEST COFFEE-DRINKING, THE VALUES HOVER AROUND 1
5 AND ARE NO LONGER STATISTICALLY SIGNIFICANT; CORRECT?
6 A CORRECT.
7 Q AND AS THOSE VALUES AND THE NUMBER OF
8 STUDIES ACCUMULATES, THE CONFIDENCE INTERVAL GETS
9 TIGHTER AND TIGHTER; CORRECT?
10 A YES.
11 Q AND SINCE 1995, NONE OF THE VALUES THAT HAVE
12 BEEN REPORTED IN THIS CUMULATIVE META-ANALYSIS REFLECT A
13 STATISTICALLY SIGNIFICANT INCREASED RISK FROM COFFEE
14 CONSUMPTION AND PANCREATIC CANCER IN THE HIGHEST VERSUS
15 LOWEST; CORRECT?
16 A YES, EXCEPT FOR THE FINAL CUMULATIVE
17 ANALYSIS, THE LOWER BOUND IS .99. AND I'M JUST SAYING,
18 IF THAT WERE ANOTHER ONE-HUNDREDTH, THAT WOULD BE
19 STATISTICALLY SIGNIFICANT. AND THAT'S WHY THE AUTHOR
20 SAID THERE'S NO "APPRECIABLE." IT STILL DOESN'T MEAN
21 THERE'S NOT SOME SLIGHT RISK.
22 Q AND SO LET'S SEE WHAT THE TURATI AUTHORS HAD
23 TO SAY WITH RESPECT TO THEIR OWN DATA. AND AGAIN, LET'S
24 STAY ON PAGE NO. 5.
25 AND RETURNING TO THE DISCUSSION, AT THE SAME
26 PARAGRAPH THAT WE WERE LOOKING AT, DIRECTING YOUR
27 ATTENTION, DR. INFANTE, TO THAT PARAGRAPH THAT WE WERE
28 DISCUSSING EARLIER, HERE THE TURATI AUTHORS OBSERVE:

1 "THE PATTERN OBSERVED IN THE CUMULATIVE
2 META-ANALYSIS, WITH THE DECREASE OF THE POOLED
3 RELATIVE RISK OVER TIME TO APPROACH UNITY
4 SINCE THE MID 1990S, IS LIKELY DUE TO FALSE
5 POSITIVE RESULTS IN EARLIER STUDIES."
6 DO YOU SEE THAT?
7 A YES.
8 Q AND THE --
9 A BUT I MEAN, THAT'S SPECULATION.
10 Q WELL, IT'S --
11 A THEY DON'T HAVE AN ANALYSIS TO SHOW THAT.
12 THAT'S THEIR INTERPRETATION OF IT.
13 Q IT IS THEIR INTERPRETATION OF THE DATA THEY
14 ANALYZED; CORRECT?
15 A YES.
16 Q YES. ALL RIGHT.
17 LET'S TAKE A LOOK AT SOME OF THE OTHER
18 META-ANALYSES THAT YOU HAVE RELIED ON AND REVIEWED IN
19 THE CONTEXT OF PANCREATIC CANCER. AND LET ME START WITH
20 THE GENKINGER META-ANALYSIS, WHICH IS EXHIBIT 1072.
21 A ALL RIGHT.
22 Q AND WE'LL GET YOU A HARD COPY OF THIS.
23 BUT DO YOU -- CAN YOU IDENTIFY THIS DOCUMENT
24 FOR US, EXHIBIT 1072, DR. INFANTE?
25 A (REVIEWS DOCUMENT.)
26 YES. THIS IS THE GENKINGER STUDY OF -- IT
27 SAYS "2011" ON IT. SO I DON'T THINK -- IN 2011 OR '12,
28 IT WAS PUBLISHED.

1 (EXHIBIT 1072 MARKED FOR
2 IDENTIFICATION.)
3 Q BY MR. SCHURZ: AND YOU REVIEWED THIS IN
4 DEVELOPING YOUR OPINIONS IN THIS CASE; CORRECT?
5 A YES.
6 Q YOU RELIED ON THIS IN DEVELOPING YOUR
7 OPINIONS; CORRECT?
8 A WELL, IT'S ONE DOCUMENT I RELIED ON, YES.
9 Q AND THIS IS A POOLED ANALYSIS OF THE DATA
10 CONCERNING THE COHORT STUDIES RELATING TO COFFEE
11 CONSUMPTION AND PANCREATIC CANCER; CORRECT?
12 A YES.
13 Q ALL RIGHT. NOW, LET ME DIRECT YOUR
14 ATTENTION TO PAGE 11 OF EXHIBIT 1072.
15 A IS THERE A PAGE NUMBER ON THIS ONE? MY COPY
16 STARTS AT 305.
17 Q IF YOU LOOK AT THE BOTTOM, YOU'LL SEE IN
18 HANDWRITING A BATES NUMBER WITH A -- A NUMBER THERE.
19 A ALL RIGHT.
20 Q AND DO YOU HAVE PAGE 11 IN FRONT OF YOU?
21 A YES.
22 Q AND DIRECTING YOUR ATTENTION TO THE AUTHORS'
23 CONCLUSION, WHICH APPEARS AT THE RIGHT-HAND COLUMN AT
24 THE BOTTOM. AND DO YOU SEE THAT, WHERE IT BEGINS "IN
25 SUMMARY"?
26 A YES.
27 Q AND GENKINGER AUTHORS CONCLUDE:
28 "IN SUMMARY, WE FOUND NO ASSOCIATION

1 BETWEEN INTAKES OF TEA AND COFFEE DURING
2 ADULTHOOD AND PANCREATIC CANCER RISK IN THIS
3 POOLED ANALYSIS."
4 DO YOU SEE THAT?
5 A YES.
6 Q ALL RIGHT. LET'S TAKE A LOOK AT THE THIRD
7 META-ANALYSIS THAT YOU REVIEWED AND RELIED UPON IN
8 DEVELOPING YOUR OPINIONS RELATING TO PANCREATIC CANCER.
9 AND THAT'S THE DONG 2011, AT EXHIBIT 908.
10 A ALL RIGHT. I MEAN, IN MY SLIDE, I HAVE THE
11 IDENTICAL DATA THAT THEY HAVE IN THESE PAPERS.
12 (EXHIBIT 908 MARKED FOR IDENTIFICATION.)
13 Q BY MR. SCHURZ: AND YOU REVIEWED THE DONG
14 ARTICLE, WHICH IS IDENTIFIED HERE AT 908; CORRECT?
15 A YES.
16 Q AND YOU RELIED ON IT IN DEVELOPING YOUR
17 OPINIONS; CORRECT?
18 A YES. IT DOESN'T SHOW A POSITIVE
19 ASSOCIATION, BUT I REVIEWED IT. SO WHEN YOU SAY I
20 RELIED UPON IT, I REVIEWED ALL OF THE LITERATURE. I
21 DIDN'T RELY; I TOOK IT INTO CONSIDERATION. IT DOESN'T
22 MEAN THAT THIS IS A STUDY THAT SHOWED POSITIVE EVIDENCE
23 BECAUSE VERY CLEARLY, IN MY SLIDE, IT DOESN'T SHOW THAT.
24 Q IN FACT, NONE OF THE META-ANALYSES YOU
25 RELIED ON SHOWED ANY POSITIVE EVIDENCE OF AN INCREASED
26 STATISTICALLY SIGNIFICANT RISK ASSOCIATED WITH
27 PANCREATIC CANCER; CORRECT?
28 A WELL, NOT A STATISTICALLY SIGNIFICANT

1 INCREASED RISK, BUT THE TURATI STUDY THAT WE JUST
2 DISCUSSED AND WHERE THEY SAID "NO APPRECIABLE INCREASED
3 RISK," YOU'VE GOT A 13 PERCENT INCREASE, AND IT'S
4 ONE-HUNDREDTH AWAY FROM BEING STATISTICALLY SIGNIFICANT.
5 Q ALL RIGHT. LET'S TAKE A LOOK AT WHAT THE
6 DONG AUTHORS CONCLUDE AT EXHIBIT 908. AND LET ME DIRECT
7 YOUR ATTENTION TO 006. AND WE'RE IN THE LAST PARAGRAPH
8 ON PAGE 006 ON EXHIBIT 908.
9 AND DO YOU HAVE THAT IN FRONT OF YOU?
10 A I'M GETTING IT. ALL RIGHT.
11 Q AND HERE THE DONG AUTHORS OBSERVE:
12 "IN SUMMARY, THERE IS SUBSTANTIAL
13 EVIDENCE FROM BOTH LABORATORY AND ANIMAL
14 STUDIES ON THE FAVORABLE INFLUENCE OF COFFEE
15 ON THE RISK OF PANCREATIC CANCER."
16 DO YOU SEE THAT?
17 A YES.
18 Q YOU DID NOT REVIEW THE ANIMAL DATA RELATING
19 TO COFFEE IN THIS CASE; CORRECT?
20 A CORRECT.
21 Q AND YOU DID NOT REVIEW THE EXPERIMENTAL DATA
22 ON COFFEE AS PART OF YOUR WORK IN THIS CASE; CORRECT?
23 A CORRECT.
24 Q SO CONTINUING ON, THE AUTHORS CONCLUDE --
25 AND THIS IS THE LAST SENTENCE OF DONG, 908 --
26 MR. METZGER: COULD WE HAVE THE COMPLETE SENTENCE
27 READ, NOT JUST A FRAGMENT, YOUR HONOR? IF HE'S GOING TO
28 READ FROM THE ARTICLE, I'D LIKE THE COMPLETE SENTENCE

1 READ.
2 THE COURT: ALL RIGHT. GO AHEAD. COMPLETE
3 SENTENCE. IT'S IN FRONT OF EVERYBODY. GO AHEAD, READ
4 IT, THE COMPLETE SENTENCE.
5 MR. SCHURZ: IF YOUR HONOR WOULD LIKE, I'M HAPPY
6 TO READ THE WHOLE THING.
7 THE COURT: ALL RIGHT.
8 Q BY MR. SCHURZ: (READING:)
9 "ALTHOUGH WELL-DESIGNED STUDIES -- IN
10 PARTICULAR, RANDOMIZED CLINICAL STUDIES AMONG
11 HIGH-RISK POPULATIONS -- ARE NEEDED TO PROVIDE
12 VALUABLE INSIGHTS INTO COFFEE CONSUMPTION AND
13 THE RISK OF PANCREATIC CANCER, OUR META-
14 ANALYSIS, WHICH INCLUDED 14 PROSPECTIVE COHORT
15 STUDIES, CONFIRMED THAT COFFEE CONSUMPTION IS
16 INVERSELY ASSOCIATED WITH THE RISK OF
17 PANCREATIC CANCER."
18 CORRECT?
19 A YES. AND THAT'S WHAT THEIR STUDY SHOWS, AND
20 THAT'S WHAT I'VE INDICATED IN MY SLIDE, THAT -- AND I'LL
21 ALSO DRAW YOUR ATTENTION, THEY SAID THAT RANDOMIZED
22 CLINICAL TRIALS ARE NEEDED TO REALLY ANSWER THE
23 QUESTION. AND THAT IS A POINT THAT I MADE YESTERDAY.
24 Q AND WHAT THE AUTHORS ARE INTERESTED IN HERE
25 IS WHETHER THOSE RANDOMIZED TRIALS WOULD CONFIRM THAT
26 COFFEE EXERTS A PROTECTIVE EFFECT ON THE RISK OF
27 PANCREATIC CANCER, WHICH IS --
28 MR. METZGER: OBJECTION --

1 Q BY MR. SCHURZ: -- WHY THEY STATE:
2 "OUR META-ANALYSIS CONFIRMED THAT COFFEE
3 CONSUMPTION IS INVERSELY ASSOCIATED WITH THE
4 RISK OF PANCREATIC CANCER."
5 CORRECT?
6 MR. METZGER: OBJECTION; ARGUMENTATIVE.
7 THE COURT: OVERRULED.
8 THE WITNESS: I THINK YOU'RE SAYING THIS IS WHAT
9 THE AUTHORS THOUGHT. I DON'T SEE -- I DON'T GET THIS IS
10 WHAT THE AUTHORS THOUGHT FROM WHAT'S IN THIS PARAGRAPH.
11 THEY'RE SAYING THAT THE WAY TO REALLY ANSWER
12 THE QUESTION IS THROUGH RANDOMIZED CLINICAL TRIALS, AND
13 I AGREE WITH THAT.
14 Q BY MR. SCHURZ: AND THEIR DATA, ANALYZED
15 HERE, SHOWED AND DEMONSTRATED THAT COFFEE CONSUMPTION IS
16 INVERSELY ASSOCIATED WITH THE RISK OF PANCREATIC CANCER;
17 CORRECT?
18 MR. METZGER: OBJECTION; ASKED AND ANSWERED.
19 THE WITNESS: YES, AND --
20 THE COURT: OVERRULED.
21 THE WITNESS: -- THAT'S WHAT I INDICATED IN MY
22 SLIDE TOO. I'M NOT DISAGREEING WITH IT, THEIR
23 CONCLUSION.
24 Q BY MR. SCHURZ: OKAY.
25 A THAT INCLUDES ALL OF IT.
26 Q OKAY.
27 A ALL RIGHT.
28 Q LET'S TURN TO THE NEXT META-ANALYSIS THAT

1 YOU RELIED ON, WHICH IS THE YU ANALYSIS, AT EXHIBIT
2 10998.
3 AND DO YOU HAVE EXHIBIT 10998 IN FRONT OF
4 YOU, DR. INFANTE?
5 A YES, I DO.
6 (EXHIBIT 10998 MARKED FOR
7 IDENTIFICATION.)
8 Q BY MR. SCHURZ: AND THIS IS THE FOURTH
9 META-ANALYSIS THAT YOU RELIED ON IN EVALUATING
10 PANCREATIC CANCER AND COFFEE CONSUMPTION; CORRECT?
11 A WELL, IT'S ONE OF THEM THAT I PRESENTED,
12 YES. AGAIN, WHEN YOU SAY "RELIED UPON," I PRESENTED
13 THEM SO I WOULD PRESENT ALL THE DATA.
14 AND THIS STUDY DOES NOT SHOW -- YU DOES NOT
15 SHOW AN INCREASED RISK. IN FACT, THERE'S A SIGNIFICANT
16 REDUCTION. THAT'S INDICATED IN MY SLIDE. I'M NOT
17 DISAGREEING WITH THAT AT ALL.
18 Q YOU'RE NOT DISAGREEING WITH THE YU AUTHORS'
19 CONCLUSION THAT COFFEE EXERTS A PROTECTIVE EFFECT WITH
20 RESPECT TO COFFEE AND PANCREATIC CANCER?
21 MR. METZGER: OBJECTION; ARGUMENTATIVE. THAT'S A
22 DIFFERENT --
23 THE COURT: OVERRULED.
24 THE WITNESS: WELL, I WOULD DISAGREE WITH THAT,
25 YES.
26 Q BY MR. SCHURZ: OKAY. ALL RIGHT.
27 A I'M SAYING THERE'S A SIGNIFICANT REDUCTION.
28 I WOULDN'T SAY THAT THAT INDICATES A PROTECTIVE EFFECT,

1 IN MY OPINION, BECAUSE YOU CAN'T DETERMINE THAT FROM AN
2 OBSERVATIONAL STUDY.
3 Q AND WHAT THE YU AUTHORS CONCLUDED, BASED
4 UPON THEIR REVIEW OF THE COHORT STUDIES RELATED TO
5 PANCREATIC CANCER, IS THAT THERE WAS A STATISTICALLY
6 SIGNIFICANT DECREASED RISK ASSOCIATED WITH COFFEE
7 CONSUMPTION AND PANCREATIC CANCER; CORRECT?
8 A YES. AND THAT'S -- AGAIN, THAT'S WHAT I
9 HAVE IN MY SLIDE. THAT'S WHAT I'VE INDICATED.
10 Q BUT YOU WOULD DISAGREE, ONCE AGAIN, WITH THE
11 YU AUTHORS' CONCLUSION THAT COFFEE APPEARS TO BE
12 ASSOCIATED WITH AN INVERSE ASSOCIATION WITH PANCREATIC
13 CANCER; CORRECT?
14 A WELL, I DON'T KNOW IF THAT'S A CONCLUSION
15 FROM THEIR DATA. THAT'S AN INTERPRETATION OF IT. AND
16 I'M SAYING YOU CAN'T MAKE THAT DETERMINATION FROM AN
17 OBSERVATIONAL STUDY.
18 Q ALL RIGHT. NOW, YOU MENTIONED IARC AND
19 IARC'S EARLIER REVIEW OF PANCREATIC CANCER. AND IF I
20 COULD SHOW YOU IN YOUR DEMONSTRATIVE, WHICH WAS AT SLIDE
21 95, IARC DID HAVE AN ULTIMATE CONCLUSION WITH RESPECT TO
22 PANCREATIC CANCER, DID THEY NOT?
23 A YES.
24 Q AND THE CONCLUSION THAT IARC REPORTED WITH
25 RESPECT TO PANCREATIC CANCER IS THAT:
26 "THERE IS INADEQUATE EVIDENCE IN HUMANS
27 THAT COFFEE-DRINKING IS CARCINOGENIC IN THE
28 PANCREAS."

1 CORRECT?
2 A WELL, I DON'T -- RIGHT. YES, THAT'S WHAT
3 THAT SAYS.
4 Q OKAY. LET'S TALK A LITTLE BIT ABOUT THE
5 COHORT STUDIES THAT YOU REVIEWED RELATING TO PANCREATIC
6 CANCER AND COFFEE CONSUMPTION.
7 NOW, DR. INFANTE, WOULD YOU AGREE THAT THE
8 GREAT MAJORITY OF COHORT STUDIES ON COFFEE CONSUMPTION
9 AND PANCREATIC CANCER DO NOT REPORT AN ELEVATED RISK OF
10 PANCREATIC CANCER ASSOCIATED WITH COFFEE CONSUMPTION?
11 A YES. THE COHORT STUDIES, YOU'RE REFERRING
12 TO?
13 Q YES.
14 A YES.
15 Q SHOWING YOU EXHIBIT 00663. THIS IS THE
16 BHOO-PATHY 2013 STUDY FROM THE EUROPEAN PROSPECTIVE
17 INVESTIGATION INTO NUTRITION AND CANCER, OR ALSO
18 REFERRED TO AS THE EPIC STUDY.
19 AND DR. INFANTE, THIS STUDY WAS INCLUDED
20 AMONG YOUR RELIANCE MATERIALS IN THIS CASE?
21 A YOU KNOW, I DON'T -- I DON'T RECALL THAT
22 BEING IN ONE OF MY SLIDES. SO LET ME TRY TO REFER TO
23 THE SLIDES.
24 (REVIEWS DOCUMENTS.)
25 (EXHIBIT 663 MARKED FOR IDENTIFICATION.)
26 MR. METZGER: YOUR HONOR, I WOULD LIKE THE
27 PREDICATE QUESTION: HAS HE SEEN THIS STUDY? HAS HE
28 READ, REVIEWED, OR CONSIDERED IT?

1 THE COURT: WHAT DID --
2 MR. METZGER: PARDON?
3 THE COURT: WHAT'S YOUR -- WHAT DID YOU SAY,
4 "PREDICATE QUESTION"?
5 MR. METZGER: YEAH, THE FOUNDATIONAL QUESTION:
6 HAS HE READ, REVIEWED, OR CONSIDERED THE STUDY? IT
7 APPEARS TO HAVE BEEN ADVANCE-PUBLISHED. IT'S NOT A
8 FINAL DOCUMENT, AND IT WASN'T IN THE SLIDES. I HAVE A
9 FEELING THAT HE HASN'T SEEN THIS. SO I'D LIKE --
10 THE COURT: AND THAT WAS THE QUESTION, WHETHER HE
11 HAD CONSIDERED IT OR RELIED ON IT.
12 MR. METZGER: WELL, THAT WASN'T THE QUESTION.
13 THAT'S WHAT I'M ASKING THE INITIAL QUESTION BE.
14 MR. SCHURZ: I'M WELL AWARE OF HOW TO LAY A
15 FOUNDATION.
16 THE WITNESS: WELL, I'M REVIEWING MY SLIDES TO SEE
17 IF IT WAS INCLUDED.
18 Q BY MR. SCHURZ: RIGHT.
19 A I DON'T SEE IT ON THERE, NO.
20 Q OKAY. DID YOU REVIEW THIS STUDY?
21 A NO.
22 Q OKAY. I'LL REPRESENT TO YOU THAT THIS IS
23 THE LARGEST STUDY ON PANCREATIC CANCER, IN TERMS OF THE
24 NUMBER OF CASES --
25 MR. METZGER: OBJECTION, YOUR HONOR. 721, VAGUE.
26 HE HASN'T REVIEWED IT; HE CAN'T EXAMINE HIM ABOUT IT.
27 THE COURT: WELL, WE'RE WAITING FOR A QUESTION.
28 MR. METZGER: WELL, HE'S MAKING A REPRESENTATION.

1 I'D LIKE A QUESTION, NOT A REPRESENTATION.
2 MR. SCHURZ: THE FOUNDATION, YOUR HONOR, IS, HERE
3 IS THE LARGEST COHORT STUDY --
4 MR. METZGER: OBJECTION --
5 MR. SCHURZ: -- RELATING TO PANCREATIC CANCER.
6 THE COURT: ALL RIGHT. ASK A QUESTION.
7 Q BY MR. SCHURZ: THIS IS THE LARGEST STUDY
8 RELATING TO PANCREATIC CANCER THAT'S BEEN PUBLISHED;
9 CORRECT?
10 MR. METZGER: OBJECTION; 721(B) --
11 THE WITNESS: I DON'T KNOW. I'D HAVE TO REVIEW --
12 MR. METZGER: HOLD IT; HOLD IT.
13 OBJECTION; 721(B).
14 THE COURT: OVERRULED.
15 MR. METZGER: WHAT? I'M SORRY, YOUR HONOR.
16 THE COURT: THE WITNESS SAID HE DOESN'T KNOW.
17 NEXT QUESTION.
18 Q BY MR. SCHURZ: YOU DID NOT PERFORM A
19 SYSTEMATIC REVIEW OF THE COHORT STUDIES, DID YOU, DR.
20 INFANTE?
21 MR. METZGER: OBJECTION. AS TO PANCREATIC CANCER
22 OR AS TO ALL COHORT STUDIES? WHAT'S THE QUESTION?
23 OBJECTION; VAGUE.
24 THE COURT: ALL RIGHT. THE OBJECTION IS
25 SUSTAINED. REPHRASE YOUR QUESTION, PLEASE.
26 MR. SCHURZ: I'D BE HAPPY TO, YOUR HONOR.
27 Q DR. INFANTE, DID YOU PERFORM A SYSTEMATIC
28 REVIEW OF ALL OF THE COHORT STUDIES RELATING TO COFFEE

1 CONSUMPTION AND PANCREATIC CANCER?
2 A WELL, I'M LOOKING AT -- I BELIEVE THAT I
3 DID.
4 (REVIEWS DOCUMENTS.)
5 LET ME LOOK.
6 (REVIEWS DOCUMENTS.)
7 WELL, IN THE COHORT STUDIES, IF YOU LOOK AT
8 MY SLIDE 119, IT STARTS WITH NOMURA 1981. SO YES, I
9 DID. LOOKS LIKE I MISSED THIS ONE, BUT I -- ONE, TWO,
10 THREE, FOUR...
11 I REVIEWED 21 STUDIES THAT I IDENTIFIED.
12 Q ON THE COHORT STUDIES RELATING TO COFFEE AND
13 PANCREATIC CANCER, YOU DID NOT REVIEW THE BHOO-PATHY
14 POOLED ANALYSIS; CORRECT?
15 MR. METZGER: OBJECTION; ASKED AND ANSWERED.
16 THE WITNESS: CORRECT.
17 MR. SCHURZ: OKAY.
18 THE COURT: OBJECTION OVERRULED.
19 Q BY MR. SCHURZ: SO THIS WAS INCLUDED IN YOUR
20 RELIANCE MATERIALS --
21 MR. METZGER: OBJECTION; LACKING IN FOUNDATION.
22 HE DOESN'T KNOW THAT.
23 THE COURT: OVERRULED.
24 Q BY MR. SCHURZ: CORRECT?
25 MR. METZGER: OBJECTION; LACKING IN FOUNDATION,
26 CALLING FOR SPECULATION.
27 THE COURT: OVERRULED.
28 THE WITNESS: ARE YOU TALKING ABOUT THE BHOO-PATHY

1 STUDY?
2 Q BY MR. SCHURZ: YES.
3 A NO, I DIDN'T REVIEW IT. I APPARENTLY MISSED
4 IT.
5 Q SO THIS WAS PRODUCED TO YOU BY COUNSEL AS
6 PART OF YOUR PREPARATION, AND YOU CHOSE NOT TO REVIEW
7 THIS; CORRECT?
8 MR. METZGER: OBJECTION; LACKING FOUNDATION.
9 THE WITNESS: I DON'T RECALL SEEING THIS. IF I
10 HAD, I WOULD HAVE REVIEWED IT.
11 Q BY MR. SCHURZ: ALL RIGHT. SO YOU'RE NOT --
12 A IF THEY DID PRODUCE IT TO ME, I -- SOMEHOW I
13 OVERLOOKED IT OR MISSED IT. I DIDN'T --
14 THE COURT: ALL RIGHT. THE WITNESS DIDN'T SEE IT
15 OR REVIEW IT. NEXT QUESTION.
16 MR. SCHURZ: OKAY.
17 Q IN FACT, AT THE TIME YOU FORMED YOUR
18 OPINIONS AT YOUR DEPOSITION, YOU'D ONLY REVIEWED IN
19 THEIR ENTIRETY THREE COHORT STUDIES ON COFFEE AND
20 PANCREATIC CANCER; IS THAT CORRECT?
21 A NO, I DON'T -- I DON'T RECALL.
22 Q ALL RIGHT. LET'S TALK --
23 A WELL, WAIT A SECOND. LET ME LOOK. I DON'T
24 THINK THAT'S CORRECT. WELL, WAIT A MINUTE.
25 (REVIEWS DOCUMENTS.)
26 AS OF THE TIME OF MY DEPOSITION, THAT'S
27 CORRECT.
28 Q BY MR. SCHURZ: ALL RIGHT. AT THE TIME YOU

1 FORMED YOUR INITIAL OPINIONS THAT YOU COMMUNICATED AT
2 YOUR DEPOSITION, YOU'D READ THREE OF THE COHORT STUDIES
3 RELATING TO COFFEE CONSUMPTION AND PANCREATIC CANCER IN
4 THEIR ENTIRETY; CORRECT?
5 MR. METZGER: DID I HEAR "IN ENTIRETY" AT THE END?
6 THE COURT: ARE YOU TALKING ABOUT IN REFERENCE TO
7 THIS CASE?
8 MR. SCHURZ: YES.
9 THE WITNESS: WELL, MAYBE I REVIEWED MORE THAN
10 THAT, BUT I HAD DATA IN THE CHART, IN EXHIBIT 227, ON
11 THREE COHORT STUDY RESULTS THAT DEMONSTRATED SIGNIFICANT
12 INCREASES.
13 Q BY MR. SCHURZ: OKAY.
14 A SO SINCE I -- SINCE I HAD LOOKED
15 PRELIMINARILY AT THE DATA AND I HADN'T COMPLETED ALL THE
16 DATA ON THE COHORT STUDIES, I PUT DOWN SOME OF THE
17 RESULTS THAT WERE -- THAT SHOWED SIGNIFICANTLY ELEVATED
18 RISKS, WITH THE INTENTION THEN TO COMPLETE THE REVIEW,
19 WHICH I DID.
20 Q RIGHT. OKAY.
21 A SO HOW MANY I HAD ACTUALLY -- I CERTAINLY
22 HAD LOOKED AT THEM, OR I WOULDN'T HAVE BEEN ABLE TO
23 IDENTIFY THEM THREE OF THEM THAT SHOWED POSITIVE
24 FINDINGS.
25 Q OKAY. LET'S TALK ABOUT THOSE THREE THAT YOU
26 DID REVIEW PRIOR TO YOUR DEPOSITION. AND LET'S START
27 WITH THE HARNACK COHORT STUDY, AT EXHIBIT 1158.
28 AND IF YOU'D LOOK AT THE SCREEN, DR.

1 INFANTE, CAN YOU IDENTIFY THIS DOCUMENT AS THE HARNACK
2 STUDY OF 1997?
3 A YES.
4 (EXHIBIT 1158 MARKED FOR
5 IDENTIFICATION.)
6 Q BY MR. SCHURZ: AND YOU REVIEWED THIS STUDY
7 AS PART OF YOUR WORK IN THIS CASE?
8 A YES.
9 Q AND YOU RELIED ON IT IN FORMING YOUR
10 OPINIONS; CORRECT?
11 A YES.
12 EXCUSE ME, YOUR HONOR. I WONDER IF -- COULD
13 I HAVE A BATHROOM BREAK?
14 THE COURT: DO YOU WANT TO TAKE A RECESS?
15 THE WITNESS: YES.
16 THE COURT: ALL RIGHT. WE'LL TAKE A FIVE-MINUTE
17 RECESS.
18 (RECESS.)
19 THE COURT: BACK ON THE RECORD IN CERT VS.
20 STARBUCKS. COUNSEL ARE PRESENT. DR. INFANTE IS ON THE
21 STAND. MR. SCHURZ WAS INQUIRING.
22 COUNSEL, YOU MAY PROCEED.
23 MR. SCHURZ: THANK YOU, YOUR HONOR.
24 Q BEFORE THE BREAK, DR. INFANTE, WE WERE JUST
25 ABOUT TO DISCUSS THE HARNACK ARTICLE, WHICH IS EXHIBIT
26 1158. DO YOU HAVE THAT IN FRONT OF YOU?
27 A YES.
28 Q AND THIS IS ONE OF THE DOCUMENTS OR ARTICLES

1 YOU RELIED UPON IN FORMING YOUR OPINIONS; CORRECT?
2 A YES.
3 Q AND IF WE TAKE A LOOK AT EXHIBIT 1158, AND
4 GO TO TABLE NO. 4 AT PAGE 0004, WE CAN SEE THE DATA THAT
5 YOU HAVE IDENTIFIED AS INDICATING A STATISTICALLY
6 SIGNIFICANT INCREASE IN RISK FOR CONSUMERS OF OVER 17.5
7 CUPS OF COFFEE PER WEEK.
8 DO YOU HAVE WHAT IS IDENTIFIED AS TABLE
9 NO. 4 ON PAGE 4 OF THE HARNACK ARTICLE IN FRONT OF YOU?
10 A TABLE 4. YES, I DO.
11 Q NOW, IF WE LOOK IMMEDIATELY TO THE RIGHT OF
12 THE VALUES THAT YOU CHOSE TO IDENTIFY, WE SEE A CATEGORY
13 OF "NEVER-SMOKERS"; CORRECT?
14 A YES.
15 Q AND HERE THE HARNACK INVESTIGATORS ANALYZE
16 THE RELATIVE RISK FOR NEVER-SMOKERS IN THE IOWA WOMEN'S
17 HEALTH STUDY; CORRECT?
18 A THEY DID THAT ANALYSIS, YES. AND THEY ALSO
19 DID AN ANALYSIS THAT I RELIED ON THAT SAYS IT'S ADJUSTED
20 FOR CIGARETTE SMOKING, AMONG OTHER FACTORS. BUT THIS IS
21 A DIFFERENT ANALYSIS, AMONG THE NEVER-SMOKERS.
22 Q AND IN THE NEVER-SMOKERS, THE AUTHORS REPORT
23 THAT THERE IS NO STATISTICALLY SIGNIFICANT INCREASE
24 ASSOCIATED WITH COFFEE CONSUMPTION AT THIS LEVEL;
25 CORRECT?
26 A WELL, THEY SHOW A RELATIVE RISK OF 1.74.
27 AND THE LOWER BOUND, AT THE 95 CONFIDENCE INTERVAL, IS
28 .8. SO THAT IS NOT STATISTICALLY SIGNIFICANT.

1 BUT THEN YOU'RE ALSO REDUCING THE NUMBER OF
2 CASES IN HALF IN THAT ANALYSIS. IF YOU LOOK AT THE
3 ANALYSIS THAT I RELIED UPON, YOU'VE GOT 35 CASES. AND
4 IN THAT ANALYSIS, THERE IS AN ADJUSTMENT FOR AGE AND
5 SMOKING STATUS AND PACK-YEARS OF SMOKING.
6 Q AND SMOKING IS A RISK FACTOR FOR PANCREATIC
7 CANCER; CORRECT?
8 A CORRECT. AND THEY'VE ADJUSTED FOR SMOKING
9 IN THE FIRST ANALYSIS. THAT'S A SEPARATE GROUP OF
10 INDIVIDUALS WHO ARE NONSMOKERS.
11 Q AND AS A GENERAL RULE --
12 A IT'S STILL SHOWING AN ELEVATED RISK, EVEN
13 THOUGH IT'S NOT SIGNIFICANT, BUT THAT COULD BE A
14 DIFFERENT POPULATION TOO.
15 Q NOW, DR. INFANTE, YOU INDICATED THAT THE
16 TOTAL COHORT INVOLVES A LARGER GROUP OF CASES; CORRECT?
17 A YES.
18 Q AND --
19 A WELL, IT'S TWICE AS MANY. YOU'VE GOT 35
20 VERSUS 17 AMONG THE NONSMOKERS.
21 Q RIGHT. AND THE FACT THAT IT HAS MORE CASES
22 GIVES THE UNDERLYING VALUES GREATER STABILITY AND LOWER
23 CONFIDENCE INTERVALS; CORRECT -- OR NARROWER CONFIDENCE
24 INTERVALS; CORRECT?
25 A WELL, THAT'S A CONSEQUENCE OF THE LARGER
26 NUMBERS.
27 Q RIGHT. AND SINCE THE HARNACK 1997 ARTICLE,
28 THERE'S BEEN A FURTHER ANALYSIS, AN UPDATE OF THE IOWA

1 WOMEN'S HEALTH STUDY, AS IT RELATES TO COFFEE
2 CONSUMPTION AND PANCREATIC CANCER, HASN'T THERE?
3 A WELL, I DON'T KNOW -- I DON'T RECALL. IS IT
4 ONE OF THE -- IS THERE ONE OF THE OTHERS THAT I REVIEWED
5 THAT IS AN UPDATE?
6 Q DO YOU KNOW?
7 A I DON'T RECALL.
8 Q OKAY. TAKE A LOOK, IF YOU WOULD, AT THE
9 GENKINGER ANALYSIS, WHICH WE WERE DISCUSSING EARLIER --
10 AT EXHIBIT 1072, WHICH YOU HAVE IN FRONT OF YOU.
11 A (ATTEMPTS TO LOCATE DOCUMENT.)
12 Q AND DO YOU HAVE EXHIBIT 1072 IN FRONT OF
13 YOU?
14 A THAT'S WHAT I'M LOOKING TO SEE. YES, I DO.
15 Q OKAY. TAKE A LOOK AT TABLE NO. 1 OF EXHIBIT
16 1072, AT PAGE 003.
17 A WHAT PAGE, ZERO --
18 Q 03.
19 A 03.
20 Q AND I'M LOOKING AT TABLE NO. 1. AND DO YOU
21 HAVE THAT IN FRONT OF YOU?
22 A YES.
23 Q AND DIRECTING YOUR ATTENTION TO THE TABLE
24 WHICH LISTS -- IN THE COLUMN THAT LISTS COHORTS, DO YOU
25 SEE THE INITIALS OR THE ACRONYM FOR THE IOWA WOMEN'S
26 HEALTH STUDY THERE, THAT APPEARS AS THE FIFTH ROW?
27 A YES.
28 Q AND DID YOU REVIEW, DR. INFANTE, THE

1 GENKINGER UPDATED ANALYSIS WITH RESPECT TO THE DATA OF
2 THE IOWA WOMEN'S HEALTH STUDY IN TERMS OF PANCREATIC
3 CANCER AND COFFEE CONSUMPTION?
4 A NO. I THINK I HAVE IT IN THE META-ANALYSIS
5 SECTION.
6 Q AND AT THE TIME THAT THE GENKINGER ANALYSIS
7 WAS PERFORMED IN 2012, THERE WERE, IN FACT, 166 CASES
8 THAT ARE REPORTED OUT OF THE IOWA WOMEN'S HEALTH STUDY;
9 CORRECT?
10 A YES.
11 Q AND WITH RESPECT TO THE VALUES THAT ARE
12 REPORTED HERE -- AND I'LL DIRECT YOUR ATTENTION TO PAGE
13 7 OF THE STUDY, AND FIGURE NO. 1. AND HERE WE'RE GOING
14 TO LOOK SPECIFICALLY AT THE TOP, WHICH IS RELATING TO
15 COFFEE, WHICH IS AT A.
16 AND DO YOU HAVE TABLE 1?
17 A FIGURE 1?
18 Q EXCUSE ME. DO YOU HAVE FIGURE 1, SECTION A,
19 IN FRONT OF YOU?
20 A RIGHT.
21 Q AND HERE THE GENKINGER INVESTIGATORS REPORT
22 THE RELATIVE RISK AND CONFIDENCE INTERVALS FOR THE IOWA
23 WOMEN'S HEALTH STUDY OF THE 166 CASES THAT WERE
24 ANALYZED; CORRECT?
25 A THAT'S WHAT I'M LOOKING FOR. WHERE IS IT
26 UNDER -- A, B, OR C?
27 Q IT'S A, AND IT'S -- A RELATES TO COFFEE.
28 A (REVIEWS DOCUMENT.)

1 THIS RELATES TO COFFEE? WHERE DOES IT SAY
2 THAT?
3 Q AT THE BOTTOM.
4 A OKAY.
5 (REVIEWS DOCUMENT.)
6 Q SO WOULD YOU AGREE, DR. INFANTE, THAT THE
7 UPDATED REVIEW OF THE IOWA WOMEN'S HEALTH STUDY
8 PERFORMED BY GENKINGER SHOWED A STATISTICALLY
9 SIGNIFICANT DECREASED RISK OF PANCREATIC CANCER BEING
10 REPORTED OUT OF THE IOWA WOMEN'S HEALTH STUDY, BASED ON
11 166 CASES?
12 A WELL, I CAN'T TELL FROM THAT FIGURE. I
13 CAN'T TELL WHERE THE BAR STOPS. MAYBE WE COULD LOOK
14 AT -- ARE THESE DATA REPRESENTED IN A TABLE?
15 Q WELL, WOULD YOU AGREE WITH ME --
16 UNDERSTANDING THAT IT'S DIFFICULT TO DISCERN EXACTLY
17 WHERE THAT CONFIDENCE INTERVAL IS -- THAT IT REFLECTS A
18 SUBSTANTIALLY REDUCED RISK OF PANCREATIC CANCER IN
19 COFFEE CONSUMPTION BEING REPORTED OUT OF THE IOWA
20 WOMEN'S HEALTH STUDY FOR 166 CASES?
21 A WELL, THE DATA THAT I REPORTED WAS AMONG
22 POSTMENOPAUSAL WOMEN. ARE THESE POSTMENOPAUSAL WOMEN,
23 OR ARE THESE MORE WOMEN FROM THE IOWA STUDY? IT COULD
24 BE A DIFFERENT POPULATION.
25 Q THIS IS THE ENTIRE POPULATION OF THE IOWA
26 WOMEN'S HEALTH STUDY.
27 A WELL, IF IT'S THE ENTIRE POPULATION, THEN IT
28 DOESN'T CONTRADICT WHAT I HAVE IN MY SLIDE, BECAUSE THE

1 DATA I PRESENTED WAS FOR POSTMENOPAUSAL WOMEN.
2 Q YOU CHOSE A SUBGROUP ANALYSIS OF A MUCH
3 SMALLER GROUP OF CASES; CORRECT?
4 A I WAS SHOWING WHAT THE RISK WAS AMONG
5 POSTMENOPAUSAL WOMEN. AND IN FACT, IT SHOWS A
6 SIGNIFICANT DOSE RESPONSE IN A '97 STUDY. I DON'T SEE
7 THAT THEY EVALUATED THESE DATA FOR DOSE RESPONSE, AND I
8 DON'T SEE AN EVALUATION FOR POSTMENOPAUSAL WOMEN.
9 SO THEY'RE DIFFERENT ANALYSES, AND IT'S A --
10 THEY DON'T INCLUDE A SEPARATE ANALYSIS FOR
11 POSTMENOPAUSAL WOMEN, WHICH IS WHAT I CITED ON SLIDE
12 119.
13 Q MY QUESTION, DR. INFANTE: WOULD YOU AGREE
14 THAT THE REPORT OUT FROM GENKINGER OF THE IOWA WOMEN'S
15 HEALTH STUDY THAT'S INCLUDED IN THE 2012 ANALYSIS
16 REFLECTS A DECREASED RISK ASSOCIATED WITH COFFEE
17 CONSUMPTION AND PANCREATIC CANCER?
18 A AMONG ALL WOMEN, YES. BUT IT DOESN'T ANSWER
19 THE QUESTION ABOUT POSTMENOPAUSAL WOMEN, WHAT THEIR RISK
20 IS --
21 Q OKAY.
22 A -- WHICH IS WHAT I CITED IN MY SLIDE 119.
23 Q LET'S TALK ABOUT SOME OF THE OTHER COHORT
24 STUDIES, THE TWO OTHER COHORT STUDIES THAT YOU REVIEWED
25 IN THEIR ENTIRETY PRIOR TO YOUR DEPOSITION.
26 AND LET'S START WITH THE NILSSON STUDY.
27 IT'S EXHIBIT 1644. AND WE'LL GET YOU A HARD COPY. BUT
28 BASED UPON WHAT YOU SEE IN FRONT OF THE SCREEN, DO YOU

1 RECOGNIZE THIS AS THE NILSSON 2010 STUDY?
2 A YES.
3 (EXHIBIT 1644 MARKED FOR
4 IDENTIFICATION.)
5 Q BY MR. SCHURZ: AND YOU REVIEWED THIS STUDY
6 AS PART OF YOUR WORK IN THIS CASE?
7 A YES.
8 Q AND YOU RELIED ON THIS STUDY IN FORMING YOUR
9 OPINIONS WITH RESPECT TO PANCREATIC CANCER AND COFFEE
10 CONSUMPTION; CORRECT?
11 A YES. I MEAN, WHEN YOU ASK ME IF I RELY ON
12 THE STUDY, I DON'T KNOW EXACTLY WHAT YOU MEAN WHEN YOU
13 SAY "RELY" ON IT, BECAUSE I PRESENTED STUDIES THAT HAD
14 NEGATIVE FINDINGS TOO.
15 SO YOU WANT TO SAY, "WELL, YOU RELIED ON A
16 STUDY THAT SHOWS -- THAT DOESN'T SHOW ANY INCREASED
17 RISK." I REVIEWED ALL OF THE INFORMATION. I CONSIDERED
18 BOTH POSITIVE AND NEGATIVE STUDIES IN DRAWING MY
19 CONCLUSION.
20 SO I WOULDN'T SAY THAT I DREW AN
21 INTERPRETATION OF THE DATA --
22 THE COURT: ALL RIGHT. THAT'S ENOUGH. WE DON'T
23 NEED A LONG FILIBUSTER.
24 DID YOU CONSIDER THE STUDY?
25 THE WITNESS: YES.
26 THE COURT: ALL RIGHT. LET'S PROCEED.
27 MR. SCHURZ: I'LL USE THAT TERMINOLOGY SINCE
28 "RELY" SEEMS TO BE CAUSING PROBLEMS.

1 Q LET ME DIRECT YOU IN EXHIBIT 1644 TO TABLE
2 NO. 3, AT PAGE 0006.
3 A (ATTEMPTS TO LOCATE DOCUMENT.)
4 Q AND DO YOU HAVE TABLE 3 IN FRONT OF YOU?
5 A 06?
6 Q YES.
7 A TABLE 3. YES, I DO.
8 Q OKAY. AND IF WE LOOK AT THE RESULTS FOR
9 PANCREATIC CANCER IN THIS TABLE, WHICH APPEARS TOWARDS
10 THE BOTTOM, THERE IS NO STATISTICALLY SIGNIFICANT
11 ASSOCIATION BETWEEN TOTAL COFFEE CONSUMPTION AND
12 PANCREATIC CANCER; CORRECT?
13 A YES. THE MULTIVARIANT ANALYSIS SHOWS 1.5,
14 AND THE CONFIDENCE INTERVAL IS BETWEEN .57 AND 3.92.
15 Q OKAY.
16 A AND I HAVE THOSE DATA IN MY SLIDES.
17 Q AND LET'S TAKE A LOOK AT TABLE NO. 5, WHICH
18 IS AT PAGE 10.
19 A (REVIEWS DOCUMENT.)
20 Q AND HERE WE SEE THE DATA THAT'S PROVIDED FOR
21 BOILED COFFEE. DO YOU SEE THAT?
22 A YES.
23 Q AND THIS IS WHERE THE AUTHORS FOUND SOME
24 POSITIVE STATISTICALLY SIGNIFICANT ASSOCIATION; CORRECT?
25 A YES, THEY DID.
26 Q SO THEY'VE REPORTED SIGNIFICANT ASSOCIATION
27 BETWEEN COFFEE CONSUMPTION AND PANCREATIC CANCER, WAS
28 WITH BOILED COFFEE; CORRECT?

1 A YES, AND THAT'S WHAT'S INDICATED IN MY
2 SLIDE. I HAVE THE RESULTS FOR TOTAL COFFEE AND BOILED
3 COFFEE.
4 Q WHAT IS BOILED COFFEE, AS IT'S ANALYZED HERE
5 IN THE NILSSON STUDY?
6 A I ASSUME IT'S COFFEE THAT WAS BOILED,
7 WHEREAS THE TOTAL COFFEE WOULD BE COFFEE CONSUMPTION
8 REGARDLESS OF HOW IT WAS PREPARED.
9 THE COURT: IS THERE A DISTINCTION BETWEEN BOILED
10 COFFEE AND BREWED COFFEE?
11 MR. SCHURZ: YES, THERE IS, YOUR HONOR. AS IT'S
12 ANALYZED BY THESE AUTHORS, THERE IS A DISTINCTION.
13 THE COURT: OKAY.
14 Q BY MR. SCHURZ: DIRECTING YOUR ATTENTION TO
15 PAGE 2 OF EXHIBIT 1644. AND IF I COULD DIRECT YOUR
16 ATTENTION TO -- IT'S THE THIRD PARAGRAPH ON THE RIGHT --
17 EXCUSE ME, LEFT-HAND SIDE. DO YOU SEE THAT?
18 A YES.
19 Q AND THE AUTHORS HERE DESCRIBE WHAT THEY'RE
20 REFERRING TO AS "SCANDINAVIAN BOILED COFFEE." DO YOU
21 SEE THAT?
22 A YES.
23 Q AND THE AUTHORS REPORT:
24 "SCANDINAVIAN BOILED COFFEE -- ONCE VERY
25 COMMON ACROSS SWEDEN, BUT NOW LIMITED
26 PRIMARILY TO THE LARGE RURAL AREAS OF NORTHERN
27 SWEDEN -- IS PREPARED BY HEATING A MIXTURE OF
28 COARSELY GROUND COFFEE BEANS AND WATER TO A

1 BOIL, WHICH RESULTS IN HIGH DITERPENE
2 CONCENTRATION."
3 DO YOU SEE THAT?
4 A YES.
5 Q OKAY. SO YOUR OBSERVATIONS WITH RESPECT TO
6 THE POSITIVE ASSOCIATION ARE PREDICATED ON THE
7 SCANDINAVIAN BOILED COFFEE AS OPPOSED TO THE BREWED
8 COFFEE VALUES THAT THE NILSSON INVESTIGATORS REPORTED;
9 CORRECT?
10 A I REPORTED THE RESULTS OF BOTH.
11 Q NOW, LET'S TAKE A LOOK AT THE THIRD COHORT
12 STUDY THAT YOU REVIEWED PRIOR TO YOUR DEPOSITION, AND
13 THAT WAS THE LIN COHORT STUDY, COMING OUT OF JAPAN. AND
14 SHOWING YOU NOW WHAT IS EXHIBIT 1446.
15 AND DO YOU HAVE EXHIBIT 1446 IN FRONT OF
16 YOU?
17 A YES, I DO.
18 (EXHIBIT 1446 MARKED FOR
19 IDENTIFICATION.)
20 Q BY MR. SCHURZ: DID YOU CONSIDER THIS
21 DOCUMENT?
22 A YES.
23 Q OKAY. AND LET'S LOOK AT THE DATA THAT THE
24 AUTHORS REPORT. AND IF I COULD DIRECT YOUR ATTENTION TO
25 PAGE 3 OF EXHIBIT 1446. WE'RE GOING TO TAKE A LOOK AT
26 TABLE ROMAN NUMERAL II. AND DO YOU HAVE THAT IN FRONT
27 OF YOU?
28 A YES.

1 Q OKAY. NOW, LET ME DIRECT YOUR ATTENTION
2 FIRST TO THE RIGHT-HAND SIDE OF TABLE NO. II OF EXHIBIT
3 1446, WHICH PROVIDES THE VALUES FOR FEMALES. DO YOU SEE
4 THAT?
5 A YES.
6 Q AND THE LIN INVESTIGATORS REPORT THERE IS NO
7 STATISTICALLY SIGNIFICANT ASSOCIATION BETWEEN COFFEE
8 CONSUMPTION AT ANY AMOUNT AND PANCREATIC CANCER IN
9 FEMALES; CORRECT?
10 A YEAH, AND THAT'S WHAT I REPORTED IN MY
11 SLIDE.
12 Q AND TURNING TO THE MALES ON THE -- NOW ON
13 THE LEFT-HAND SIDE OF THE TABLE, THERE IS NO
14 STATISTICALLY SIGNIFICANT ASSOCIATION BETWEEN PANCREATIC
15 CANCER IN MALES AND COFFEE CONSUMPTION AT ANYWHERE
16 BETWEEN ONE TO TWO CUPS PER MONTH AND TWO TO THREE CUPS
17 PER DAY; CORRECT?
18 A YES. THAT'S MORE THAN FOUR CUPS PER DAY.
19 Q RIGHT. AND SO LIN SHOWS A STATISTICALLY
20 SIGNIFICANT POSITIVE ASSOCIATION BETWEEN COFFEE
21 CONSUMPTION AND PANCREATIC CANCER IN ONE OUT OF THE TEN
22 CATEGORIES OF CONSUMPTION INVESTIGATED; CORRECT?
23 A WHAT WAS THE LAST PHRASE YOU ADDED ON? I
24 DIDN'T FOLLOW, WITH THE --
25 Q SURE. THE LIN ANALYSIS SHOWS A
26 STATISTICALLY SIGNIFICANT POSITIVE ASSOCIATION BETWEEN
27 COFFEE CONSUMPTION AND PANCREATIC CANCER IN ONLY ONE OUT
28 OF THE TEN EXPOSURE CATEGORIES EVALUATED BY THESE

1 AUTHORS; CORRECT?
2 A WELL, I DIDN'T COUNT THE NUMBER OF EXPOSURE
3 CATEGORIES, BUT IN THE HIGHEST EXPOSURE CATEGORY, THEY
4 HAVE A SIGNIFICANTLY INCREASED RISK OF PANCREATIC
5 CANCER. AND THAT'S ADJUSTED FOR CIGARETTE SMOKING ALSO.
6 Q IN MEN AND NOT IN WOMEN; CORRECT?
7 A CORRECT. YES.
8 Q YES. AND THERE WAS NO DOSE RESPONSE IN
9 EITHER MALES OR FEMALES OBSERVED IN THE LIN 2002 STUDY;
10 CORRECT?
11 A WHERE -- YOU KNOW, I DON'T -- I'M GOING TO
12 HAVE TO LOOK AT THE DATA THERE, ANALYSES AND DOSE
13 RESPONSE.
14 Q OKAY. I DON'T WANT TO TAKE THE TIME TO DO
15 THAT. IF YOU DON'T KNOW, WE'LL MOVE ON.
16 I'D LIKE TO TURN, THEN, TO A NEW CATEGORY OF
17 THE MATERIALS YOU ANALYZED WITH RESPECT TO COFFEE
18 CONSUMPTION AND PANCREATIC CANCER AND SPECIFICALLY TALK
19 ABOUT THE CASE CONTROLS THAT YOU LOOKED AT.
20 A THE CASE-CONTROL STUDIES?
21 Q YES.
22 A OKAY.
23 Q NOW, I'D LIKE TO DISCUSS SOME OF THE
24 SPECIFIC CASES YOU IDENTIFIED IN YOUR ANALYSIS.
25 BUT AS A THRESHOLD MATTER, YOU DID NOT
26 SEGREGATE OUT, IN YOUR ANALYSIS OF THE CASE-CONTROL
27 STUDIES, THOSE STUDIES THAT FAILED TO ADJUST FOR TOBACCO
28 USE; CORRECT?

1 A (REVIEWS DOCUMENT.)
2 I DON'T HAVE THEM ON MY SLIDE. I'D HAVE TO
3 LOOK THROUGH MY NOTES TO SEE WHICH ONES INDICATE THAT,
4 IF I INDICATED IT --
5 Q ALL RIGHT.
6 A -- WHICH IS EXHIBIT 227.
7 Q AND AS WE TALKED ABOUT BEFORE, TOBACCO AND
8 SMOKING IS A RISK FACTOR FOR PANCREATIC CANCER; CORRECT?
9 A YES.
10 Q SO AS A GENERAL RULE, YOU WOULD WANT TO
11 FOCUS ON THOSE STUDIES THAT HAVE MADE AN ADJUSTMENT FOR
12 SMOKING IN THEIR ANALYSIS OF PANCREATIC CANCER AND
13 COFFEE CONSUMPTION; CORRECT?
14 A YEAH, OR NEVER-SMOKERS.
15 Q OKAY. ALL RIGHT.
16 A YEAH, THEY'RE TWO DIFFERENT GROUPS.
17 Q ALL RIGHT. SO LET'S TALK ABOUT A COUPLE
18 OF -- JUST A COUPLE OF EXAMPLES.
19 LET ME FIRST ASK YOU TO TAKE A LOOK AT THE
20 WYNDER STUDY FROM 1986, WHICH IS EXHIBIT 10983. AND YOU
21 CONSIDERED THIS STUDY IN FORMING YOUR OPINIONS, DR.
22 INFANTE?
23 A YES. I CONSIDERED ALL THE STUDIES IN THESE
24 SLIDES IN FORMING MY OPINIONS.
25 (EXHIBIT 10983 MARKED FOR
26 IDENTIFICATION.)
27 Q BY MR. SCHURZ: OKAY. AND YOU CITE THIS
28 STUDY AS EVIDENCE OF AN ASSOCIATION BETWEEN COFFEE

1 CONSUMPTION AND PANCREATIC CANCER; CORRECT?
2 A YES. IN FEMALES.
3 Q ALL RIGHT. NOW, LET ME DIRECT YOUR
4 ATTENTION TO THE AUTHORS' CONCLUSIONS; AND SPECIFICALLY,
5 AT PAGE 0004 OF EXHIBIT 10983.
6 A (REVIEWS DOCUMENT.)
7 Q AND IT'S THE FIRST FULL PARAGRAPH THAT
8 APPEARS ON THE LEFT-HAND SIDE, LEFT-HAND COLUMN. DO YOU
9 HAVE THAT IN FRONT OF YOU?
10 A YES.
11 Q AND THE AUTHORS OF THE WYNDER STUDY OBSERVE:
12 "THE FINDINGS OF THE PRESENT STUDY
13 SUGGEST THAT DECAFFEINATED COFFEE CONSUMPTION
14 IS NOT A FACTOR IN THE ETIOLOGY OF PANCREATIC
15 CANCER IN HUMANS."
16 DO YOU SEE THAT?
17 A THAT'S WHAT THEY'RE SAYING THERE, YES.
18 Q AND THE AUTHORS FIND THAT THERE'S NO
19 EVIDENCE OF A DOSE RESPONSE; CORRECT?
20 A WELL, LET ME READ IT.
21 (REVIEWS DOCUMENT.)
22 YES. AND THEY'RE SAYING THAT BECAUSE THEY
23 DIDN'T FIND IT IN MEN, THEY ONLY FOUND IT IN WOMEN, THAT
24 THE TWO RESULTS CANCEL EACH OTHER OUT.
25 Q AND THE ABSENCE OF A DOSE RESPONSE AND THE
26 FAILURE TO REPLICATE IN MEN AND WOMEN LEADS THEM TO
27 CONCLUDE THAT:
28 "THE ELEVATED RISK FOUND IN THE SUBGROUP

1 OF WOMEN ARGUES AGAINST A CAUSATIVE
2 RELATIONSHIP BETWEEN DECAFFEINATED COFFEE-
3 DRINKING AND PANCREATIC CANCER."
4 CORRECT?
5 A WELL, THAT'S THEIR INTERPRETATION OF IT, BUT
6 I DON'T RECALL THAT THEY DID AN ANALYSIS TO SHOW THAT.
7 I MEAN, THEY HAVE DIFFERENT RESULTS FOR MEN AND WOMEN.
8 SO SINCE THEY DID, THEY SAID, "WELL, ONE CANCELS THE
9 OTHER OUT." SO I DON'T AGREE.
10 THE COURT: IS THERE A COMPARABLE STUDY WITH
11 REGARD TO CAFFEINATED COFFEE?
12 MR. SCHURZ: THERE ARE A NUMBER OF THEM.
13 THE COURT: I MEAN, BY THE SAME --
14 MR. SCHURZ: OH, BY THE WYNDER INVESTIGATORS? NO,
15 NOT THAT I'M AWARE OF, YOUR HONOR.
16 THE COURT: ALL RIGHT.
17 Q BY MR. SCHURZ: ALL RIGHT. LET'S TAKE A
18 LOOK AT ANOTHER OF THE CASE-CONTROL STUDIES THAT YOU
19 IDENTIFIED; AND SPECIFICALLY, THE GHADIRIAN 1990
20 ARTICLE, AT EXHIBIT 1082.
21 AND DO YOU SEE THE GHADIRIAN ARTICLE,
22 EXHIBIT 1082, IN FRONT OF YOU?
23 A YES.
24 (EXHIBIT 1082 MARKED FOR
25 IDENTIFICATION.)
26 Q BY MR. SCHURZ: AND DID YOU CONSIDER THE
27 GHADIRIAN ARTICLE IN DEVELOPING YOUR OPINIONS IN THIS
28 CASE?

1 A YES.
2 Q ALL RIGHT. DIRECTING YOUR ATTENTION TO PAGE
3 1, AND JUST FOCUSING ON THE ABSTRACT OF THE GHADIRIAN
4 PAPER, EXHIBIT 1082; AND SPECIFICALLY, THE LAST
5 SENTENCE, WHERE THE AUTHORS OBSERVE:
6 "COFFEE DRINKERS WERE COLLECTIVELY AT
7 LOWER RISK THAN NONDRINKERS, PARTICULARLY WHEN
8 COFFEE WAS CONSUMED WITH MEALS, NOT ON AN
9 EMPTY STOMACH."
10 DO YOU SEE THAT?
11 A YES.
12 Q YOU RELY ON THIS STUDY AS EVIDENCE OF AN
13 ASSOCIATION BETWEEN COFFEE CONSUMPTION AND AN INCREASED
14 RISK OF PANCREATIC CANCER; CORRECT?
15 A FOR DECAFFEINATED COFFEE ONLY.
16 Q OKAY.
17 A I HAVE THE RESULTS FOR THE REGULAR COFFEE
18 AND TOTAL COFFEE IN MY SLIDE, AND I INDICATE WHAT THEY
19 ARE.
20 Q ALL RIGHT. AND DID YOU CONSIDER THE
21 AUTHORS' CONCLUSIONS AS YOU INTERPRETED THEIR DATA?
22 A NO, I DON'T CONSIDER CONCLUSIONS WHEN I
23 INTERPRET THE DATA. I EVALUATE THE DATA -- OR I
24 INTERPRET THE DATA.
25 Q LET'S TURN --
26 A THE INTERPRETATION IS A MATTER OF THEIR
27 PERSONAL INTERPRETATION.
28 Q OKAY. LET'S TURN TO ANOTHER CASE-CONTROL

1 STUDY YOU REVIEWED AND INCLUDED AMONG YOUR MATERIALS.
2 AND THAT'S THE SILVERMAN STUDY, EXHIBIT 1949.
3 A WHAT YEAR?
4 Q AND THIS IS AN ARTICLE FROM 1998.
5 AND DID YOU CONSIDER THIS ARTICLE IN FORMING
6 YOUR OPINIONS IN THIS MATTER?
7 A YES. I CONSIDERED ALL OF THE LITERATURE.
8 (EXHIBIT 1949 MARKED FOR
9 IDENTIFICATION.)
10 Q BY MR. SCHURZ: AND YOU -- SPECIFICALLY, YOU
11 RELY ON IT AS EVIDENCE OF A STATISTICALLY SIGNIFICANT
12 ELEVATED RISK AMONG AFRICAN-AMERICANS, COFFEE DRINKERS,
13 AND PANCREATIC CANCER; CORRECT?
14 A YES.
15 Q ARE YOU FAMILIAR WITH HOW THE SILVERMAN
16 AUTHORS INTERPRET THEIR OWN DATA?
17 A WELL, I HAVEN'T READ THEIR INTERPRETATION,
18 BUT I PRESENT -- IN MY SLIDE, I PRESENT THE DATA FOR
19 MALES AND FEMALES, WHITES AND BLACKS.
20 Q NOW, LET ME DIRECT YOU TO PAGE 8 OF THE
21 EXHIBIT 1949. ON THE LEFT-HAND COLUMN, IT'S THE SECOND
22 FULL PARAGRAPH. AND DO YOU HAVE THAT IN FRONT OF YOU?
23 A YES.
24 Q ALL RIGHT. AND THE SILVERMAN AUTHORS
25 OBSERVE:
26 "NUMEROUS STUDIES OF PANCREATIC CANCER
27 HAVE EXAMINED THE RELATIONSHIP BETWEEN COFFEE-
28 DRINKING AND PANCREATIC CANCER RISK. ALTHOUGH

1 RESULTS OF MOST STUDIES DO NOT SUPPORT AN
2 ASSOCIATION, POSITIVE FINDINGS FROM A SMALL
3 NUMBER OF STUDIES HAVE RAISED THE POSSIBILITY
4 OF A WEAK ASSOCIATION FOR HEAVY COFFEE
5 DRINKING.
6 "HOWEVER, THERE IS A GENERAL CONSENSUS
7 THAT ANY WEAK EFFECT IS LIKELY TO BE A RESULT
8 OF RESIDUAL CONFOUNDING BY SMOKING OR OTHER
9 SOURCES OF CONFOUNDING OR BIAS. OUR RESULTS
10 ARE CONSISTENT WITH THIS VIEW."
11 DO YOU SEE THAT?
12 A YES.
13 Q AND I TAKE IT THAT YOU DO NOT CONCUR WITH
14 THE SILVERMAN AUTHORS' OBSERVATION THAT THE WEAK
15 ASSOCIATION IS ATTRIBUTABLE TO RESIDUAL CONFOUNDING FROM
16 TOBACCO; CORRECT?
17 A WELL, THAT'S THEIR INTERPRETATION. I MEAN,
18 THEY CITE TWO SOURCES FOR THAT.
19 Q ALL RIGHT. NOW, LET'S TAKE A LOOK AT THEIR
20 ANALYSIS OF THE -- THAT YOU HAVE RELIED ON IN THIS CASE,
21 WHICH WE CAN FIND AT PAGE 7. AND IT'S TABLE NO. 6. I'M
22 SORRY, IT'S PAGE -- STRIKE THAT. IT'S NOT -- IT'S PAGE
23 6.
24 A ARE WE STILL ON SILVERMAN?
25 Q WE ARE, AND PAGE 6 OF THAT STUDY. LET ME
26 KNOW WHEN YOU'RE THERE.
27 A OKAY.
28 Q NOW, YOU'VE INDICATED AND REPORTED DATA WITH

1 RESPECT TO THE -- WITH RESPECT TO AFRICAN-AMERICAN
2 COFFEE DRINKERS; CORRECT?
3 A THAT'S INCORRECT. I PRESENTED THE DATA FOR
4 WHITES AND AFRICAN-AMERICANS AND MALES AND FEMALES.
5 Q AND YOU CITE THE EVIDENCE WITH RESPECT TO
6 AFRICAN-AMERICANS AS PART OF YOUR EVIDENCE OF A
7 STATISTICALLY SIGNIFICANT ELEVATED RISK; CORRECT?
8 A IT WAS BORDERLINE.
9 Q OKAY. AND WHEN THE SILVERMAN AUTHORS
10 PERFORMED AN ANALYSIS AMONG AFRICAN-AMERICAN NONSMOKERS,
11 THE ODDS RATIO AS REPORTED IN THIS ARTICLE WAS 1.0, WITH
12 A CONFIDENCE INTERVAL OF 0.4 TO 2.6; CORRECT?
13 A YES. AMONG NONSMOKERS; CORRECT.
14 Q ALL RIGHT. SO UNDER THE -- THE SILVERMAN
15 DATA SHOWS NO INCREASED RISK WHATSOEVER FOR AFRICAN-
16 AMERICAN NONSMOKERS, AS REPORTED BY THE AUTHORS;
17 CORRECT?
18 A YES, AMONG NONSMOKERS. BECAUSE YOU HAVE TO
19 LOOK AND SEE IF THE OTHER ANALYSES WERE ADJUSTED FOR
20 SMOKING. BECAUSE, I MEAN, QUITE A LARGE PORTION OF THE
21 POPULATION SMOKES.
22 SO IF YOU HAVE A POSITIVE FINDING IN
23 NONSMOKERS, THAT ADDS CONSIDERABLE EVIDENCE; BUT IF YOU
24 DON'T, THAT ADDS SOME EVIDENCE. BUT ON THE OTHER HAND,
25 A LARGE PORTION OF THE POPULATION SMOKES, SO THERE'S
26 SOME INTERACTION WITH THAT.
27 AND THE QUESTION IS, WHO IS THE BEST GROUP
28 TO STUDY? AND A LOT OF THESE STUDIES, THEY ADJUST FOR

1 CIGARETTE SMOKING AND FIND SIGNIFICANT ASSOCIATIONS.
2 AND THEN YOU POINTED OUT, WELL, THERE WERE
3 SOME OF NONSMOKERS THAT THEY DIDN'T FIND AN ASSOCIATION,
4 AND THAT'S IMPORTANT ALSO.
5 AND THEN IT'S A QUESTION OF, WELL, WHICH IS
6 THE CORRECT ANALYSIS TO LOOK AT, IF YOU'RE LOOKING AT
7 RISK FROM COFFEE CONSUMPTION TO THE GENERAL POPULATION?
8 IS IT THAT THERE'S NO RISK FOR NONSMOKERS, SO YOU
9 SHOULDN'T SMOKE IF YOU'RE GOING TO DRINK COFFEE?
10 IN OTHER WORDS, IT'S A QUESTION OF WHAT'S
11 THE -- WHAT'S THE APPROPRIATE ANALYSIS TO LOOK AT COFFEE
12 RISK FOR THIS CANCER IN THE GENERAL POPULATION.
13 Q AND WOULD YOU AGREE, DR. INFANTE, THAT IN
14 LOOKING AT THE PANCREATIC CANCER EPIDEMIOLOGY, IT'S
15 IMPORTANT TO LOOK AT THOSE STUDIES THAT HAVE MADE
16 ADJUSTMENTS FOR SMOKING AND TOBACCO USE?
17 A YES.
18 Q OKAY. LET'S TURN NOW AND TALK TO SOME OF
19 YOUR OPINIONS AS IT RELATES TO BLADDER CANCER.
20 THE COURT: IF YOU'RE GOING TO SWITCH TO ANOTHER
21 SUBJECT, LET ME JUST INTERRUPT FOR A MOMENT. PLEASE
22 STAY IN YOUR SEATS.
23 (OTHER MATTER HEARD.)
24 THE COURT: BACK ON THE RECORD IN CERT VS.
25 STARBUCKS.
26 MR. SCHURZ.
27 MR. SCHURZ: THANK YOU, YOUR HONOR.
28 Q DR. INFANTE, I'D LIKE TO NOW TURN TO THE

1 OPINIONS THAT YOU HAVE OFFERED WITH RESPECT TO BLADDER
2 CANCER. AND SPECIFICALLY, LET'S START WITH THE
3 META-ANALYSES THAT YOU SUMMARIZED IN YOUR DEMONSTRATIVE
4 AT 106, AND THEN IT CONTINUES ON AT 107. WE'LL TAKE A
5 LOOK AT BOTH.
6 NOW, THE META-ANALYSES THAT YOU REVIEWED
7 INCLUDE THE SALA, ZEEGERS, YU, ZHOU, AND BAI
8 META-ANALYSES; CORRECT?
9 A YES.
10 Q LET'S START WITH THE SALA ARTICLE, WHICH IS
11 EXHIBIT 10816.
12 AND JUST TAKING A LOOK AT THE MONITOR, DO
13 YOU RECOGNIZE THE SALA ARTICLE, EXHIBIT 10816?
14 A YES.
15 (EXHIBIT 10816 MARKED FOR
16 IDENTIFICATION.)
17 Q BY MR. SCHURZ: AND DID YOU CONSIDER THIS
18 STUDY IN FORMING YOUR OPINIONS IN THIS MATTER?
19 A YES.
20 Q NOW, DIRECTING YOUR ATTENTION TO PAGE 005 OF
21 EXHIBIT 10816. AND SPECIFICALLY, TO TABLE NO. 3. DO
22 YOU HAVE THAT IN FRONT OF YOU?
23 A TABLE 3. YES.
24 Q AND WE'VE ALSO GOT IT ON THE MONITOR, IF
25 THAT'S EASIER TO READ.
26 A (REVIEWS DOCUMENT.)
27 Q DR. INFANTE, ARE YOU FAMILIAR WITH TABLE
28 NO. 3?

1 A WELL, I REVIEWED IT, YES.
2 Q OKAY. AND THIS PROVIDES THE RISK OF BLADDER
3 CANCER FOR NUMBER OF CUPS OF COFFEE PER DAY IN
4 NONSMOKERS; CORRECT?
5 A YES.
6 Q AND LOOKING AT NONSMOKERS OR NEVER-SMOKERS
7 IS APPROPRIATE HERE, AS WELL, BECAUSE SMOKING IS A
8 CONFOUNDER, IS IT NOT, FOR BLADDER CANCER?
9 A YES.
10 Q ALL RIGHT. AND THE RELATIVE RISK FOR EVER-
11 COFFEE DRINKERS TO NEVER-COFFEE DRINKERS, AS REPORTED IN
12 SALA, IS 1.0; CORRECT?
13 A I'M SORRY. WHERE ARE YOU?
14 Q I'M SORRY. IF YOU TAKE A LOOK AT TABLE 3 --
15 A YES.
16 Q -- ON THE LEFT-HAND SIDE, WE SEE THE COLUMN
17 WHERE IT IDENTIFIES EVER-COFFEE DRINKERS. AND THE VALUE
18 THAT IS REPORTED BY THE SALA INVESTIGATORS IS 1.0;
19 CORRECT?
20 A YES.
21 Q ALL RIGHT. SO WITH RESPECT TO COMPARING
22 NEVER-COFFEE DRINKERS WITH EVER-COFFEE DRINKERS, THE
23 SALA INVESTIGATORS DO NOT REPORT ANY INCREASED RISK OR
24 DECREASED RISK; CORRECT?
25 A CORRECT.
26 Q ALL RIGHT. AND NOW WE SEE THE EXPOSURE
27 CATEGORIES THAT ARE IDENTIFIED BY THE SALA
28 INVESTIGATORS. AND WE SEE THAT FOR ONE TO TWO CUPS PER

1 DAY, AGAIN, THE ODDS RATIO IS 1.0. AND FOR THREE TO
2 FIVE CUPS PER DAY, IT REMAINS AT 1.0. AND AT SIX TO
3 NINE CUPS PER DAY, IT REMAINS AT 1.0. CORRECT?
4 A YES.
5 Q SO AT EACH OF THESE LEVELS OF CONSUMPTION,
6 THE SALA INVESTIGATORS FAIL TO FIND ANY ASSOCIATION AT
7 ALL WITH RESPECT TO INCREASED CONSUMPTION OF COFFEE AND
8 BLADDER CANCER; CORRECT?
9 A YES.
10 Q ALL RIGHT. NOW, YOU HAVE --
11 A BUT AT THE HIGHEST DOSE, THEY DID.
12 Q AND THAT'S THE VALUE THAT YOU'VE INCLUDED IN
13 YOUR CHART, OR HIGHLIGHTED IN YOUR CHART, IS IT NOT:
14 THE TEN CUPS PER DAY, OF 1.8; CORRECT?
15 A YEAH, BECAUSE THE HIGHEST EXPOSED GROUP
16 SHOWS THE HIGHEST RISK.
17 Q RIGHT. AND SO FROM -- AND IT JUMPS FROM NO
18 ASSOCIATION WHATSOEVER, AT SIX TO NINE CUPS PER DAY, TO
19 A RELATIVE -- OR AN ODDS RATIO OF 1.8 AT TEN CUPS PER
20 DAY; CORRECT?
21 A CORRECT.
22 Q RIGHT. AND THE P TREND THAT IS REFLECTED --
23 OR THE DOSE RESPONSE TREND HERE IS NOT STATISTICALLY
24 SIGNIFICANT; CORRECT?
25 A CORRECT.
26 Q ALL RIGHT. NOW --
27 A .15, TO BE SPECIFIC.
28 Q YEAH. NOW, THE SALA META-ANALYSIS WAS ONE

1 OF THE STUDIES YOU CRITICIZED DR. BOFFETTA FOR FAILING
2 TO CONSIDER, WAS IT NOT?
3 A YES.
4 Q AND IT WAS INCLUDED IN HIS RELIANCE
5 MATERIALS, WAS IT NOT?
6 A IT WAS INCLUDED IN WHOSE RELIANCE MATERIALS?
7 Q DR. BOFFETTA'S.
8 A I DON'T KNOW WHAT HIS RELIANCE MATERIALS
9 WERE.
10 Q HAVE YOU REVIEWED THE AUTHORS OF THE SALA
11 STUDY?
12 A HAVE I REVIEWED THE AUTHORS?
13 Q DO YOU KNOW WHO THE AUTHORS OF THE SALA
14 STUDY ARE?
15 A I DON'T RECALL, AS I SIT HERE.
16 Q SO DIRECTING YOUR ATTENTION TO PAGE 1 OF
17 EXHIBIT 10816. AND I DIRECT YOUR ATTENTION SPECIFICALLY
18 TO THE NAME OF PAOLO BOFFETTA, AS A CO-AUTHOR OF THE
19 SALA STUDY. DO YOU SEE THAT?
20 A WELL, YES.
21 Q DID YOU KNOW WHETHER DR. BOFFETTA WAS ONE OF
22 THE LISTED AUTHORS OF THE SALA STUDY?
23 A YOU KNOW, IT DIDN'T ENTER MY MIND IF HE WAS
24 OR WASN'T.
25 Q THANK YOU. LET'S TAKE A LOOK AT A SECOND OF
26 THE META-ANALYSES THAT YOU REVIEWED AND HAVE CONSIDERED
27 IN DEVELOPING YOUR OPINIONS, DR. INFANTE; SPECIFICALLY,
28 THE ZEEGERS, WHICH IS EXHIBIT 2955.

1 ALL RIGHT. NOW, FIRST, YOU CITE THE
2 META-ANALYSIS FROM ZEEGERS FROM 2001; CORRECT? IN YOUR
3 CHART, AT DEMONSTRATIVE 106; CORRECT?
4 A CORRECT.
5 (EXHIBIT 2955 MARKED FOR
6 IDENTIFICATION.)
7 Q BY MR. SCHURZ: DID YOU CONSIDER, IN YOUR
8 ANALYSIS OF THE ZEEGERS, THE SUBSEQUENT SYSTEMATIC
9 REVIEW PUBLISHED BY ZEEGERS IN 2003? SHOWING YOU NOW
10 WHAT IS MARKED AS EXHIBIT 2955.
11 A NO. I DON'T HAVE THAT IN MY SLIDE HERE, SO
12 I APPARENTLY DIDN'T FIND THIS ONE.
13 Q AND DIRECTING YOUR ATTENTION TO PAGE 1 OF
14 EXHIBIT 2955 --
15 MR. METZGER: OBJECTION --
16 Q BY MR. SCHURZ: -- THE ZEEGERS AUTHORS --
17 MR. METZGER: HOLD ON. EXCUSE ME.
18 OBJECTION, YOUR HONOR. HE HASN'T SEEN THIS
19 BEFORE. AND THIS IS NOT A META-ANALYSIS; IT'S A REVIEW.
20 SO --
21 THE COURT: I HAVEN'T HEARD A QUESTION YET.
22 MR. METZGER: WELL, I'D LIKE THE PREDICATE AS
23 TO -- HE'S ALREADY SAID HE HASN'T SEEN IT.
24 THE COURT: WELL, LET'S HEAR THE QUESTION.
25 Q BY MR. SCHURZ: ARE YOU AWARE, DR. INFANTE,
26 OF THE ZEEGERS AUTHORS' CONCLUSION IN THEIR SYSTEMATIC
27 REVIEW, PUBLISHED TWO YEARS AFTER THEIR PRIOR SYSTEMATIC
28 REVIEW THAT YOU'RE RELYING ON?

1 MR. METZGER: OBJECTION; LACKING IN FOUNDATION.
2 THE WITNESS: WELL, HE --
3 THE COURT: THE QUESTION IS, ARE YOU AWARE?
4 MR. METZGER: IF HE HASN'T SEEN THIS --
5 THE COURT: THE QUESTION IS, ARE YOU AWARE? IT
6 CALLS FOR A "YES" OR "NO."
7 THE WITNESS: NO. THE ANSWER IS NO. AND I DIDN'T
8 REVIEW THIS AS PART OF A META-ANALYSIS BECAUSE IT'S NOT
9 A META-ANALYSIS.
10 THE COURT: OKAY. NEXT QUESTION.
11 Q BY MR. SCHURZ: AND THE 2001 WAS A
12 SYSTEMATIC REVIEW; CORRECT -- AND A META-ANALYSIS;
13 CORRECT?
14 A I ONLY HAVE THE DATA HERE. I DON'T KNOW THE
15 TITLE OF IT. YOU'D HAVE TO SHOW IT TO ME.
16 Q ALL RIGHT. AND AS PART OF YOUR
17 COMPREHENSIVE LITERATURE REVIEW, IT DID NOT INCLUDE
18 LOOKING FOR FURTHER STATEMENTS BY THE AUTHORS OF
19 META-ANALYSES THAT YOU REVIEWED; CORRECT?
20 A YOU MEAN FURTHER STATEMENTS OF
21 META-ANALYSES? I'VE REVIEWED THE META-ANALYSES. IF
22 SOMEONE HAS A STATEMENT ABOUT SOMEONE ELSE'S
23 META-ANALYSIS, I WOULDN'T REVIEW THE STATEMENT. I
24 WOULD -- IF I COULD FIND IT, I WOULD LOOK AT THE
25 META-ANALYSIS.
26 Q IN 2001, THE ZEEGERS AUTHORS PUBLISHED A
27 META-ANALYSIS AND SYSTEMATIC REVIEW; CORRECT?
28 A YES.

1 Q AND IN 2003, THE ZEEGERS AUTHORS PUBLISHED A
2 FURTHER SYSTEMATIC REVIEW; CORRECT?
3 A BUT NOT A META-ANALYSIS, SO I DIDN'T INCLUDE
4 IT IN MY -- THEY DON'T HAVE ANY NEW META-ANALYSES IN
5 THE -- THAT I CAN SEE. I MEAN, I'VE NEVER LOOKED AT IT
6 BEFORE.
7 Q ALL RIGHT. AND --
8 A I SEE THAT THERE'S A META-ANALYSIS, AND IT'S
9 AN INTERPRETATION.
10 Q OKAY. NOW, LET'S TURN TO ANOTHER OF THE
11 META-ANALYSES THAT YOU DID REVIEW: THE BAI ANALYSIS, AT
12 EXHIBIT 599.
13 AND SHOWING YOU NOW WHAT'S APPEARED ON THE
14 MONITOR. DO YOU RECOGNIZE THE BAI ANALYSIS, PUBLISHED
15 IN 2014?
16 A YES.
17 (EXHIBIT 599 MARKED FOR IDENTIFICATION.)
18 Q BY MR. SCHURZ: DID YOU CONSIDER THIS IN
19 DEVELOPING YOUR OPINIONS IN THIS MATTER?
20 A YES.
21 Q NOW, THIS META-ANALYSIS CONSIDERS ONLY THREE
22 OF THE BLADDER AND COFFEE CONSUMPTION COHORT STUDIES;
23 CORRECT?
24 A THREE OF THE WHICH? THE COHORT STUDIES, DID
25 YOU SAY?
26 Q THIS BAI ANALYSIS CONSIDERS ONLY THREE OF
27 THE BLADDER AND COFFEE CONSUMPTION COHORT STUDIES;
28 CORRECT?

1 A WELL, IN MY CHART, I HAVE 4 COHORT STUDIES
2 AND 17 CASE-CONTROL STUDIES.
3 Q RIGHT. AND THIS IS A FLUID CONSUMPTION
4 STUDY; CORRECT?
5 A YES.
6 Q SO IT ONLY INCLUDES A SUBSET OF THE BLADDER
7 COHORT STUDIES; CORRECT?
8 A WELL, I'LL HAVE TO LOOK THROUGH IT NOW TO
9 SEE WHICH COHORTS. IT SAYS IT INCLUDES FOUR COHORTS.
10 THAT'S WHAT I HAVE, FOUR COHORT STUDIES.
11 Q WELL, LET'S -- I THINK I CAN MAKE THIS
12 SIMPLER. ON YOUR SLIDE, YOU IDENTIFY A TOTAL OF 11
13 COHORT STUDIES; CORRECT?
14 A ON BAI? NO, I HAVE FOUR COHORT STUDIES.
15 Q I'M SORRY?
16 A FOUR.
17 Q SHOWING YOU DEMONSTRATIVE 105. THIS IS YOUR
18 TABLE OF COFFEE AND BLADDER CANCER COHORT STUDIES;
19 CORRECT?
20 A YES.
21 Q AND YOU IDENTIFY 11 STUDIES; CORRECT?
22 A LET ME SEE. WHERE IS IT?
23 Q IT'S ALSO ON YOUR MONITOR, IF THAT'S
24 SIMPLER.
25 A WERE ARE YOU ASKING ME TO LOOK AT BAI ON
26 THAT?
27 Q NO. YOU IDENTIFY 11 COHORT STUDIES
28 EVALUATING COFFEE AND BLADDER CANCER; CORRECT?

1 A YES.
2 Q ALL RIGHT. AND THE BAI ANALYSIS, THE
3 META-ANALYSIS THAT YOU'VE INCLUDED, REVIEWED, AS YOU'VE
4 INDICATED, WHAT YOU BELIEVE ARE FOUR OF THOSE COHORT
5 STUDIES; CORRECT?
6 A YES; RIGHT.
7 Q ALL RIGHT. SO BAI IS ONLY LOOKING AT A
8 SMALL MINORITY OF THE STUDIES; CORRECT?
9 A WHAT I DON'T KNOW IS IF HE DIDN'T INCLUDE
10 OTHERS. I'D HAVE TO LOOK BACK TO REVIEW IT NOW TO SEE
11 WHY HE DIDN'T INCLUDE THE OTHERS.
12 AS I MENTIONED EARLIER, THERE WERE SOME OF
13 THEM THAT HAD PRETTY POOR METHODOLOGY THAT WERE INCLUDED
14 IN THE PREVIOUS META-ANALYSES. MAYBE THEY REJECTED ONES
15 THAT THEY FELT WEREN'T OF GOOD QUALITY.
16 BUT I CAN'T REMEMBER, AS I SIT HERE, SO I'LL
17 HAVE TO LOOK BACK AT THIS TO ANSWER YOUR QUESTION
18 SPECIFICALLY.
19 Q AND DID YOU DO A METHODOLOGICAL REVIEW OF
20 THESE 11 COHORT STUDIES THAT YOU'VE INCLUDED ON YOUR
21 DEMONSTRATIVE, AS TO WHETHER ANY OF THEM WERE OF POOR
22 QUALITY?
23 A LET ME SEE.
24 (REVIEWS DOCUMENT.)
25 NO, I DON'T HAVE IT IN MY NOTES HERE,
26 WHETHER I HAVE NOTES ON THE ARTICLE OR NOT. I'D HAVE TO
27 PULL THE ARTICLES TO LOOK AT THEM AND SEE WHAT MY
28 MARGINAL NOTES ARE.

1 Q ALL RIGHT. SO NOW LET'S LOOK AT ANOTHER
2 META-ANALYSIS, WHICH IS EXHIBIT 10463.
3 A WHICH ONE IS IT?
4 Q THIS IS THE HUANG 2014 META-ANALYSIS, TITLED
5 "COFFEE CONSUMPTION AND UROLOGIC CANCER RISK: A
6 META-ANALYSIS OF COHORT STUDIES."
7 DID YOU CONSIDER THIS STUDY IN FORMING YOUR
8 OPINIONS IN THIS MATTER?
9 A 2014. I'M NOT SEEING IT ON MY CHART HERE IN
10 TERMS OF META-ANALYSES, SO I DIDN'T REVIEW THIS ONE.
11 (EXHIBIT 10463 MARKED FOR
12 IDENTIFICATION.)
13 Q BY MR. SCHURZ: IS THERE A REASON THAT YOU
14 CHOSE THE BAI STUDY FROM 2014, WHICH REVIEWED A SMALL
15 SUBSET, VERSUS THE HUANG ARTICLE, WHICH IS SOLELY ON
16 COFFEE CONSUMPTION AND SHOWED NO SIGNIFICANT INCREASE?
17 MR. METZGER: WELL, OBJECTION; LACKING IN
18 FOUNDATION AND ARGUMENTATIVE --
19 THE WITNESS: I DIDN'T THINK IT --
20 MR. METZGER: PETER, EXCUSE ME.
21 OBJECTION; LACKING IN FOUNDATION AND
22 ARGUMENTATIVE AS PHRASED.
23 THE COURT: OVERRULED.
24 Q BY MR. SCHURZ: SO YOU DIDN'T COME ACROSS
25 THE HUANG META-ANALYSIS AS PART OF YOUR WORK IN THIS
26 CASE; CORRECT?
27 A CORRECT. I MEAN, IT'S 2014. I DON'T
28 KNOW -- IT SAYS IT WAS PUBLISHED ONLINE IN MARCH. I

1 APPARENTLY MISSED IT.
2 Q OKAY. LET'S MOVE ON.
3 YOU DID CITE IN YOUR DEMONSTRATIVE THE YU
4 META-ANALYSIS, OF EXHIBIT 10998, WHICH YOU HAVE UP THERE
5 AMONG THE STUDIES THAT WE DISCUSSED BECAUSE IT ALSO
6 ADDRESSES PANCREATIC CANCER.
7 AND YOU CONSIDERED THIS STUDY IN DEVELOPING
8 YOUR OPINIONS WITH RESPECT TO BLADDER CANCER, AS WELL,
9 DID YOU NOT?
10 A THE YU 2011?
11 Q YES.
12 A YES. AND IT SHOWS A SIGNIFICANT DECLINE.
13 YES, I CONSIDERED IT. I REVIEWED IT.
14 Q AND THE OVERALL -- AND TURNING ATTENTION TO
15 PAGE 0004 OF EXHIBIT 10998, AND FIGURE 2, THE --
16 A EXCUSE ME. I NEED TO FIND IT.
17 Q IF IT'S SIMPLER, YOU CAN JUST LOOK AT --
18 WE'RE JUST GOING TO LOOK AT THE ONE FIGURE, AND THEN
19 WE'RE FINISHED WITH THIS.
20 A ALL RIGHT.
21 Q AND THE YU INVESTIGATORS REPORT AN OVERALL
22 RELATIVE RISK OF 0.83, WITH A CONFIDENCE INTERVAL
23 BETWEEN 0.73 AND 0.94; CORRECT?
24 A YES. AND THAT'S WHAT I HAVE IN MY SLIDE.
25 Q RIGHT. AND SO THIS META-ANALYSIS EVALUATING
26 BLADDER CANCER SHOWS A STATISTICALLY SIGNIFICANT
27 DECREASED RISK OF BLADDER CANCER; CORRECT?
28 A YES.

1 Q ALL RIGHT. LET'S TAKE A LOOK NOW AT THE
2 LAST OF THE META-ANALYSES THAT YOU EVALUATED, AND THAT'S
3 THE ZHOU META-ANALYSIS, AT EXHIBIT 11015.
4 AND DID YOU CONSIDER THE ZHOU META-ANALYSIS
5 IN FORMING YOUR OPINIONS WITH RESPECT TO COFFEE
6 CONSUMPTION AND BLADDER CANCER?
7 A YES.
8 (EXHIBIT 11015 MARKED FOR
9 IDENTIFICATION.)
10 Q BY MR. SCHURZ: NOW, ZHOU IS A META-ANALYSIS
11 OF BOTH CASE-CONTROL AND COHORT STUDIES; CORRECT?
12 A YES.
13 Q AND YOU'VE REPORTED THE RESULTS WITH RESPECT
14 TO BOTH: BOTH THE CASE-CONTROL, AS WELL AS THE COHORT
15 STUDIES, IN YOUR SLIDES; CORRECT?
16 A YES.
17 Q ALL RIGHT. NOW, FOR THE COHORT STUDIES, THE
18 ZHOU INVESTIGATORS FOUND NO STATISTICALLY SIGNIFICANT
19 RISK OF BLADDER CANCER; CORRECT?
20 A YES.
21 Q AND THERE WAS SOME INCONSISTENCY IN THEIR
22 FINDINGS FOR THE CASE-CONTROL STUDIES; CORRECT?
23 A WELL, I DON'T RECALL. I'D HAVE TO LOOK BACK
24 TO REFRESH MY MEMORY. WHAT ARE YOU REFERRING TO?
25 Q OKAY. WHAT I'D LIKE TO DISCUSS IS HOW THE
26 ZHOU INVESTIGATORS EVALUATED THE INCONSISTENCY THAT THEY
27 FOUND IN THEIR DATA.
28 MR. METZGER: OBJECTION; LACKING FOUNDATION.

1 THE COURT: OVERRULED.
2 Q BY MR. SCHURZ: AND ADDRESSING YOUR
3 ATTENTION TO PAGE 007 OF EXHIBIT 11015. DO YOU HAVE
4 THAT IN FRONT OF YOU?
5 A I'M GETTING IT. YES.
6 Q AND SPECIFICALLY, I'LL DIRECT YOUR ATTENTION
7 TO THE RIGHT-HAND SIDE, WHERE THE AUTHORS OBSERVE:
8 "THUS, CONSIDERING THE DISCREPANCY
9 BETWEEN THE FINDINGS FROM CASE-CONTROL AND
10 COHORT STUDIES, HOSPITAL-BASED AND POPULATION-
11 BASED CASE-CONTROL STUDIES, CAUTION IS NEEDED
12 IN INTERPRETING THE RESULTS FROM THE CASE-
13 CONTROL STUDIES."
14 DO YOU SEE THAT?
15 A YES.
16 Q ALL RIGHT. AND THE ZHOU AUTHORS CONTINUE,
17 DO THEY NOT, AND SUGGEST THAT MAYBE ONE OF THE ISSUES
18 THAT IS INFLUENCING THE CASE-CONTROL STUDIES IS THE
19 PRESENCE OF SELECTION BIAS AND RECALL BIAS THAT MAY BE
20 CONTRIBUTING TO THE ASSOCIATIONS THAT ARE SEEN; CORRECT?
21 A WHERE DO YOU SEE THEM SAY -- WELL, YOU KNOW,
22 THAT'S WHAT THEY'RE SAYING, BUT I WOULD SAY THAT THEIR
23 DATA DON'T SUPPORT THAT, BECAUSE THEY HAVE A DOSE
24 RESPONSE IN NONSMOKERS -- THEIR META-ANALYSIS OF 23
25 CASES, AS I PRESENTED.
26 SO IF THEY HAVE A DOSE RESPONSE IN
27 NONSMOKERS, I THINK THAT'S PRETTY PERSUASIVE EVIDENCE.
28 Q WELL, LET'S EVALUATE HOW THE ZHOU AUTHORS

1 INTERPRET THEIR EVIDENCE. AND IF I COULD DIRECT YOUR
2 ATTENTION TO PAGE 006, THE PRECEDING PAGE.
3 A OKAY. LET ME GET THERE.
4 ALL RIGHT.
5 Q ALL RIGHT. AND SPECIFICALLY, I'M GOING TO
6 FOCUS ON THE RIGHT-HAND COLUMN AND THE LAST PARAGRAPH.
7 AND DO YOU HAVE THAT IN FRONT OF YOU?
8 A YES.
9 Q ALL RIGHT. AND IF YOU'D MOVE TO THE THIRD
10 SENTENCE HERE ON PAGE 06, EXHIBIT 11015, THE ZHOU
11 AUTHORS OBSERVE:
12 "THE POTENTIAL BIAS OF CASE-CONTROL
13 STUDIES, SUCH AS SELECTION BIAS AND RECALL
14 BIAS, MIGHT CONTRIBUTE TO THE DISCREPANCY
15 BETWEEN CASE-CONTROL AND COHORT STUDIES."
16 DO YOU SEE THAT?
17 A YES.
18 Q ALL RIGHT. NOW, ZHOU -- THE ZHOU
19 INVESTIGATORS LOOKED AT THE QUALITY OF THE UNDERLYING
20 CASE-CONTROL STUDIES REGARDING BLADDER CANCER TO
21 EVALUATE THE POTENTIAL FOR SELECTION BIAS; CORRECT?
22 A WHERE ARE YOU? I DON'T -- AS I SIT HERE,
23 I'VE LOOKED AT A LOT OF DATA. SO LET'S LOOK AT WHAT --
24 WHY DON'T YOU DIRECT ME TO THE SPECIFIC.
25 Q WELL, IF YOU CONTINUE ON IN THE SAME
26 PARAGRAPH, THEY TALK ABOUT THE ANALYSIS THEY PERFORMED
27 FOR SELECTION BIAS.
28 A (REVIEWS DOCUMENT.)

1 Q AND HAVE YOU FAMILIARIZED YOURSELF WITH THE
2 ZHOU DISCUSSION AS IT RELATES TO RECALL BIAS AND
3 SELECTION BIAS?
4 A YES. I MEAN, THEY'RE SPECULATING HERE THAT
5 THEY MIGHT TEND TO RECALL -- THEY MIGHT TEND TO
6 OVERESTIMATE AS TO COFFEE CONSUMPTION, THAN CONTROLS.
7 THAT'S POSSIBLE, BUT I DON'T SEE THAT THEY HAVE EVIDENCE
8 OF IT. THEY'RE JUST SPECULATING ABOUT IT.
9 Q WELL, DIDN'T THE ZHOU AUTHORS, IN FACT,
10 PERFORM AN EVALUATION TO FIND THAT ONLY 5 OF THE 20
11 CASE-CONTROL STUDIES SHOWED NO SIGNIFICANT DIFFERENCE IN
12 RESPONSE RATE FOR THE CASE AND CONTROL GROUPS,
13 SUGGESTING THAT THERE MAY BE SOME SELECTION BIAS?
14 A YES, BUT I MEAN, THAT'S ALWAYS A
15 POSSIBILITY. I'M SAYING THEY DON'T KNOW THAT. THEY'RE
16 SURMISING IT OR SPECULATING ABOUT IT. IT'S POSSIBLE.
17 I'M JUST SAYING THEY DON'T HAVE EVIDENCE THAT THERE IS.
18 Q WELL, AND WHAT THEY'RE OBSERVING IS THAT,
19 BASED ON THEIR ANALYSIS, THEY BELIEVE THAT THERE'S A
20 PRESENCE OF SELECTION BIAS; CORRECT?
21 MR. METZGER: OBJECTION AS TO WHAT THEY BELIEVE,
22 YOUR HONOR. THAT'S SPECULATIVE.
23 THE COURT: SUSTAINED.
24 Q BY MR. SCHURZ: SO LET'S TAKE A LOOK AT HOW
25 THEY CONCLUDE. THE AUTHORS OBSERVED THE POTENTIAL FOR
26 RECALL BIAS AND SELECTION BIAS AND OBSERVED THAT WITH
27 RESPECT TO RECALL BIAS, THIS RECALL BIAS COULD ALSO
28 AFFECT THE ASSOCIATION TOWARD A MUCH -- POSITIVE

1 ASSOCIATION BETWEEN COFFEE CONSUMPTION AND BLADDER
2 CANCER RISK; CORRECT?
3 A YES.
4 Q AND THEN THE AUTHORS FURTHER OBSERVE:
5 "IN THIS RESPECT, COHORT STUDIES ARE
6 PREFERABLE THAN CASE-CONTROL STUDIES."
7 CORRECT?
8 A YES.
9 Q SO THE ZHOU AUTHORS CONCLUDED THAT AS
10 BETWEEN THOSE CASE-CONTROL STUDIES AND COHORT STUDIES
11 EVALUATING BLADDER CANCER AND COFFEE CONSUMPTION, THE
12 COHORT STUDIES WERE PREFERABLE, AS THEY WOULD NOT BE
13 SUBJECT TO THE SAME SELECTION BIAS AND RECALL BIAS AS
14 THE CASE-CONTROL STUDIES; CORRECT?
15 A FROM THAT STANDPOINT, THEY WOULD BE
16 PREFERABLE, YES; BUT THEY DON'T KNOW THAT THERE'S THE
17 RECALL BIAS. AND WHEN YOU EVALUATE STUDIES, YOU LOOK AT
18 BOTH COHORT AND CASE-CONTROL STUDIES, JUST AS IARC DOES
19 IN ITS EVALUATIONS.
20 Q AND AS BETWEEN THE TWO, THE ZHOU AUTHORS
21 CONCLUDED THAT PREFERENCE SHOULD BE GIVEN TO COHORT
22 STUDIES; CORRECT?
23 A THAT'S WHAT THEY CONCLUDED, YES.
24 Q OKAY. SO LET'S TALK ABOUT SOME OF THE
25 COHORT STUDIES THAT YOU EVALUATED AS PART OF YOUR REVIEW
26 OF BLADDER CANCER AND COFFEE CONSUMPTION.
27 AND LET'S START BY TAKING A LOOK AT THE
28 POWERPOINT SLIDE THAT YOU HAVE OF THE COHORT STUDIES AT

1 DEMONSTRATIVE 105. AND DOES THIS INCLUDE A
2 COMPREHENSIVE SET OF THE COHORT STUDIES YOU EVALUATED IN
3 THIS CASE?
4 A YES.
5 Q ALL RIGHT. SHOWING YOU NOW THE ROSS STUDY,
6 WHICH IS EXHIBIT 10798.
7 A DID YOU SAY "ROSS"?
8 Q YES.
9 A WHAT YEAR?
10 Q 2011.
11 A (REVIEWS DOCUMENT.)
12 I DON'T SEEM TO HAVE THAT ONE IN MY REVIEW.
13 (EXHIBIT 10798 MARKED FOR
14 IDENTIFICATION.)
15 Q BY MR. SCHURZ: SO MY NEXT QUESTION IS: DID
16 YOU CONSIDER THE ROSS 2011 STUDY AS PART OF YOUR
17 COMPREHENSIVE SYSTEMATIC REVIEW OF THE BLADDER AND
18 COFFEE LITERATURE?
19 A I MISSED THAT ONE.
20 Q OKAY.
21 A IT'S NOT IN THERE, NO.
22 Q ALL RIGHT. WE CAN PUT THAT ASIDE, THEN.
23 I TAKE IT YOU'RE NOT FAMILIAR WITH THE
24 CONCLUSIONS OF THE ROSS STUDY; CORRECT?
25 A I HAVEN'T READ IT.
26 Q ALL RIGHT. SO ON YOUR POWERPOINT
27 DEMONSTRATIVE -- LET'S GO BACK TO THE DEMONSTRATIVE, AT
28 105. WE SEE THE COHORT STATUTES THAT YOU DID IDENTIFY.

1 AND THE LAST ONE APPEARS TO HAVE BEEN PUBLISHED IN 2009;
2 CORRECT?
3 A YES.
4 Q AND DID YOU LIMIT YOUR LITERATURE REVIEW TO
5 THOSE STUDIES THAT WERE PUBLISHED UP THROUGH 2009?
6 A I'M LOOKING AT MY NOTES HERE. IT LOOKS LIKE
7 I DIDN'T REVIEW ANY AFTER 2009; CORRECT.
8 Q ALL RIGHT. WELL, LET'S TAKE A LOOK AT SOME
9 OF THE EARLIER ONES THAT YOU DID REVIEW. AND LOOKING
10 AT -- LET'S START WITH THE SNOWDEN, AT EXHIBIT 1969.
11 AND DID YOU CONSIDER THE SNOWDEN 1984
12 ARTICLE IN DEVELOPING YOUR OPINIONS IN THIS MATTER?
13 A YES.
14 (EXHIBIT 1969 MARKED FOR
15 IDENTIFICATION.)
16 Q BY MR. SCHURZ: ALL RIGHT. AND IF I COULD
17 DIRECT YOUR ATTENTION TO TABLE NO. 1, WHICH YOU CAN FIND
18 AT PAGE NO. 2 OF THE SNOWDEN ARTICLE. LET ME KNOW WHEN
19 YOU'RE THERE.
20 A OKAY. I'M THERE.
21 Q ALL RIGHT. AND DIRECTING YOUR ATTENTION TO
22 THE DATA THAT IS BEING PROVIDED FOR BLADDER CANCER AND
23 COFFEE CONSUMPTION, THIS STUDY SHOWS NO STATISTICALLY
24 SIGNIFICANT INCREASED RISK; CORRECT?
25 A THAT'S CORRECT.
26 Q AND THE P TREND FOR THE DOSE RESPONSE WAS
27 0.13, MEANING THAT THERE IS NO STATISTICALLY SIGNIFICANT
28 DOSE RESPONSE; CORRECT?

1 A CORRECT.
2 Q ALL RIGHT.
3 A WELL, WAIT A SECOND.
4 Q DO YOU SEE WHERE IT PROVIDES A TREND P
5 EQUALS 0.13?
6 A YES, BUT -- AND YOU KNOW WHAT? IN MY CHART,
7 I HAVE "SIGNIFICANT DOSE RESPONSE." SO LET ME LOOK
8 FURTHER IN THIS DOCUMENT, SEE IF THERE'S SOME OTHER
9 PLACE WHERE THEY'RE MENTIONING IT. BECAUSE IF THERE
10 ISN'T, I HAVE AN ERROR IN MY SLIDE, AND THAT'S WHAT I
11 WANT TO FIND OUT.
12 (REVIEWS DOCUMENT.)
13 WELL, YOU KNOW, IT'S NOT SIGNIFICANT. AND
14 THAT'S AN ERROR IN MY SLIDE, SO LET ME CORRECT THAT.
15 Q SO IN THIS RESPECT, THE SLIDE THAT WE WERE
16 JUST LOOKING AT, DEMONSTRATIVE 105, HAS A MISTAKE WITH
17 RESPECT TO THE DATA AS IT'S REFLECTED ON SNOWDEN;
18 CORRECT?
19 A THE DOSE RESPONSE ISN'T SIGNIFICANT.
20 Q OKAY.
21 A SO AGAIN, YOU ASKED ME ABOUT AUTHORS'
22 CONCLUSIONS. THEY DO CONCLUDE THERE'S A POSITIVE
23 ASSOCIATION BETWEEN COFFEE CONSUMPTION AND BLADDER
24 CANCER, EVEN THOUGH THE RESULT ISN'T -- THE RESULT OF
25 THE TREND ANALYSIS WASN'T SIGNIFICANT AT THE 05 LEVEL.
26 Q ALL RIGHT. SO WITH RESPECT TO SNOWDEN, AT
27 LEAST, YOUR STATEMENT AT 105, THAT IT REFLECTS A
28 SIGNIFICANT DOSE RESPONSE TREND, IS INCORRECT; CORRECT?

1 STRIKE THAT.
2 A THAT'S CORRECT.
3 Q ALL RIGHT. LET'S TURN TO THE ZEEGERS 2001
4 STUDY, WHICH IS EXHIBIT 2254; ALSO REFERENCED IN YOUR
5 MATERIALS AT DEMONSTRATIVE 105.
6 A ZEEGERS -- WHICH YEAR DID YOU SAY?
7 Q WE'RE DELIVERING IT TO YOU. THIS IS A
8 DIFFERENT REPORT, EXHIBIT 2254.
9 AND DR. INFANTE, DID YOU CONSIDER THE
10 ZEEGERS 2001 COHORT STUDY AS PART OF YOUR ANALYSIS IN
11 THIS CASE?
12 A YES.
13 (EXHIBIT 2254 MARKED FOR
14 IDENTIFICATION.)
15 Q BY MR. SCHURZ: SO TAKING A LOOK AT PAGE 004
16 OF EXHIBIT 2254, I DIRECT YOUR ATTENTION TO TABLE NO. 2.
17 AND DO YOU HAVE THAT IN FRONT OF YOU?
18 A YES, I DO.
19 Q NOW, YOU'VE IDENTIFIED VALUES OFF OF THIS
20 TABLE THAT ARE TAKEN FROM THE SECOND COLUMN, THAT
21 INCLUDES THE RELATIVE RISK RATIOS, IN WHAT APPEARS AS
22 THE MIDDLE COLUMN. DO YOU SEE THAT?
23 A YES.
24 Q AND IF YOU LOOK AT THE LAST COLUMN, WHICH IS
25 THE FULLY ADJUSTED COLUMN FOR AGE, SMOKING, AND TEA
26 CONSUMPTION AND OTHER VARIABLES, DO YOU SEE THAT
27 ANALYSIS?
28 A YES.

1 Q AND FOR WOMEN, THERE IS NO STATISTICALLY
2 SIGNIFICANT -- STRIKE THAT.
3 FOR WOMEN, AS REPORTED IN THE ZEEGERS
4 ANALYSIS, EXHIBIT 2254, THERE IS A STATISTICALLY
5 SIGNIFICANT DECREASE IN CANCER RISK, IS THERE NOT?
6 A YES. AND I INDICATE THAT IN MY SLIDE.
7 Q AND IT REFLECTS A DOSE-RESPONSE TREND THAT
8 IS ALSO STATISTICALLY SIGNIFICANT; CORRECT?
9 A YES.
10 Q AND FOR MEN -- AGAIN, STAYING IN THE COLUMN
11 FOR THE FULLY ADJUSTED VALUES -- THERE IS NO
12 STATISTICALLY SIGNIFICANT INCREASE IN CANCER RISK WHEN
13 CONSIDERING THE FULLY ADJUSTED VALUES THAT APPEAR HERE
14 IN THE FAR RIGHT-HAND COLUMN; CORRECT?
15 A THAT'S -- THE P VALUE IS .06; CORRECT.
16 Q ALL RIGHT.
17 A I TOOK MY DATA FROM THE MIDDLE COLUMN, WHICH
18 IS ADJUSTED FOR CIGARETTE SMOKING AND YEARS OF SMOKING.
19 Q RIGHT.
20 A AND THAT'S WHAT -- THAT SHOWS A SIGNIFICANT
21 TREND --
22 Q AND SO --
23 A -- FOR MEN; FOR MEN. AND IT SHOWS A
24 SIGNIFICANT TREND IN THE OPPOSITE DIRECTION FOR WOMEN.
25 Q RIGHT. ALL RIGHT.
26 BUT WITH RESPECT TO THE FULLY ADJUSTED
27 VALUE, AS REPORTED BY ZEEGERS, WHAT THEY REFLECT IS A
28 NOT STATISTICALLY SIGNIFICANT RISK OF 1.03; CORRECT?

1 A YES, BUT MY POINT IS, THAT'S ALSO INCLUDING
2 ADJUSTMENT FOR TEA CONSUMPTION. AND I HAVEN'T SEEN DATA
3 WHICH INDICATES THAT BLADDER CANCER IS ASSOCIATED WITH
4 CONSUMPTION OF TEA.
5 Q ALL RIGHT. NOW --
6 A SO THEY'RE OVER-ADJUSTING, IN MY OPINION, IN
7 THAT ANALYSIS.
8 Q OKAY. SO YOU WOULD DISAGREE WITH THE
9 ADJUSTMENTS THAT THE ZEEGERS AUTHORS HAVE MADE WITH
10 RESPECT TO THE STUDY; CORRECT?
11 A NO, I'M NOT DISAGREEING WITH THE ADJUSTMENTS
12 THEY'VE MADE. I'M SAYING IT'S NOT NECESSARILY MORE
13 MEANINGFUL THAN THE ADJUSTMENT FOR CIGARETTE SMOKING AND
14 NUMBER OF YEARS SMOKED.
15 Q OKAY.
16 A BECAUSE THEY MAY BE -- SOMETIMES AUTHORS
17 OVER-ADJUST. AND I'M SAYING THAT I THINK THIS IS A
18 REFLECTION OF OVERADJUSTMENT BECAUSE THERE'S NO EVIDENCE
19 ASSOCIATING, THAT I'M AWARE OF, TEA CONSUMPTION WITH
20 BLADDER CANCER.
21 IT'S LIKE ADJUSTING FOR, I SUPPOSE, MEN THAT
22 HAVE GRAY HAIR. IF IT ADJUSTS FOR IT, THAT MIGHT SHOW
23 THAT OLDER MEN, THAT HAVE AN OLDER AGE, THAT WOULD
24 INCREASE THEIR RISK. IF YOU MAKE THAT ADJUSTMENT, THE
25 RISK WOULD GO AWAY.
26 SO THEY'RE ADJUSTING FOR A FACTOR THAT'S NOT
27 RELATED TO IT, IN MY OPINION.
28 Q OKAY. THANK YOU.

1 A YOU'RE WELCOME.
2 Q LET'S TALK A LITTLE BIT ABOUT THE CASE-
3 CONTROL STUDIES THAT YOU'VE RELIED ON WITH RESPECT TO
4 BLADDER CANCER.
5 NOW, FIRST, BY WAY OF BACKGROUND, DR.
6 INFANTE, WHEN YOU WORKED WITH THE FEDERAL GOVERNMENT FOR
7 OSHA AND NIOSH, YOUR DUTIES AS AN EMPLOYEE DID NOT
8 INVOLVE EPIDEMIOLOGY OF DIETARY EXPOSURES; CORRECT?
9 A CORRECT.
10 Q AND FOLLOWING YOUR GOVERNMENT SERVICE, YOUR
11 WORK AS AN ADJUNCT PROFESSOR AT GEORGE WASHINGTON
12 UNIVERSITY DID NOT ADDRESS ISSUES OF DIETARY EXPOSURE OR
13 NUTRITIONAL EPIDEMIOLOGY; CORRECT?
14 A CORRECT.
15 Q AND NONE OF YOUR CONSULTING WORK AND WORK IN
16 THE CONTEXT AS AN EXPERT WITNESS, PRIOR TO YOUR WORKING
17 WITH MR. METZGER IN 2007, ADDRESSED ISSUES WITH RESPECT
18 TO DIETARY EXPOSURES OR NUTRITIONAL EPIDEMIOLOGY;
19 CORRECT?
20 A CORRECT.
21 Q NOW, YOU'VE NEVER AUTHORED ANY PEER-REVIEWED
22 ARTICLES RELATING TO NUTRITIONAL EPIDEMIOLOGY; CORRECT?
23 A NO. I DON'T THINK THAT'S CORRECT, NO.
24 BECAUSE I THINK SOME OF THE EARLY PUBLICATION I HAD,
25 THERE ARE TWO THAT HAD TO DO WITH DIETARY INTAKE OF
26 FORMALDEHYDE -- I'M SORRY. DIETARY INTAKE OF FLUORIDE
27 AND ITS EFFECT ON ENAMEL FLUOROSIS.
28 AND THEN THERE WAS ANOTHER ONE ON NUTRITION

1 AND DIET AND A TYPE OF LESION TO TEETH THAT ARE SEEN IN
2 THE DEVELOPING COUNTRIES, WHERE THEY HAVE PROTEIN
3 CALORIE MALNUTRITION.
4 SO I HAVE PUBLISHED SOME EARLY STUFF THAT
5 HAS TO DO WITH DIET AND NUTRITION.
6 Q AND SPECIFICALLY WITH RESPECT TO DENTISTRY;
7 CORRECT?
8 A WELL, THE FIRST ONE WAS WITH RESPECT TO
9 DENTISTRY, THE FLUORIDE STUDY. THE SECOND WAS IN
10 RELATION TO GROWTH AND DEVELOPMENT, AND LIKE LINEAR
11 HYPOPLASIA IN CHILDREN IN THE DEVELOPING COUNTRIES; AND
12 ALSO, THE APACHE INDIANS IN ARIZONA.
13 Q ALL RIGHT. NOW, YOU'RE AWARE THAT
14 NUTRITIONAL EPIDEMIOLOGY IS A DISTINCT FIELD, JUST AS
15 OCCUPATIONAL EPIDEMIOLOGY IS A DISTINCT FIELD; CORRECT?
16 A WELL, THEY'RE SUBDIVISIONS OF EPIDEMIOLOGY.
17 Q AND IARC HAS SEPARATE WORKING GROUPS FOR
18 NUTRITIONAL EPIDEMIOLOGY; CORRECT?
19 A I'M NOT SURE. WHAT DO YOU MEAN, "SEPARATE
20 WORKING GROUPS"? THEY HAVE SEPARATE WORKING GROUPS FOR
21 EVERY MONOGRAPH THAT THEY DEVELOP, REGARDLESS OF WHAT IT
22 IS: IF IT'S CHEMICAL EXPOSURES OR IN THE OCCUPATIONAL
23 SETTING OR WHATEVER.
24 Q ARE YOU AWARE --
25 A EACH WORKING GROUP, THEY SELECT A NEW GROUP
26 OF WORKING GROUP MEMBERS.
27 Q AND ARE YOU AWARE THAT IARC HAS A SEPARATE
28 GROUP FOR NUTRITIONAL EPIDEMIOLOGY?

1 A SEPARATE FROM WHAT?
2 Q SEPARATE AND DISTINCT FROM ITS OCCUPATIONAL
3 OR ENVIRONMENTAL EPIDEMIOLOGY GROUPS.
4 MR. METZGER: OBJECTION; LACKING IN FOUNDATION.
5 THE WITNESS: NO, I DON'T -- I DON'T KNOW THAT. I
6 WOULD HAVE TO REVIEW WHO WAS ON THE REVIEW COMMITTEES
7 AND SEE IF SOME OF THEM WERE ALSO ON SOME OF THE OTHER
8 COMMITTEES, TO ANSWER YOUR QUESTION.
9 Q BY MR. SCHURZ: ALL RIGHT. ARE YOU FAMILIAR
10 WITH --
11 THE COURT: JUST A SECOND. MR. SCHURZ, HOW MUCH
12 LONGER ARE GOING TO BE WITH THIS WITNESS?
13 MR. SCHURZ: I WOULD SUSPECT ALL AFTERNOON, YOUR
14 HONOR.
15 THE COURT: OKAY. I HAVE TO ATTEND A MEETING THIS
16 AFTERNOON. SO I'LL BE BACK -- WE'LL RESUME AT 1:45.
17 AND YOU'LL BE ABLE TO COMPLETE BY WHAT TIME THIS
18 AFTERNOON?
19 MR. SCHURZ: WELL, I CAN TELL YOUR HONOR, WE'RE
20 WORKING THROUGH SIX SUBSTANTIVE AREAS --
21 THE COURT: JUST GIVE ME A TIME.
22 MR. SCHURZ: I THINK, 4:00 O'CLOCK; I THINK, 4:30.
23 I THINK WE'RE --
24 THE COURT: WELL, I HAVE ANOTHER HEARING THAT'S
25 GOING TO TAKE SOME TIME THIS AFTERNOON. SO SEE IF YOU
26 CAN EXPEDITE THAT. I HAVE ANOTHER MEETING SCHEDULED AT
27 3:00. I'LL SEE WHETHER --
28 AND TOMORROW -- WHAT'S THE SCHEDULE

1 TOMORROW?
2 MR. SCHURZ: WE UNDERSTAND THAT DR. HUFF IS
3 AVAILABLE. WE HAVE ONE ISSUE THAT WE WANTED TO RAISE
4 WITH YOUR HONOR, IS WE HAVE -- OKAY.
5 SO WE UNDERSTAND DR. HUFF WILL BE APPEARING
6 TOMORROW.
7 THE COURT: OKAY. AND HOW LONG IS DR. HUFF'S
8 TESTIMONY GOING TO TAKE?
9 MR. METZGER: I THINK HIS TESTIMONY WILL PROBABLY
10 TAKE ONE DAY.
11 THE COURT: ONE DAY?
12 MR. METZGER: AND THAT WOULD PROBABLY INCLUDE -- I
13 THINK WE COULD PROBABLY -- I THINK WE'LL PROBABLY
14 COMPLETE HIM, IF WE HAVE A FULL DAY. I MEAN, I'M SAYING
15 BOTH SIDES. MR. SCHURZ HAS ADVISED THAT HE DOES NOT
16 HAVE MUCH CROSS FOR HIM, SO I THINK WE SHOULD BE ABLE TO
17 GET HIM DONE IN A DAY.
18 THE COURT: ALL RIGHT. I HAVE A SCHEDULING ISSUE
19 TOMORROW TOO.
20 WHAT WERE YOU GOING TO RAISE?
21 MR. SCHURZ: THAT WAS IT, YOUR HONOR.
22 THE COURT: OKAY. I HAVE A MEETING DURING THE
23 NOON HOUR TOMORROW TOO. SO WE'LL PROBABLY GO IN THE
24 MORNING UNTIL AROUND -- PROBABLY TILL AROUND 12:15, AND
25 WE'LL RESUME AT ABOUT 2:30. SO JUST AS A HEADS-UP, YOU
26 SHOULD BE ABLE TO COMPLETE HUFF, NEVERTHELESS.
27 MR. METZGER: YOUR HONOR, I DON'T THINK WE HAVE TO
28 REALLY HURRY HERE BECAUSE DR. BAYARD, WHO IS OUR LAST

WITNESS, IS NOT AVAILABLE TILL MONDAY. SO WE WILL FINISH DR. INFANTE AND DR. HUFF THIS WEEK WITHOUT ANY PROBLEM.

THE COURT: AS LONG AS THEY'RE NOT RUSHING OUT OF TOWN. IF DR. HUFF DOESN'T FINISH TOMORROW, HE'LL BE AVAILABLE --

MR. METZGER: OH, NO, NO. HE'S AVAILABLE; HE'S AVAILABLE. I BROUGHT HIM IN FROM THE EAST COAST, AND HE'LL STAY HERE TILL HE'S DONE. AND DR. INFANTE IS ALSO AVAILABLE TOMORROW IF HE SPILLS OVER INTO TOMORROW.

THE COURT: ALL RIGHT. WE'LL BE IN RECESS, THEN, AT THIS TIME TILL 1:45.

(AT 11:51 A.M., A LUNCH RECESS WAS TAKEN UNTIL 1:45 P.M. OF THE SAME DAY.)

EXHIBIT “F”

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT 323 HON. ELIHU M. BERLE, JUDGE

CERT, Plaintiff, vs. STARBUCKS CORP, ET AL., Defendants.	SUPERIOR COURT CASE NO. BC 435759 BC 461182

REPORTER'S TRANSCRIPT OF PROCEEDINGS

Monday, September 25, 2017

(A.M. Session)

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(Appearances continued on next page.)

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INDEX FOR MONDAY, SEPTEMBER 25, 2017

(A.M. SESSION)

CHRONOLOGICAL INDEX OF WITNESSES

WITNESS	DIRECT	CROSS	REDIRECT	RECROSS
INFANTE, Peter	3(M)	65(S)		

M - Mr. Metzger

S - Mr. Schurz

EXHIBIT INDEX

EXHIBIT NO.	DESCRIPTION	FOR ID	IN EVIDENCE
60071	Infante CV		4

CASE NUMBER: BC 411192/BC435759
CASE NAME: CERT CASES
LOS ANGELES, CALIFORNIA MONDAY, SEPT 25, 2017
DEPARTMENT 323 ELIHU M. BERLE, JUDGE
REPORTER: DAVID A. SALYER, CSR 4410
TIME: 9:00 A.M.

-o0o-

THE COURT: All right. Counsel ready on the trial in CERT versus Starbucks?

All counsel are present.

The defendant had concluded the evidence on the defense in this case.

Is plaintiff ready to proceed?

MR. METZGER: Yes. We previously called one witness. We have our second witness here today.

THE COURT: All right.

Plaintiff, call your next witness.

MR. METZGER: Yes. The plaintiff calls Dr. Peter Francis Infante.

MR. SCHURZ: Your Honor, before we begin with the testimony of Dr. Infante, we had one matter of housekeeping.

THE COURT: Okay.

MR. SCHURZ: Your Honor will recall the demonstratives that were presented for Dr. Carolyn Scrafford, DX 73540. It came to our attention that the versions that were provided in the binders did not have -- were not properly paginated.

And as there were specific references and we moved to admit a group of those slides based on page numbers, we would

ask now to swap out the exhibits that were part of that original DX 73540 with ones that are identical with the exception that these now bear a page number on the bottom.

THE COURT: Any objection?

MR. METZGER: I haven't seen it.

THE COURT: All right. Take a look at it now.

MR. METZGER: So, your Honor, this includes material for which there was not the stipulation. So I do object.

I did stipulate that certain of this material would be --

THE COURT: All right. I'll order the parties to meet and confer and see if there are any discrepancy and clarify that.

Then we will address the issue later today.

MR. METZGER: Very well, your Honor.

THE COURT: Give the plaintiff an opportunity to review it, Mr. Schurz. Explain to Mr. Metzger what changes were made, if any, in pagination, whatever the situation, and compare the two exhibits.

MR. SCHURZ: Of course.

THE COURT: All right. Thank you.

Mr. Metzger.

MR. METZGER: Yes. The plaintiff calls Dr. Infante.

THE COURT: Dr. Infante, please come forward.

THE CLERK: Sir, please raise your right hand.

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PETER FRANCIS INFANTE,

having been called as a witness and sworn testified as follows:

THE WITNESS: I do.

THE CLERK: And can you please state and spell your name for the record.

THE WITNESS: Yes. Peter Francis Infante. Last name is spelled I-N-F, as in Frank, A-N-T-E.

THE CLERK: Thank you.

THE COURT: Good morning, Dr. Infante.

THE WITNESS: Good morning, your Honor.

THE COURT: Please have a seat.

Mr. Metzger, you may proceed.

MR. METZGER: Thank you, your Honor.

DIRECT EXAMINATION

BY MR. METZGER:

Q. Dr. Infante, welcome back.

I believe you sat in that seat about three years ago.

A. Yes. It's been a while.

Q. Okay. I have -- let's see.

Dr. Infante, I'm going to provide you a copy of your curriculum vitae, which has been marked as Exhibit 60071.

A copy has been provided to defense counsel and to the clerk.

Could you confirm that Exhibit 60071 is your curriculum vitae?

A. Yes, it is.

Q. All right.

MR. METZGER: Your Honor, I'll offer Exhibit 60071 into evidence.

THE COURT: Any objection?

MR. SCHURZ: No objection, your Honor.

THE COURT: All right. Exhibit 60071 will be admitted into evidence.

(Exhibit 60071 received in evidence.)

Q. BY MR. METZGER: And, Dr. Infante, let's see. I see you have a copy of your report. That is Exhibit 60072.

Is that the report or list of opinions that you prepared for the phase two -- for the second phase of this case?

A. Yes, it is.

Q. All right. And a copy has been provided to defense counsel and to the clerk.

All right. Briefly, since it has been three years, you are an epidemiologist, correct, doctor?

A. Yes.

Q. And you worked in the '70s as an epidemiologist at the National Institute for Occupational Safety and Health doing epidemiologic studies regarding toxic substances and cancer and other effects?

A. Correct.

Q. And from 1970 to '83 you were a director of the Office of Carcinogen Identification and Classification at the Department of Labor -- United States Department of Labor; is that correct?

A. Correct, in the Occupational Safety and Health Administration.

Q. And then you were director of standards review for the Occupational Safety and Health Administration from '83 to 2002?

A. Correct.

Q. And after that you were a professor of environmental and occupational health until 2011 at George Washington University, correct?

A. Correct.

Q. All right. Now, in the first phase trial you testified about the relationship between coffee consumption and a number of cancers.

Do you recall that?

A. Yes.

Q. And do you recall what cancers you had reviewed and testified to at that time?

A. As I recall it was childhood leukemia, maybe bladder cancer and perhaps pancreatic cancer.

Q. Okay. And since you testified during the first phase one trial, have you subsequently reviewed and studied the epidemiologic studies regarding coffee consumption and other cancers?

A. Yes, I have.

Q. Okay. And how many cancers or what cancers?

A. Well, all of what would be considered the major cancers that people contract and die from.

Q. Okay.

A. I think approximately 20.

Q. Okay. And did you attempt to review the case-control studies regarding coffee consumption and the major cancers?

A. Yes.

Q. And the cohort studies?

A. Yes.

Q. And the meta-analyses?

A. Yes.

Q. Did you attempt to review and study all of the epidemiologic studies and literature regarding coffee consumption and cancers, at least those that are in the English language?

A. Yes.

Q. All right. Now, did you review any randomized control trials regarding coffee consumption and cancer?

A. I'm not aware that there are any.

Q. Right. Okay.

And what is the significance of that to you?

A. Well, in dietary epidemiology because there are so many components to the diet, it's generally considered that the only way you can make a determination of causality would be to do a controlled clinical trial.

MR. SCHURZ: Your Honor, we'll object and move to strike.

There has been no foundation that Dr. Infante has any foundation to opine with respect to dietary epidemiology.

His entire career has been in the area of occupational

epidemiology. He has no basis for offering opinions to this Court about dietary epidemiology.

THE COURT: Objection overruled.

You may cross-examine on the subject and make a motion to strike.

Mr. Metzger, you may proceed.

Q. BY MR. METZGER: Well, Dr. Infante, are there any governmental agencies which are of the view that one cannot determine causality with respect to food substances and cancer or other diseases in the absence of controlled trials?

A. Well, yes. The Food and Drug Administration. They are the responsible agency for food safety.

Q. All right. Very good.

So have you ever concluded causality based upon observational epidemiologic studies?

A. Yes.

Q. In what context?

A. Well, I mean, if you're talking about occupational now?

Q. Whatever context you choose.

A. Well, yes.

In fact, I conducted a study that was published in 1977 on benzene exposure and leukemia. And I concluded, and so did the rest of the world conclude, that on the basis of that study benzene was a cause of acute leukemia.

Q. Okay. And that was based on observational epidemiology, correct?

A. Yes, in the occupational setting, where there

were fewer confounding factors than you have to deal with when you're doing a dietary epidemiology.

Q. Okay. All right.

So for this case in the second phase now you have -- regarding your review of the epidemiologic studies in the English language regarding all different types of cancers, could you tell us generally what you found.

A. Well, in terms of -- I found that, in my opinion from the science that I evaluated, that there were a number of studies that showed positive associations.

I mean, there are quite a few studies, in fact. But what I meant to say was that show positive associations for a number of cancers.

There are studies that show inverse associations for three cancers. And then there are other studies, the remainder, I don't think they show any evidence yet one way or the other.

Q. All right. So let's talk about those.

When you say a positive association, by that do you mean an increased risk of the cancer?

A. Yes.

Q. All right. And for which cancer sites or cancers did you find that there were studies indicating increased risk of cancer?

A. Well, there were 12 that I -- it was my opinion there was some evidence of an increased risk.

Q. And what are those cancers?

A. They are bladder cancer, childhood acute

leukemia, childhood brain cancer, colorectal cancer, gastric cancer, kidney cancer, laryngeal cancer, lung cancer, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer and prostate cancer.

MR. SCHURZ: Your Honor, we would ask that the record reflect that Dr. Infante is reading from his list of opinions.

THE COURT: All right. Thank you.

Q. BY MR. METZGER: And from your review of the studies, was the evidence stronger for some of these cancers than others?

A. Yes.

Q. For which did you consider the evidence to be stronger?

A. Well, I thought the evidence that -- the positive evidence was the strongest for childhood acute leukemia and I would say secondarily for gastric cancer and for ovarian cancer.

Q. All right. And you mentioned that there were, I believe, three cancers for which the studies reported inverse associations?

A. Correct.

Q. And which were those?

A. Endometrial cancer, lung cancer and skin cancer.

Q. Did you say you lung cancer?

A. I'm sorry. I meant endometrial cancer, liver cancer and skin cancer.

Q. All right. And do you consider the evidence to be strong for the inverse association between coffee

consumption and endometrial cancer?

A. No.

Q. Why not?

A. Because of the amount of confounding in those studies. I don't think it's possible to make a determination on causality.

Q. Okay. And regarding the studies of coffee consumption and liver cancer, the inverse association that's been reported, do you consider that association to be strong?

A. No, I don't.

Q. And why not?

A. For the same reason. There's multiple confounding factors that aren't adequately dealt with in the epidemiological studies.

Q. Okay. And do you consider the inverse association that's been reported regarding coffee consumption and skin cancer to be strong?

A. No, I don't.

Q. And why not?

A. For the same reason.

Q. All right. In addition to reading the studies regarding coffee consumption and particular cancers, did you also read studies regarding coffee consumption and total cancer or total cancer mortality?

A. Yes.

Q. And what exactly is that?

A. Well, total cancer -- a study of total cancer mortality would be a study that combines all of the

site-specific cancers into the general category of cancer.

So it would be any cancer that an individual developed that would be the analysis for total cancers.

Q. And approximately how many studies did you find that assessed coffee consumption and total cancer?

A. I think for that literature -- I think I reviewed -- let's see -- there were 14 cohort studies that I reviewed.

Q. These were all cohort studies?

A. Correct.

Q. Okay. And regarding those studies, what did you find?

A. Well, I found that of the 14 studies, there were four that showed statistically significant increase in risk of total cancer.

There were three that showed increased risks of total cancer that were not statistically significant.

There were six that showed no association.

Then there was one that showed an inverse association.

MR. SCHURZ: And again, your Honor, we would observe that Dr. Infante is simply reading from his opinions, Exhibit 60072.

THE COURT: Thank you.

Q. BY MR. METZGER: All right. And, Dr. Infante, what did you conclude -- based upon your review of those studies of coffee consumption and total cancer, what did you conclude?

A. Well, looking at total cancer, quite frankly I

was surprised there were so many that were positive.

My conclusion on the basis of reviewing those studies is that, you know, one cannot conclude there's, like, an absence of cancer risk from coffee consumption.

Q. Okay. Now, did you -- you are familiar, of course, with the International Agency for Research on Cancer?

A. Yes, I am.

Q. And how do you consider that organization? What is your view of it?

A. Well, the International Agency for Research on Cancer is the expert cancer committee for the World Health Organization. And the entire world depends on their evaluations for substances or agents that cause cancer in terms of cancer warnings.

So like, for example, in the United States the Occupational Safety and Health Administration follows and adopts their evaluations of what causes cancer in terms of hazard warnings and labeling.

And there's also -- for the entire world now we have a globally harmonized system of classifying substances and informing people about the cancer hazards. And the IARC -- it's a shortening of the International Agency for Research on Cancer -- it's their evaluations that the world depends upon.

I've been -- a number of times I have been -- I've served as an expert epidemiologist for these working groups that meet in Lyon, France.

Q. Okay. What is the mission of the International Agency for Research on Cancer?

A. Well, there's a research component to it that does epidemiological studies throughout the world. Then there's, you know, an educational component to it.

Then they have what's called the IARC monograph program where they publish monographs that are a compilation of the evaluations that they do for specific chemicals or agents or workplaces.

So those monographs are published by the World Health Organization. And it's that component of IARC that informs the public about the cancer risks from various exposures.

Q. Now, when you say the cancer risk, does IARC actually assess risk or does IARC evaluate and conclude whether chemicals and other substances cause cancer?

A. Well, they determine if there's a risk of cancer, what the risk of cancer is. In other words, is there sufficient evidence on a qualitative basis.

They don't usually do a quantitative dose response.

Q. Okay. All right.

Now, did the International Agency for Research on Cancer issue a monograph some years ago regarding coffee?

A. Yes.

Q. And in the last year, in 2016, was a working group convened to update the evaluation of the International Agency for Research on Cancer on coffee?

A. Yes.

Q. All right. Has the International Agency for Research on Cancer published the new monograph on its evaluation of the carcinogenicity of coffee?

A. No.

Q. All right. Is there any summary that has been published regarding the working group's meeting?

A. Yes. The summary of the evaluation has been published in The Lancet Oncology.

This is routine. After IARC does an evaluation, there's very shortly -- within, I would say, three months of that evaluation, a summary is published in Lancet Oncology and then that's followed by a publication of the full monograph.

Q. All right. And have you read the short summary that was published in Lancet Oncology?

A. Yes.

Q. All right. And what is the International Agency for Research on Cancer's current assessment of the carcinogenicity of coffee to humans?

A. Well, they place it in their category 3.

Q. What is that?

A. Category 3 is that it's not classifiable as to its carcinogenicity to humans.

Q. Okay. And did the International Agency for Research on Cancer post on its website some information to explain what that means?

A. Yes. They have a document they published subsequent to the meeting. It was like a question and answer document.

Q. And what does it say regarding what that classification means for coffee?

A. Well, I didn't -- do you mind if I -- I have a

copy of it, but rather than mischaracterizing it --

MR. SCHURZ: I want to impose an objection.

We're not here to have Dr. Infante read us documents he pulled off a website.

So it's hearsay.

THE COURT: Those documents are hearsay.

If he has an opinion, he can express the opinion without reading.

Q. BY MR. METZGER: Can you give us the essence, the gist, of what IARC's conclusion means?

A. Yes. What it means is that they said it's not classifiable, which means they looked at quite a large number of studies. So they can't conclude whether or not it causes an elevated risk of cancer or is associated with a reduced risk of cancer. It's not possible to determine.

Q. And why is that?

A. Well, I think the problems that you have with --

MR. SCHURZ: Well, I'll interpose an objection. It calls for speculation.

The question is why did IARC make the conclusion. This witness has no foundation for understanding what the basis is of IARC's conclusion.

THE COURT: All right. Thank you.

The objection is overruled.

Q. BY MR. METZGER: Go ahead, Dr. Infante.

A. I'm sorry. Could you ask the question again.

Q. Yes.

What's your understanding of why IARC concluded that it

cannot presently be determined whether consumption of coffee does or does not cause human cancer?

A. Well, I mean, there were several reasons why. But in general they felt they couldn't rule out chance, bias or confounding from evaluating the studies. And, you know, they talked about, I believe, exposure misclassification. And.

Also there were several sites where they felt there wasn't enough information available, several cancer sites.

Q. All right. And do you agree with IARC's recent conclusion that the current state of the epidemiologic literature is inadequate to determine whether consumption of coffee does or does not cause human cancer?

A. I agree with that determination.

Q. All right. Now, Dr. Infante, did you review the PowerPoint slides that Dr. Alexander presented for his presentation?

A. Yes.

Q. Okay.

MR. SCHURZ: I'll interpose an objection.

That was not part of his reliance materials, obviously. It was never presented, nor has he ever offered any opinions in a deposition with respect to responding to anything from Dr. Alexander.

Quite the opposite. In his deposition he was asked, did you review Dr. Alexander's opinions.

Dr. Infante said no.

Do you intend to offer any opinions with respect to

Dr. Alexander?

Dr. Infante responded no.

THE COURT: All right. Objection overruled subject to a motion to strike.

Counsel may proceed.

Q. BY MR. METZGER: Dr. Infante, in the PowerPoint slides that Dr. Alexander presented, did you note that he listed two cancers for which he concluded there was an independent inverse association?

A. Yes.

Q. And what were those two cancers?

A. Endometrial cancer and liver cancer.

Q. Okay. All right.

And are those two of the cancers that you reviewed the literature for in your work for this case?

A. Yes.

Q. All right. So I would like to ask you, did you pay particular attention regarding those cancers, those two cancers?

A. Particular attention to what?

Q. To reviewing the literature regarding those cancers.

A. Yes.

Q. And could you tell us -- tell the Court what methodology you employed in assessing Dr. Alexander's conclusion that those two cancers, endometrial cancer and liver cancer, were independently inversely associated with coffee consumption.

A. Well, I reviewed the case-control studies, cohort studies and meta-analyses to see, all right, what is this literature showing.

Then I also reviewed the literature on confounding factors related to those cancers -- related to endometrial cancer and liver cancer -- with the purpose of determining whether or not those confounding factors were considered in the epidemiological studies and to what extent they were considered.

Q. All right. And as part of your work in this case, did you prepare lists of the factors that had been reported in epidemiologic studies as being positively and inversely associated with endometrial cancer and liver cancer?

A. Yes, I did.

Q. And is that an appendix to your report?

A. Yes, it is.

Q. All right. How many factors did you identify from your review of the epidemiologic literature apart from coffee as being inversely associated with endometrial cancer?

A. Well, I mean, there are quite a few of them.

I mean, I haven't memorized all of them, but I can refer to my appendix.

Q. Could you refer to your appendix and tell us which factors you identified as being significantly inversely associated with the development of endometrial cancer.

MR. SCHURZ: I'll interpose an objection that Dr. Infante is just being instructed to read from a document, so it's hearsay.

THE COURT: The witness should not be reading from documents.

Ask the witness questions about his work and his conclusions.

MR. METZGER: Well, your Honor, we could put this up in a PowerPoint slide. Defense was reading what they did from PowerPoint slides. I don't see the difference.

MR. SCHURZ: No, we were not. I object to the characterization.

THE COURT: You can present through a PowerPoint slide, but the witness should respond by not just reading.

Q. BY MR. METZGER: Well, Dr. Infante, from your memory, can you tell us some of the factors that epidemiologic studies had reported to be inversely associated with the development of endometrial cancer.

A. Yes. In other words, factors that are related to a reduced risk?

Q. Yes.

A. Well, cigarette smoking is one of the major confounders.

Cigarette smoking -- there are quite a number of studies that show that cigarette smoking is associated with a reduced risk of endometrial cancer.

Then there are individuals that have a healthy diet have a significantly reduced risk.

Individuals in other studies that were considered to have a Mediterranean diet, that's associated with reduced risk.

There were individuals that have a high-fiber diet, reduced risk.

Individuals that take bisphosphonates to increase calcium content, they have a reduced risk of endometrial cancer.

Also the age that you begin menstruation and when you reach menopause has an effect of reducing the risk of endometrial cancer.

The number of children you have. In other words, if you have more children versus fewer children, you have a lower risk. If you have a child at all versus women that have no children, you have a lower risk of endometrial cancer.

So there are, you know, a number of factors.

So tea has been shown to reduce the risk of endometrial cancer.

And, well, vegetables. We've talked about diet. But specifically analyses have been done separately for fruits and vegetables, and it's been shown to be associated with a reduced risk of endometrial cancer.

Q. Did you review studies regarding aspirins and nonsteroidal anti-inflammatory agents in endometrial cancer?

A. Yes.

Q. And what did those show?

A. They were also associated with the reduced risk of endometrial cancer.

Q. And did you review studies regarding oral contraceptives and intrauterine devices?

A. Yes.

Q. And what did those indicate?

A. They are also associated with a reduced risk of endometrial cancer.

Q. Do you recall studies regarding vitamins or nutrients and endometrial cancer?

A. Yes, there were some vitamins associated with a reduced risk of endometrial -- several different vitamins that were associated with the reduced risk of endometrial cancer.

Q. Okay. And what did you conclude --

A. Oh, and physical activity, I believe, also.

Q. And what did you conclude regarding these studies, epidemiologic studies, that reported inverse associations between these factors and endometrial cancer?

A. What I concluded was that they were not adequately, you know -- they were not adequately accounted for or adjusted for in the epidemiological studies, that there was confounding from these.

And because of that, in my opinion, you can't really make a -- determine about a specific dietary component and, you know, conclude that it confers a benefit in terms of cancer or an elevated cancer risk.

MR. SCHURZ: And, your Honor, we would object and again move to strike on the lack of foundation as to this witness' understanding and ability to provide any opinions with respect to the interaction of specific dietary components and the benefits that they may or may not confer.

His entire experience is as an occupational epidemiologist.

THE COURT: Objection overruled, subject to the cross-examination and a motion to strike.

Q. BY MR. METZGER: All right. Well, let's talk about that, Dr. Infante.

Over your career have you studied not just occupational epidemiology but cancer epidemiology?

A. Yes. My career has really been essentially, for the most part, in cancer epidemiology.

Q. And over your career have you also studied chronic disease epidemiology?

A. Yes, I have.

And I've also actually done some research in dietary epidemiology.

Q. Okay. And is some of that published?

A. That wasn't cancer, but it was dietary epidemiology related to, like, fluoride intake and vitamin/mineral substitutes and the effects on developing teeth.

Q. Now, incidentally, while we're on the topic of endometrial cancer, you mentioned smoking. And we'll talk about that in a moment.

But were there any epidemiologic studies regarding coffee consumption and endometrial cancer that were done or assessed, the risk of endometrial cancer, among never smokers?

A. I believe so, yes.

Q. And what did you find regarding that?

A. Well, among never smokers there was, like, an elevated two-fold risk of endometrial cancer, which tells me

that concern about confounding from cigarette smoking when you're evaluating endometrial cancer is justified.

But I'm not the only one that thinks that. People in dietary epidemiology have that opinion as well, in terms of the component of cigarette smoking reducing the risk. Because when a group is evaluated that did not smoke, they, in fact, had an elevated risk of endometrial cancer.

Q. All right. And regarding the association between cigarette smoking and endometrial cancer, did you review any meta-analyses regarding that topic?

A. Yes, I did.

Q. And what did you conclude from your review of the meta-analyses regarding cigarette smoking and endometrial cancer?

A. Well, there are a number of studies that indicate that there's an inverse association between cigarette smoking and risk of endometrial cancer.

Q. So cigarette smoking, according to those studies, is reducing the risk of cancer for the endometrial?

A. Yes.

In fact in some studies you had only, like, a 50 percent of the risk of what you would expect, if what you would expect would be a risk of 1, which means no increase or decrease.

You know, in some studies the risk was, like, .5, which means that for cigarette smokers had a 50 percent reduction in endometrial cancer.

Q. Does that mean that cigarette smoking doesn't

cause cancer?

A. Well, it has a beneficial effect, apparently, for endometrial cancer. But I think -- I hope that most of the public knows that there are quite a number of cancers that are caused by cigarette smoking.

Q. Okay. And has there been a mechanism or an explanation proposed for why cigarette smoking reduces the risk of endometrial cancer?

A. Well, there has been a proposal, but I don't think that it's confirmed.

Q. All right. And what is the proposal?

A. I think it was --

MR. SCHURZ: Interpose an objection that the witness has already stated that there is no explanation. There has been a proposal and further stated that it's not confirmed.

So we're being asked now to hear the speculation of an unconfirmed proposal. So for that reason it lacks foundation, and it's not been accepted within the medical community and should not be a part of this testimony.

THE COURT: All right. Thank you.

Objection overruled.

You may continue.

THE WITNESS: Yes. That cigarette smoking has anti-estrogenic effects, so there is a mechanism that's been proposed.

Q. BY MR. METZGER: Okay. All right.

So you mentioned so many different factors that have been significantly inversely associated with endometrial

cancer in epidemiologic studies.

From your review of the epidemiologic studies of coffee consumption and endometrial cancer, did any of those studies control or adjust for all of the factors that have been reported to reduce the risk of endometrial cancer?

A. No.

Q. Is that important?

A. Yes.

Q. Why?

A. Because if you have -- if you don't consider a confounding factor when you're trying to evaluate the risk of, let's say, a single exposure in, let's say, endometrial cancer, you have confounding, which means you then cannot separate the individual effect from the coffee on the outcome in terms of the relative risk of the cancer.

Q. All right. I would like you to assume that Dr. Alexander's definition of an independent association was one that was -- was one where there was no appreciable confounding bias or chance.

Assuming that to be true, would you agree with Dr. Alexander's conclusion that there is an independent association for coffee consumption and endometrial cancer?

MR. SCHURZ: Same objection, your Honor. Outside of scope.

This witness testified during his deposition that he had not read Dr. Alexander's opinion and would not be commenting upon Dr. Alexander's opinion.

THE COURT: Overruled.

THE WITNESS: No.

Q. BY MR. METZGER: Okay. And why is that?

A. Because there's obviously quite a number of confounding factors that aren't considered. And even some of them that were considered, I'm not -- I don't believe that they're adequately adjusted for in the studies.

Q. Okay. All right.

Now, the other cancer that Dr. Alexander indicated was inversely associated with coffee consumption was liver cancer.

And before this case, had you become familiar with liver cancer from your research?

A. Yes. I'm familiar with liver cancer.

I mean, I've published articles from the occupational setting, articles on the risk of liver cancer.

Q. And is there anything about liver cancer which makes liver cancer different from most other cancers?

A. That makes it different?

Well, I mean, it's a cancer of the liver, that specific target organ.

But the other thing about -- I mean, there are two forms of -- major forms of liver -- I won't say major forms.

You have hepatocellular carcinoma, which is the liver cancer that most people develop and die from.

And you have angiosarcoma of the liver, which is not a -- it's a vascular lesion of the liver, not a cancer of the parenchyma of the liver.

So with hepatocellular cancer, which is the common liver cancer, you have the -- major factors related to an

elevated risk of liver cancer are chronic liver disease. Both hepatitis B and C and other factors that relate to chronic liver disease. It's the chronic liver disease that places people at, you know, a high risk of developing liver cancer.

Q. And in reviewing the epidemiologic studies regarding coffee consumption and liver cancer, did you pay attention in the studies to whether the investigators addressed liver disease and, in particular, the hepatitis viruses and other infectious causes of liver cancer?

A. Yes.

Q. And what did you find?

A. I found that most of the studies related to coffee consumption and liver cancer did not evaluate the effect of liver infections, mainly hepatitis B and C, on the risk of liver cancer.

The reason they -- you would think that, well, it's a very -- it's the most recognized risk factor for liver cancer. Why was it not considered in epidemiologic studies where you have coffee consumption and liver cancers.

The reason is because the information on the consumption of coffee in these studies is based on a questionnaire. And you can't determine -- or rather they didn't -- I don't know why they didn't ask. They didn't ask information on the questionnaires. Maybe people wouldn't know or it would be too much noise in it. But when you're doing a questionnaire-type survey study, you're not drawing blood samples, so there's no test.

You know, in most of these studies there is no blood

samples being evaluated to determine if the individual has a chronic liver disease or not or has hepatitis specifically.

Q. All right. And was that acknowledged by the authors of these studies as a limitation of their studies?

A. Yes. There must be, you know, 10, 12 authors that have specifically, when they've done their study, they've said that they could not control for infectious hepatitis. So the results they found, they couldn't really depend on them.

Then some of them recommend that, you know, because of that, a controlled clinical trial would need to be done.

Q. Okay. All right.

Were there any other factors that you considered regarding liver cancer as affecting these studies?

A. Are there other factors -- you mean that would -- that play a role in the risk of liver cancer?

Q. Sure.

A. Well, yeah.

There are both positive and negative confounders.

Q. As far as the factors that have been reported, did you consider factors that have been reported to reduce the risk of liver cancer?

A. Yes, there are a few.

Q. And what were those?

A. Well, there were some studies that showed that tea or green tea reduced the risk of liver cancer.

And there may have been a study of, I think, maybe water consumption.

Well, actually what it is, it's like -- I want to say

potable drinking water or uncontaminated water.

There is evidence that drinking contaminated water is associated with an elevated risk of liver cancer and that -- in fact, there was an intervention study done showing that then when you remove people from the contaminated water, the risk of their liver cancer was reduced.

So to me that's pretty powerful evidence of causality. It's evidence of causality that the contaminated water is what caused the liver cancer.

When you remove the contamination, then the risk goes down.

Q. Okay. Could you tell us a little bit more about that. What did that study involve or entail?

A. Well, it was a study that was done in -- I think it was done in China where individuals were using drinking water that was contaminated. And then they were switched to -- when this was recognized, the high risk of liver cancer, they were switched to well water.

Then following them over time, the risk of liver cancer subsided.

Q. Okay. So that's like an intervention study?

A. Yes, it is.

It is an intervention study.

Q. Okay. All right.

From your review of the epidemiologic studies regarding coffee consumption and liver cancer, did you make any observations regarding misclassification of exposure?

A. Yes. Well, yes.

Q. And tell us what you observed or concluded.

A. I just want to make sure we're talking about the same thing here.

There is misclassification of exposure in terms of evaluating coffee intake.

Q. Yes.

A. That's one phase of it.

Q. Okay.

A. And one of the problems with these studies is that you're evaluating coffee consumption at baseline, which means that when the individual gets enrolled into the study, you're doing a history of their coffee consumption.

Then as you follow them over time, people change. Some people are going to change their coffee habits. Some are going to drink more. Some are going to drink less.

So when that happens, and you're assuming that they used to have a certain level, there is a misclassification which is going to bias you towards the null of no association. Because some people that you classified as low coffee consumers are eventually going to be high coffee consumers. Some individuals that had baselines that were high coffee consumers, if they reduce coffee consumption for health reasons or whatever, you have them in a high category of coffee consumption, but, in fact, they're drinking less so they have a lower risk.

So what you're doing with a dose response curve, if there was an increase, you're flattening it, because you're raising the bottom end and lowering the upper. So you have

misclassification of exposure, which then biases you toward the null.

Q. Is that a substantial problem in epidemiologic studies if you misclassify exposure?

A. Yes. And -- yes, it is.

And even if it's differential, even if it's a non-differential classification, meaning that you do the same things with the controls that you do with the cases, it's still going to flatten the dose-response curve.

Then on the other hand, you can have differential exposure classification, which means in one group you're misclassifying more than in the other.

That situation can result in either, you know, showing erroneously an increased risk or erroneously a decreased risk.

Q. Okay. Are you familiar with a concept known as reverse causation?

A. Yes, I am.

Q. And could you explain to the Court what reverse causation is.

A. Well, yes.

In epidemiology in terms of causation, you have exposure and then you're evaluating disease.

So did that exposure cause -- then you're looking for disease outcome.

With reverse --

Q. Hold the mic a little closer to you.

A. Oh, I'm sorry.

With reverse causation, just what the name implies,

what you do is you identify -- you have individuals that have -- let's say that are at a high risk. So you identify individuals that are high risk of developing liver cancer, and their exposure is based on their diagnosis.

So it's reversed.

Q. I see.

A. Maybe I can explain that another way.

Q. Yeah, try.

A. Well, for example, like I said before, one of the major risk factors for liver cancer is chronic liver disease.

Well, patients that have chronic liver disease, their physicians sometimes recommend that they reduce or eliminate their coffee consumption. Sometimes they're not feeling good so they reduce it on their own.

So when that happens, you're taking some of the individuals that you have in your study that have -- they are at a high risk of liver disease, their coffee consumption is then going to be zero, or less than zero, so you're putting the non-coffee consumers in a high-risk group.

Then if you have some of the others that, let's say, have chronic liver disease and they don't quit, but they consume less and less, then the risk for those is lower.

As a result of that, you get an inverse association because you're really putting them into a low -- you're doing this inadvertently. You don't know it, but you're putting them into a low-exposure group. And the reason they're not drinking coffee is because they have liver disease which is

associated with a high risk of liver cancer.

So you end up with an inverse dose response.

And, you know, there are a number of investigators that have mentioned reverse causation in terms of coffee consumption and the inverse association with liver cancer.

Q. Let me see if I understand.

So if someone has liver disease, which often devolves into liver cancer, and they end up with liver cancer and they're included in the study, they may have at the outset of the study been reported to be a coffee drinker but during the course of the study they ceased drinking coffee.

So it's actually the cancer that's causing the exposure rather than the exposure causing the cancer; is that it?

A. Correct.

MR. SCHURZ: Let me interpose an objection with respect to both Mr. Metzger's characterization and this witness' speculation with respect to an unidentified study and teasing out a whole range of behaviors relating to nutrition about which this witness has never done any research and knows nothing about.

THE COURT: Objection overruled.

THE WITNESS: Well, I cite it in my -- I don't know if I'm supposed to say, but I reviewed several studies -- and they're in my report -- where the investigators talk about that the inverse association between coffee consumption and liver cancer may be spurious.

Q. BY MR. METZGER: Spurious?

A. Yes.

Q. Is that the term that the authors of these studies themselves use?

A. Yes.

Q. And in about how many studies regarding coffee consumption and liver cancer did the investigators themselves characterize the association as spurious, or possibly spurious?

A. Well, four that I'm certainly aware of.

Bravi, 2007 study, Larsson 2007, Chuang 2009 and Tanaka, 2007.

That's a pretty common thought, reverse causality between coffee consumption and liver cancer.

Q. Okay.

THE COURT: Let me see if I understand.

Are you suggesting that in studies based upon studying those who have cancer and going back to see if they drank coffee?

THE WITNESS: I'm talking specifically about liver cancer.

THE COURT: All right. Liver cancer.

THE WITNESS: Yes, liver cancer.

THE COURT: So that is the methodology, determining people who are suffering from liver cancer, and then to reverse it, not to see whether coffee drinkers incur disease of liver cancer, but to find those who have liver cancer and then find out if they drank coffee? Is that what you're suggesting?

THE WITNESS: Well, no.

What I'm suggesting is that individuals who are at a high risk of liver cancer -- for example, they have hepatitis B and C -- that there are a number of reports that talk about their physicians recommend that they don't drink coffee, or maybe they're not feeling good with hepatitis so they stop drinking themselves.

So at the outset of the study they're classified as not drinking -- could I maybe use a board?

MR. METZGER: Sure.

THE WITNESS: Your Honor?

THE COURT: Yes. Go ahead.

MR. METZGER: Let me take this down.

THE WITNESS: So when you're doing a study and you're determining, okay, what is the coffee consumption of these individuals that you're enrolling at baseline, and let's say this line represents an inverse association, so the more coffee you drink, the lower is your risk of liver cancer.

The problem is that individuals who have chronic liver disease that are at high risk, they're recommended that they don't drink coffee. So they get put in the no or low coffee consumption group.

So it's like their risk is high.

Why? Because they have hepatitis or other liver diseases.

So if they don't -- if they don't drink coffee -- and, see, they don't know in these studies which ones have hepatitis. There are 12 or 14 investigators that have identified this relationship and said that, well, we don't

know if it's spurious because they don't have information on hepatitis, the group.

So what it is, they don't drink coffee. So now they have the highest risk.

Why? Because they have chronic liver disease, a very high risk.

Then you'll have some that maybe haven't totally discontinued, but they're drinking some.

So now some of the individuals with chronic liver disease, you know, are in this group. So they're here. And so on.

You get down here, they drink less. You're down here.

Then the ones who drink the most, you know, you're going to have a much lower prevalence in that group of coffee consumers. So that means that those that drink the highest amount of coffee, they have the lowest risk of liver disease.

Why? Because those that have chronic liver disease, which is a major factor for liver cancer, there aren't going to be as many in the high coffee consumption group.

THE COURT: My question was really directed as to the concern as to the examination of the appropriate group.

In this study are they examining coffee drinkers or are they examining those with liver cancer disease?

THE WITNESS: Well, they are enrolling them in the study and then they're trying to determine what they died from.

THE COURT: But is a precondition of entering into the study those individuals suffering from cancer?

THE WITNESS: No, not in a cohort study, no. They don't -- they don't have cancer when they're enrolled in the study.

But they can have -- but individuals can have, and they do have chronic liver disease, hepatitis and other liver diseases.

What I'm saying is when they're doing the dose-response analysis, and when they do it at the baseline when they're entering these individuals into the study, those that have the highest risk of cancer, of liver cancer, will be put in the lowest coffee consumption group. And they have the highest risk.

THE COURT: I understand your point there.

But what I'm asking is that those that are in the study, are they chosen as a random sample or are they chosen because they, in fact, are suffering from liver cancer?

THE WITNESS: No.

They're chosen to evaluate their coffee consumption and what their outcome of cancer would be.

But there is a bias in the study.

THE COURT: But is that a random sample of individuals that have the disease, don't have the disease or just unknown?

THE WITNESS: Well, see, that's the thing. They don't know if they have chronic liver disease or not when they enroll them.

THE COURT: Okay.

THE WITNESS: Because of that, those that have chronic liver disease are most likely to be put in the low coffee

consumption group because of recommendations that they eliminate or reduce their coffee consumption. And they're at the highest risk.

That's why you call it reverse causality. Like, their coffee consumption has to do really with their chronic liver disease. That's dictating how much coffee they drink.

THE COURT: All right. Thank you.

THE WITNESS: Okay.

MR. METZGER: Okay. All right.

Q. So you mentioned earlier, Dr. Infante, that you had identified a few factors that reduced the risk of liver cancer from your review of epidemiologic studies?

A. Yes.

Q. And I think you mentioned tea and green tea and uncontaminated water.

What was your conclusion regarding those factors, regarding how those might impact the coffee liver cancer epidemiologic studies?

A. Well, I mean, there's some association with these three factors. So the point is that you would want to -- you would want to entertain or control for those when you're doing your study of coffee consumption and liver cancer.

Q. So when you say there's an association, you mean an inverse association?

A. Yes.

Q. Okay.

A. Because you always then want to ask the

question, is the inverse association related to the coffee consumption or is it related to some other factor also in the diet.

Q. Okay.

A. You know, this is the problem with occupational epidemiology.

You take into your body a lot of dietary factors, and you take into your body a lot of medicine. You have lifestyle factors. The cigarette smoking would be one lifestyle factor. And how do all of these things interact. Then how do they impact on the risk, let's say, of liver cancer that you ultimately estimate from that population.

Q. I believe in that statement you just gave that you said this is the problem with occupational epidemiology?

A. I'm sorry. I meant dietary. Excuse me.

Q. All right. So from your review and study of the epidemiologic studies regarding coffee consumption and liver cancer, did any of those studies control or adjust for tea consumption, green tea consumption or consumption of uncontaminated water?

A. I don't know that they controlled for contaminated -- for uncontaminated water, but some of them controlled for I think tea or green tea. Because there were tea and coffee consumption studies where they were studied together.

But my point is I'm not saying that the green tea or the tea or the uncontaminated water is responsible for the reduction. My point is that you need to entertain these other

risk factors when you're evaluating and trying to estimate the effect of, let's say, liver cancer from, you know, a single dietary element, coffee.

Q. Okay. All right.

And what is the consequence, as an epidemiologist, to you of not assessing these other factors that have been reported to reduce the risk of liver cancer in the studies of coffee consumption and liver cancer?

A. Well, I would say that then your estimate of risk is pretty shaky. It makes it difficult to estimate the risk from a single component in the diet.

Q. Where there are other confounding factors that have not been accounted for?

A. Yes.

Q. Okay.

A. Well, I could go even further and say that even sometimes when they are accounted for and they statistically adjust for it -- let's take, like, cigarettes -- that was endometrial cancer. When they adjust for some of these other factors, they don't state how they adjust for these factors. They would like to know what are they doing, and depending the models they're using --

Q. Okay.

A. Are they assessing the independent effect of these other components of the diet or other lifestyle factors that also have an impact on the risk of that disease.

Q. That raises another issue I would like to ask you.

Regarding endometrial cancer and coffee consumption, is consumption of coffee correlated with cigarette smoking?

A. Oh, yes, it is. That's an important factor I hadn't discussed.

Q. What does that mean?

A. That means that individuals who drink more coffee, there's a -- they also smoke more cigarettes.

So when you're doing a study and you're looking at an increase in coffee consumption and you're looking at, let's say, the risk of endometrial cancer, well, the highest coffee consumers are also going to be those that have the highest smoking habit, highest percentage, because there's that -- everybody talks about the correlation between.

So those that drink coffee smoke more. Those that smoke more drink more coffee compared to the average person.

Q. And there are studies that show that?

A. Yes.

Q. And you have a lot of those studies?

A. Yeah, I reviewed them. I have a section here.

THE COURT: So how do you determine if there is a cause and effect between the smoking and the cancer as opposed to the coffee?

You could say that those individuals may also eat a lot of strawberries. So where is the causation, eating strawberries, smoking or drinking coffee?

THE WITNESS: Well, it's not a -- strawberries wouldn't be a confounder unless there is some evidence that strawberries either protect or confer some elevated risk of

liver cancer.

Q. BY MR. METZGER: But his Honor's question is how can you determine causation when you have coffee consumption and smoking being highly correlated with each other?

A. Well, I mean that's the difficulty.

I mean, that correlation is known. So it's matter of interpreting the observations in the study.

In other words, the high coffee consumers smoke more, then is that reduction in risk because of coffee consumption or is it due to more cigarette smoking?

THE COURT: Well, I --

THE WITNESS: Which makes it impossible to estimate, then, the single effect from coffee. It makes it impossible. You can't estimate the effect from coffee only because of that.

It's confounding. It's a confounding factor.

Q. BY MR. METZGER: So where you have factors that are highly correlated, like cigarette smoking and coffee consumption, are you saying that scientifically it's impossible to separate those and conclude causality?

A. I would say it's very difficult, yes.

Q. Okay. All right.

So I think we've covered the two cancers that Dr. Alexander concluded were independently inversely associated with coffee consumption.

You mentioned, I think, a third cancer that you found there in the studies to be inversely associated, and that was skin cancer.

A. Yes.

Q. And when you investigate whether there is an association between cigarette smoking and skin cancer or melanoma, specifically?

A. Yes. Specifically smoking cigarettes reduces your risk of skin melanoma.

Q. Okay. All right.

Is that, in your opinion, a confounder of the inverse association between coffee consumption and skin cancer?

A. Yes, it is.

Q. For what reason?

A. Well, it's a confounder because cigarette smoking is known to reduce the risk of melanoma and there's a pretty good correlation between cigarette smoking and coffee consumption.

So if those who -- again, those who then drink more coffee, smoke more, then that would result in a reduction in the risk of melanoma.

Q. Okay.

A. So then the question is, well, is that reduction due to the cigarette smoking or is it due to the coffee?

And then, okay, what is the individual risk of those two components? And that's what you can't separate out, because you've got confounding from two major factors related to skin melanoma.

Q. Okay. All right.

So now I'd like to turn, if we could, to the studies or the relationship between coffee consumption and cancers where

you found the risk to be increased.

A. Okay.

Q. Okay. So let's start, if we could, with childhood leukemia.

You testified at great length about these studies during the phase-one trial. So I don't want to repeat that. That's already in evidence, although it's in our dim memories at this point.

But did you update your research regarding the studies concerning coffee consumption and childhood leukemia?

A. Yes, I did.

Q. Okay. And since you testified at trial here in 2014, have any additional studies been published which relate to coffee consumption and childhood leukemia?

A. Yes, there's been a few, yes.

Q. And would you tell us about them, please.

A. Well, the Orsi 2015 case-control study. I think I testified in 2013. So this study --

Q. 2014, you testified.

A. 2014. Yeah, okay.

So the Orsi 2015 case-control study shows that mothers who drank more than two cups of coffee per day had a significantly elevated odds ratio of acute lymphatic leukemia among their children. So that's one study.

Q. Stop one moment.

How did that study relate to the other studies that you had testified about earlier?

A. Well, I mean it relates to them in the context

that it provides further evidence.

I think of all the studies related to maternal coffee consumption in childhood leukemia, I think there's only one that didn't show an effect. So something like seven out of eight studies are positive.

That's why I think there's pretty strong evidence for childhood -- for maternal coffee consumption and childhood leukemia.

Q. So from your prior testimony seven of the eight studies reported increased risk of childhood leukemia from maternal consumption of coffee during pregnancy. And the Orsi study added to that body of literature; is that correct?

A. It was only six or seven. I don't remember.

There was only one study, one epidemiological study, that didn't show an effect in my previous testimony.

So then subsequent to my testimony, there is the Orsi case-control study which shows a significant increase in acute childhood leukemia.

Then there is the meta-analysis done by Thomopoulos in 2015. And that study showed a significant increase in the risk of childhood leukemia.

MR. SCHURZ: And, again, we would object. The witness is simply reading from his prepared written report. So it's hearsay.

THE COURT: The objection is noted. Thank you.

Next question.

Q. BY MR. METZGER: And was there another meta-analysis published regarding coffee consumption and

childhood leukemia from maternal consumption?

A. Yes. There was another meta-analysis published by Yan in 2016. And that demonstrated a significant increase in childhood leukemia among mothers who drank coffee during pregnancy.

Q. Okay. So --

THE COURT: Again, is there a confounding problem with mothers who drank coffee during pregnancy who also smoked?

THE WITNESS: Well, that's interesting you ask that question because I think mothers -- as I recall from my last testimony, mothers who smoked cigarettes had a higher risk of having a child with acute leukemia.

So it can't be from confounding from cigarette smoking. Otherwise the non-smoking mothers would not have even a higher risk.

Q. BY MR. METZGER: Oh, the non-smoking mothers had a higher risk?

A. Yes. Did I say smoking? The non-smoking mothers.

So when you see that observation, what it tells you is that elevated risk of childhood leukemia from mothers who were consuming coffee is unlikely to be due to cigarette smoking because the non-smoking mothers had an even higher risk.

THE COURT: Is that scientific? Is there any reason that's been determined for that that?

THE WITNESS: You know, there are. And I think last time I mentioned there are some mechanistic studies on, you know, why maternal coffee consumption may be related to an

elevated risk of childhood leukemia.

So I think your question is, okay, why is it, then, that mothers who don't smoke have an even higher risk.

So what effect is that effect of smoking?

THE COURT: Does the smoking reduce the cancer? Are you saying that there's a concern for childhood leukemia, in that smoking has a positive effect?

THE WITNESS: For a child --

MR. METZGER: By positive, do you mean beneficial?

THE COURT: Yes, a better word.

THE WITNESS: You know, I think this is what the epidemiological data show. I don't think I would want to go out on a limb and say it's good for pregnant women to smoke, because there are a lot of other issues.

THE COURT: No, I'm not suggesting that in terms of -- what you're suggesting is, in effect, counteracting some effect that you suggest that coffee may cause?

THE WITNESS: You know, I don't know the answer to that question. I guess what you're saying is, well, is there some mechanism involved here that would be responsible for, you know, non-smoking mothers to -- well, they have a higher risk?

I think you're asking me, well, then, mothers who smoke and drink coffee, they have a lower risk. Is there some beneficial effect of coffee -- or of cigarette smoking?

I don't know the answer to that question.

THE COURT: Obviously, it's a very difficult area because there are all sorts of behavioral patterns that are not under any controls.

That was just an observation.

Q. BY MR. METZGER: Do you agree with that?

A. I'm sorry, I didn't --

Q. His Honor just asked you if this is a very difficult area because there are all sorts of behavioral patterns that are not under any controls?

A. Yeah, that you can't account for in the studies. Yes, there are, exactly.

Q. All right. So, Dr. Infante, bottom line, based upon your updated review of the epidemiologic studies regarding coffee consumption among mothers during pregnancy and the development of childhood leukemia, what is your conclusion regarding the current state of the literature on that topic?

MR. SCHURZ: Your Honor, we would register the same objection we did with respect to do Dr. Infante's testimony with respect to childhood leukemia and its increase with respect to pregnant women.

Your Honor will recall we had a motion in limine on this point. This is a reproductive effect.

The issue here that Mr. Metzger is trying to establish is that somehow during pregnancy coffee is associated with some increased risk and has some teratogenic effect.

This case is about cancer. It's about cancer of individuals and Prop 65 with respect to those issues.

It does not encompass reproductive effects. So this entire line of questioning and the conclusions or opinions he's seeking to solicit are irrelevant.

THE COURT: All right. Thank you.

THE WITNESS: Could I respond to that?

Q. BY MR. METZGER: Yes.

A. Well, I started out in my career in child development and reproductive effects and published studies on spontaneous abortion and birth defects related to various occupational exposures.

What's generally in the area I practice in is considered a reproductive effect are issues like birth defects, spontaneous abortion, and that childhood leukemia is considered a leukemia, not a reproductive effect.

Even though it's like a -- apparently it's a transplacental effect that results in cancer. And we usually think of reproductive effects, as I said, are various types of birth defects and spontaneous aborting.

Q. So you consider childhood leukemia to be a form of cancer?

A. Well, absolutely.

Q. And IARC does too; is that right?

A. Yes. They evaluated it, right, in their Working Group review.

Q. Okay. So back to my question, then.

What is your assessment of the current state of the epidemiologic literature regarding maternal consumption of coffee during pregnancy and childhood leukemia now that there's been three years since your last testimony and some new studies?

A. Well, you know, in my past testimony I thought

there was, you know, positive evidence that was strong. And I think it's even stronger now with the additional studies.

Do I think it's beyond a doubt that it's causal? I would say, you know, I don't think -- I wouldn't be willing to say it's an absolute causal effect at this point in time. I think the evidence is very strong.

Q. Okay. All right.

MR. METZGER: Your Honor, is it appropriate for a break now?

THE COURT: Okay. At this time we'll take a recess in this case.

(Recess.)

THE COURT: Calling the case of CERT versus Starbucks.

All counsel are present.

Is Dr. Infante still here?

MR. METZGER: Dr. Infante is.

We were told you were going to be hearing another matter before so we didn't have him on the stand.

THE CLERK: There is an 11 o'clock also.

THE COURT: Oh, there's an 11 o'clock?

(Clerk and court confer.)

(Proceedings held in unrelated matter.)

THE COURT: Okay. Ready to resume the trial?

MR. METZGER: Yes, your Honor.

Dr. Infante?

THE COURT: All right. We're back on the record.

Dr. Infante was testifying and Mr. Metzger was inquiring.

Counsel, you may proceed.

MR. METZGER: Thank you, your Honor.

Q. Dr. Infante we just, I believe, concluded the discussion regarding maternal consumption of coffee during pregnancy and childhood leukemia.

Have you also reviewed epidemiologic studies regarding a related issue; namely, maternal consumption of coffee during pregnancy and development of childhood brain cancer?

A. Yes.

Q. And what did you observe from your review of that body of literature?

A. Well, the Greenup 2014 study showed a significant increase of childhood brain cancer among mothers who consumed more than two cups of coffee per day. And that increase was statistically significant.

There is a more recent study by Bailey, published recently, that shows that women who drank coffee during the first trimester have a significantly elevated risk of children with brain tumors.

That study also demonstrated a dose response.

Q. Okay.

A. So those are two fairly recent studies.

And 2017 would be subsequent to the IARC review.

Q. All right. So the Bailey study is even after IARC had its -- did its working group meeting; is that correct?

A. Correct, yes.

Q. Okay. So what is your assessment or conclusion

regarding the state of the epidemiologic literature regarding maternal consumption of coffee during pregnancy and the development of childhood brain cancer?

A. Well, in my opinion there is some evidence -- there is some evidence of a positive association.

Q. Okay. All right.

A. I'm not saying it's causal. I'm saying there is some evidence of an increase.

Q. Okay.

THE COURT: Wait a second. What does that mean, some evidence?

THE WITNESS: There are some --

THE COURT: Causal is an association --

THE WITNESS: Let me explain that.

There are not a lot of studies on childhood brain cancer. I just mentioned two that demonstrate statistically significant increases and one demonstrates a dose response.

When I say it's not causal, causal is an interpretation of the epidemiology. There is no study that shows that the association is causal. That's an interpretation by people in the field and epidemiologists.

What I'm saying is these studies show significant increases related to maternal coffee consumption, but, you know, that's, you know, something that you should be concerned about, but in my opinion there's not enough literature that would -- you know, there needs to be more study of maternal coffee consumption and childhood brain cancer.

But some of the studies that are available, and

particularly the more recent one, shows a significant increase.

MR. SCHURZ: Your Honor, we would interpose an objection and move to strike based upon the fact that, as Dr. Infante has indicated, there are very few studies. He hasn't indicated how many.

There are just four.

Based upon the paucity of evidence and the lack of acceptance within the broader scientific community with respect to coffee consumption in any way being associated with childhood brain cancer, the result of the ingestion by mothers during pregnancy, we would move to strike.

THE COURT: All right. Thank you.

The Court will defer any ruling until counsel has completed the testimony.

MR. METZGER: All right.

Q. Dr. Infante, let me ask you this question.

Have you reached a conclusion as to whether the epidemiologic studies regarding maternal consumption of coffee during pregnancy and the development of childhood brain cancer is -- whether that body of literature establishes that the association is not causal?

A. No.

Q. And did you reach any conclusion that the association -- well, strike that. Excuse me.

Have you formed an opinion as to whether -- based upon the epidemiologic studies regarding maternal consumption of coffee during pregnancy and childhood brain cancer, whether

that body of literature shows a protective effect?

A. No.

Yeah, I have. And it doesn't show a protective effect.

What I'm saying is that there is some evidence here of an elevated risk that's significant. But I think that, you know, more study needs to be done.

But it certainly doesn't show that there's a, you know, protective effect for brain cancer from maternal coffee consumption.

Q. Okay. All right.

Now, I would like to turn to the topic of bladder cancer.

During the 2014 trial, you testified extensively about coffee consumption and bladder cancer from the epidemiologic studies. So I just wanted to ask you, have you reviewed literature regarding coffee consumption and bladder cancer that was published since your testimony here three years ago?

A. Yes.

Q. And what do you find from your updated review of that literature?

A. Well, the Wu 2015 meta-analysis based on 12 studies shows that among coffee consumers who were non-smokers there was a significantly elevated risk --

MR. SCHURZ: And, your Honor, we would object. The witness is simply reading from his written opinions.

THE COURT: Overruled.

THE WITNESS: There was a significantly elevated risk of bladder cancer. This is among non-smokers.

So, to me, whenever you have, let's say, coffee consumption and an elevated risk of bladder cancer, the first thing you want to think of is, well, how about cigarette smoking? Was the study controlled for cigarette smoking, because that's a major confounder for bladder cancer.

Q. Cigarette smoking is a known cause of bladder cancer?

A. It's a known cause of bladder cancer, yes. So it would be a major confounder.

So when they looked at non-smokers, they, you know, found, like, a 70 percent increase in the risk of bladder cancer among non-smokers.

Q. And was that statistically significant?

A. Yes.

Q. Okay.

A. So I guess I have further opinions about this.

Q. Go ahead.

A. Of course, this is non-smokers.

So when you relate this to the studies that, you know, contain smokers, but then they -- I mean, the coffee studies on bladder cancer that contain smokers and then they statistically adjust for the cigarette smoking, and they identify an elevated risk of bladder cancer, just so you know, from the coffee consumption, you know, I'm still thinking that, well, even though they adjusted for the cigarette smoking, maybe it's still -- a contribution of that elevated risk is from cigarette smoking.

So then when you see a study of non-smokers that

demonstrates an elevated risk, you know, I guess -- you know, I think that suggests that non-smokers have an elevated risk. So that elevated risk can't be due to cigarette smoking.

Q. Okay.

A. So that's what it says.

I mean, it certainly doesn't show that, you know, coffee has any protective effect for bladder cancer.

You know, there was an earlier study. I don't know if I presented my 2014 testimony or not, but the Zhao study, that also showed monotonic dose response among non-smokers for coffee consumption and bladder cancer.

Q. Was that --

A. There's a little bit of --

Q. So is that also a meta-analysis?

A. I would have to look back and see if it was a meta-analysis or if it was cohort or cohort study. I don't remember.

Q. All right. So what is your conclusion regarding the current state of evidence based upon the new meta-analysis in non-smokers regarding the association between coffee consumption and bladder cancer?

A. Well, I would think it provides some evidence that coffee consumption is related to an elevated risk of bladder cancer.

Q. Okay. All right.

Now, on a related topic, I don't recall whether you testified about lung cancer or not in 2014, but is lung cancer a cancer that you reviewed in the studies of coffee

consumption?

A. Yes.

Q. And lung cancer, is that the cancer that's most strongly associated with cigarette smoking?

A. Yes, it is.

Q. And in your review of the recent literature regarding coffee consumption and lung cancer, did you find any studies that you thought were significant?

A. Well, I thought since my last testimony, the Wang 2016 meta-analysis based on four cohort studies showed -- if you look at coffee consumption versus no consumption, there's like a two-fold risk of lung cancer that was significant.

But then further in that study, they found when they looked at the three studies that adjusted for cigarette smoking, they had over a two-fold risk.

So, again, with the adjustment for cigarette smoking, they're finding an elevated risk of lung cancer.

Now, do I -- so what do I conclude from that? Do I conclude from that the coffee is what, you know, caused the elevated risk of lung cancer?

No, I'm not saying that.

Because I don't -- when you statistically adjust for some of these sites of cancer that have a strong correlation, like cigarette smoking with lung cancer, even though you statistically adjust for it, I'm not sure that the statistical adjustment, you know, was adequate.

So what I'm saying is it appears to be some evidence,

but I think I would want to see further study.

MR. SCHURZ: Your Honor, we would ask that the record reflect that, once again, Dr. Infante is reading from his opinion.

THE COURT: All right. Thank you.

Q. BY MR. METZGER: Okay. Dr. Infante, one of the cancers you mentioned earlier this morning as being increased from coffee consumption in the epidemiologic studies is gastric cancer.

And I believe that's a cancer that you did not evaluate and testify about in 2014; is that your recollection?

A. Correct, yes.

Q. All right. And have you now for the second phase of trial had an opportunity to review all the epidemiologic studies, case-control studies, cohort studies and the meta-analyses regarding the consumption of coffee and gastric cancer?

A. Yes.

Q. All right. And could you tell us what you found from your review of the case-control studies regarding coffee consumption and gastric cancer.

A. Well, you know, without -- there are a lot of studies. It's hard for me to cite -- to remember to cite specific ones, but if one looks at the ten meta-analyses that have been published related to coffee consumption and gastric cancer, these meta-analyses, nine of the ten show an increased risk. And of those nine, six of them show a statistically significant increased risk.

Q. These are the meta-analyses of all the studies?
A. Yes.
Q. Okay. And there's ten meta-analyses that have been published regarding coffee consumption and gastric cancer?
A. That I identified, yes.
Q. Okay.
A. And I'm saying nine of the ten show an increased risk. And then six of the ten show a statistically significant increased risk of gastric cancer.
So to me it provides some evidence.
Q. Okay. Well, regarding "some evidence," how strong do you consider that evidence to be of a positive association?
A. Well, it is a positive association.
Q. Okay. All right.
A. You know, again, I'm not saying that it's causal. I'm not interpreting it as causal, but I'm saying there's a positive association that provides some evidence.
Q. Okay. And do you have any conclusion regarding whether, based upon the epidemiologic studies of coffee consumption and gastric cancer, that body of literature indicates a null or a protective effect?
A. I don't see how one could draw such a conclusion.
Q. Why is that?
A. Well, because, like I just said, in these nine meta-analyses nine of them are positive, and six of them show

significant instances.

Q. Let me see where we are.

Let's talk now about ovarian cancer. Is that another cancer that you did not review and testify about in 2014?

A. Correct.

Q. And have you now reviewed the case control, the cohort studies and meta-analyses regarding ovarian cancer from coffee consumption?

A. Yes.

Q. All right. Are there any particular studies regarding coffee consumption and the development of ovarian cancer that you consider to be important?

A. Oh, yes.

Q. Which study or studies?

A. Well, just recently, in 2017, published the results -- it's called EPIC studies. It's an acronym. It's a study related to European countries. I think there are over like a 100,000 participants in the study, within the study. It demonstrates -- you know, these are the cohort studies. And it demonstrates a significantly elevated risk of ovarian cancer.

Again, that was published subsequently to the IARC review. It was published in 2017.

Oh, and the study also shows a dose response, which I think is very important in epidemiological studies because of all the errors you're going to have in the exposure estimate and all which I mentioned earlier flattens the dose response.

This study, in fact, also demonstrates a dose response

so that when you have an increase in coffee consumption, you have an increase in ovarian cancer.

Q. Who is lead author of this study?

A. Gunter, 2017.

Q. Just recently published?

A. Yes.

Q. And did the Gunter study look at cancer sites other than ovarian cancer?

A. I think it may have, yes.

Q. Okay. What was the observation regarding ovarian cancer in relation to the other cancers?

A. Well, it was the site that showed the highest risk. It's the cancer site that showed the highest risk among all the cancer sites that are evaluated.

Q. All right. And from your review of the case-control studies, the cohort studies, the meta-analyses and your recent EPIC cohort study, have you formed an opinion as to whether consumption of coffee prevents or protects against ovarian cancer or have you formed an opinion on that?

A. Yes.

Q. And what is your opinion?

A. Well, I don't see how you could possibly come to the conclusion it prevents it when you have a significant elevation in risk.

I believe it's probably the largest study that's been done, and it shows a dose response.

Q. Okay. So let me -- I think that will bring us to the -- so I think that will bring us to the studies

regarding total cancer.

Can you tell us -- well, let me first ask.

Is total cancer or total cancer mortality a type of cancer or endpoint that you have not assessed in the phase one and that you did not testify about during the phase one trial?

A. I did not.

Q. And have you now had an opportunity to review the body of epidemiologic studies regarding coffee consumption and total cancer or total cancer mortality?

A. Well, I reviewed 14 cohort studies that had analyzed for total cancer mortality.

Q. Okay. These are all cohort studies?

A. Yes, all cohort studies.

Q. All right. And from your review of those 14 cohort studies, what did you observe?

A. Well, there were -- seven of them showed increases in risk of total cancer, and in four of those the result was statistically significant.

So in three there was an increase in risk, but it wasn't significant.

There were six of these studies that, in my opinion, did not show any association of total cancer.

There was one study that showed an inverse association.

Q. Okay. So what have you concluded regarding total cancer from this body of literature?

A. Well, it shows that, you know, when you combine all of these sites of cancer and look at the coffee consumption, you know, it's like almost half of them were

positive and four of them were statistically significant.

I think because when you combine so many cancer sites all into one estimate of risk, I think, you know, you get some -- some could be increased, some decreased. You put them all together and you have a slight increase.

I think -- you know, I certainly would not say, well, coffee consumption causes total cancer. But what I would draw from such an analysis is that it certainly doesn't show that there's a protective effect in terms of cancer if you're consuming coffee.

Q. Okay. All right.

MR. METZGER: Give me one moment, your Honor, just to make sure that I've covered everything.

THE COURT: Okay.

MR. METZGER: Oh, actually I haven't.

Q. Dr. Infante, having reviewed now, or having attempted to review all of the epidemiologic studies regarding coffee consumption and cancer -- at least those in the English language -- what have you concluded overall regarding the studies -- the teaching of those studies regarding coffee consumption and cancer?

A. Well, I've concluded, I think, from the 20 specific cancers that I looked at, it was my opinion that 12 showed some evidence of an increased risk. Three show inverse associations. Then in five there's essentially no association.

And these are all observational studies. They provide difficulties, because you've got confounding from known and

unknown factors. You've got exposure, misclassification. You know, you have confounding not only from other dietary factors, but you have confounding from medical conditions that predispose one to specific cancers. And you have bias in some of the studies. You have measurement error.

So, you know, in my opinion, I think it's very difficult to make a causal determination from the dietary epidemiology of coffee consumption and cancer.

I would, you know, recommend that a controlled clinical trial be conducted to try to resolve the issue.

Q. Okay. And having reviewed all these studies including studies that were published after IARC's working group met last year to do their evaluation, what is your opinion regarding IARC's conclusion from their 2016 working group meeting that the epidemiologic studies are such that one cannot determine whether consumption of coffee does or does not cause cancer?

A. Well, you know, there are some new studies that show significantly elevated risk that they didn't consider. And, you know, I think they are important studies, and they provide some more evidence.

But I think, in general, I agree with IARC's conclusion that you can't make a determination from these studies so that -- that's why they put it in category 3. You can't tell if there is a significantly elevated risk. You can't tell whether there are significant deficits because of all the methodological issues. So they conclude it's not classifiable as to the cancer risk to humans.

I think that's a reasonable interpretation of the data.

Q. Do you agree with that?

A. Yes.

Q. All right. Thank you very much, Dr. Infante.

THE COURT: All right. Thank you.

Mr. Schurz?

MR. SCHURZ: Thank you, your Honor.

So at this time, your Honor, we would offer a set of exhibits that we expect to use at least for some of Dr. Infante's cross-examination.

THE COURT: Okay.

MR. SCHURZ: And I hope that by providing these we can expedite.

May I approach the witness?

THE COURT: Yes, please.

THE WITNESS: Thank you.

CROSS-EXAMINATION

BY MR. SCHURZ:

Q. Good morning, Dr. Infante.

A. Hello.

Q. I would like to talk for a moment a little bit about your background and experience which you discussed with Mr. Metzger.

When you worked in the government, it was in the field of occupational epidemiology, correct?

A. Let me see. Occupational and environmental epidemiology.

Q. Uh-huh.

And your work in that area was not related to nutritional epidemiology, correct?

A. Not for the government -- you know, you're talking about government. Do you mean United States Government?

Q. Yes.

A. Because I worked for other governments. I worked for the World Health Organization which also a government organization. It's a health agency of the UN.

When I worked for them --

Q. I'm focusing on your experience with respect to --

MR. METZGER: Excuse me, your honor. He's interrupting the witness with his answer.

THE COURT: Wait. Let's finish one question and answer.

Dr. Infante, have you completed your answer?

THE WITNESS: No, sir.

THE COURT: Please complete your answer.

THE WITNESS: When I worked for the U.S. Federal Government, I did occupational epidemiology.

When I worked for the State Health Department in Ohio, I did environmental epidemiology.

When I worked for the World Health Organization, I did nutritional epidemiology.

But most of my career has been in occupational cancer.

Q. And in your testimony during phase one,

Dr. Infante, you testified that you worked for the -- when you worked for the federal government, your duties did not involve epidemiology of anything related to diet; is that correct?

A. When I worked for the U.S. Government, correct.

Q. And you served as an adjunct professor, correct?

A. Yes.

Q. And in your role as an adjunct professor, your work did not address diet or nutritional epidemiology either, did it?

A. Correct.

Q. And none of your consulting work prior to working with Mr. Metzger, starting in 2007, addressed any issues with respect to diet or nutritional epidemiology, correct?

A. I think that's correct.

Q. All right. And you referenced as part of your discussion with Mr. Metzger some peer-reviewed publications related to fluoride and tooth decay, correct?

A. That was one aspect of it, yes, but there were other -- there was other dietary epidemiology.

Q. Yes. And those articles are from the 1970's, correct?

A. Yes.

Q. And apart from those texts written some 40-plus years ago, you have not published in any peer-reviewed articles in nutritional epidemiology, correct?

A. Yes.

Q. All right. Now, other than your work in

dentistry in the 1970's, your work with Mr. Metzger involving french fries, you've never done any work associated with dietary exposures, specifically, in nutritional epidemiology, correct?

A. I'm sorry. Other than what did you say?

Q. Other than your work in dentistry and the articles that you wrote in the 1970's and the work that you've done with Mr. Metzger, you have not done any other work associated with dietary exposures in nutritional epidemiology, correct?

A. Yes. Correct.

Q. Now, I would like to discuss for a moment the scope of opinions that you're offering and what you're not testifying about.

Now, your opinions in this case are restricted to the epidemiological data related to coffee and cancer, correct?

A. Yes.

Q. You're not offering any opinions regarding coffee consumption and any other disease endpoint other than coffee, correct?

MR. METZGER: You said "coffee." Do you mean cancer?

MR. SCHURZ: Thank you. Let me rephrase.

Q. Dr. Infante, you're not offering any opinions regarding coffee consumption in any other disease endpoint apart from cancer, correct?

A. Correct.

Q. All right. And you're not offering any opinions that -- strike that.

You didn't offer any opinions at your deposition regarding coffee and total mortality, correct?

A. Correct.

Q. And you're not offering any opinions with respect to coffee consumption and cardiovascular disease, correct?

A. Correct.

Q. Nor are you offering any opinions regarding coffee and type 2 diabetes, correct?

A. Correct.

Q. All right. And you're not offering any opinions regarding coffee in a broader liver disease, correct?

A. Correct.

Q. All right. So let's turn now, if we can, to the nature of the review that you performed in this case.

I see there's a range of binders that are positioned behind you, correct?

A. Yes.

Q. And those are Mr. Metzger's binders, correct?

A. Yes.

Q. And those articles were provided to you for your work in phase two of this trial; is that correct?

A. Yes.

Q. And the way it worked is that Mr. Metzger provided you a DVD containing all of the studies that are reflected in those binders, coffee consumption and cancer, correct?

A. These are -- I don't know that he provided me

all of those, no.

I mean, I provided some to him, and then he put together all the information.

Q. And you provided him approximately six studies, total, correct?

A. No, that's not correct.

Q. How many did you provide him?

A. You know, I don't know because it's been over the year, first of all.

I had the epidemiological literature I think up to 2013 or 2014, all right, from the last time I testified. So then, you know, I've updated the literature. I've talked to Mr. Metzger.

You know, I would ask him for -- could he send me specific studies. Sometimes he identified a study that I didn't have that, you know, he sent to me.

So I don't know the number of the ones, you know, since, like, 2014 that I made him aware of versus the ones he made me aware of.

Q. Now, do you recall the discussion that you had at your deposition with respect to what, if any, documents you identified versus documents that were provided by Mr. Metzger?

A. You have to refresh my memory.

Q. Well, isn't it the case, Dr. Infante, that all of the materials that you reviewed as part of this case, with the exception of a couple of IARC monographs and some six articles, were actually provided by Mr. Metzger?

A. Well, I reviewed -- now, wait a minute.

I reviewed all of the IARC monographs -- there are about 116, 119 of them -- for the information in there related to, you know, causes of cancer and the degrees of evidence and what are the cancers that are associated with an increase or decreased risk, you know, from various exposures or lifestyle factors.

So he didn't provide me with any IARC monographs I looked at. I had 119 of those myself.

Q. I understand.

So let's put the IARC monographs aside. Only one of those deals with coffee, correct?

A. Yeah.

Well, there is one that deals with coffee and then there is the summary in The Lancet Oncology that deals with coffee.

Q. Of the 116 IARC monographs that you said you reviewed, one of them is relating to coffee, correct?

A. That's been published so far, correct.

Q. Yes. Okay.

Now, so you reviewed the materials that Mr. Metzger provided to you as reflected in the binders behind you.

You reviewed the IARC monographs that you've just referenced.

And you completed your evaluation of the materials that have been provided to you, correct?

A. Yes.

Q. All right. Now, you didn't do your own literature search in this case, did you, Dr. Infante, to

identify the scope of materials that you were going to review?

A. That's incorrect.

Q. Can you tell us where in all the materials that you produced, any literature search that you showed and produced as part of this case reflecting the articles and materials that you found on your own?

MR. METZGER: Objection.

THE WITNESS: There isn't such a document.

I mean, for any case I've ever been involved in, I don't drag around literature searches.

I look at the literature. I use ToxLine, PubMed, Google to see if I can identify other studies that I don't have.

If I didn't have some of those, I would discuss it with Mr. Metzger and his staff sent them to me.

Q. Now, do you recall our discussion at the deposition that you did with Mr. Kennedy in which he asked you were there any other materials that you reviewed other than those provided by Mr. Metzger?

Do you recall that discussion?

MR. METZGER: Objection, your Honor. This is improper examination.

He's impeaching before he's established a foundation for impeachment.

THE COURT: Overruled.

THE WITNESS: No, I don't know in what context.

I'm telling you how it took place. I don't know in what context you're asking me about what I said at my, you

know, deposition.

Q. BY MR. SCHURZ: What proportion of the some 1,000 articles that were provided to you by Mr. Metzger did you find on your own?

A. Well, you know, this goes back quite a few years, like I say. But, you know, quite a few.

If you look at the literature since 2014 -- you know, I did literature searches. I asked Mr. Metzger about the articles. Sometimes he found them, and then he had his staff compile them and they sent them to me. So it went back and forth.

So you're asking me like in the last three years how many did he identify versus how many did I identify. I don't know the answer.

Q. Well, you didn't produce any literature searches, correct?

A. Correct.

Q. And you did produce your email correspondence with Mr. Metzger. And that email correspondence I will represent to you identified a total of six articles that you provided to Mr. Metzger.

Does that sound about right?

MR. METZGER: Your Honor, objection. Argumentative as phrased.

Counsel is injecting himself -- his own representations into the question.

THE COURT: Please rephrase the question.

Q. BY MR. SCHURZ: You identified approximately a

total of six articles to Mr. Metzger that you wanted added to your file, correct?

A. I'm saying I don't think that's correct, no.

There might be six that I sent to him that he didn't have. But, you know, I talked to Mr. Metzger quite a bit. And, you know, if I had -- you know, I had the early literature search. Then I updated it. Then he looked for articles. And then on the basis of our exchange, then he had his office staff compile all this literature.

Then they sent me, you know, all of this literature, you know, on disks, I believe.

Q. Uh-huh. All right.

Now, as a general matter, Dr. Infante, you would never publish a peer-reviewed journal article based solely on materials given to you by the person funding your research, would you?

A. No.

Q. Now, I would like to turn for a moment to some of the testimony you've offered in benzene cases which you've referenced in your discussion with Mr. Metzger.

You had your testimony excluded, did you not, as an expert when you were serving as an expert in a benzene case?

A. Well, could you be a little more specific?

Q. You have had your testimony excluded by courts of law in actions where you were seeking to participate as an expert witness, correct?

A. Maybe a couple times I can recall out of quite a number of situations.

I mean, you're kind of cherry picking my history of having my expert testimony excluded.

Q. Well, it's interesting you use the term "cherry picking," because that's exactly what I would like to discuss.

Do you recall testifying in the case of Yolande Burst versus Shell Oil Company?

A. Yes.

Q. And that was in 2015, correct?

A. Yes.

Q. That was after you testified before this Court the first time in 2014, correct?

A. Yes.

Q. And you testified in that case on behalf of the plaintiff, correct?

A. Yes.

Q. And that was based on your review of the epidemiology and exposure to benzene, correct?

A. Yes.

Q. And you offered --

A. Exposure to benzene from gasoline, to be more specific.

Q. Thank you.

A. You're welcome.

Q. And you offered an opinion, did you not, that the exposure to benzene related to the gasoline caused the plaintiff's leukemia, correct?

A. Yes.

Well, I said it was more likely than not.

Q. And that testimony was excluded, correct?

A. Yes.

Q. And that testimony was excluded because the Court concluded that your testimony was based on an unreliable methodology, correct?

A. Well, that's what the Court said.

But, you know, that determination was made by a judge who to my knowledge had no scientific training, and certainly no training in epidemiology.

And, in fact, subsequent to that ruling, I had over 45 scientists from around the world send an amicus brief asking the Court to reverse its decision and allow me to testify because they agreed with my opinion that benzene in gasoline was a cause of acute leukemia.

THE COURT: All right. At this time we're going to take our recess for the noon hour.

We'll resume trial at 1:30 this afternoon. Thank you, counsel.

(At 12:00 noon, a recess was taken until 1:30 p.m. of the same day.)

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT 323 HON. ELIHU M. BERLE, JUDGE

CERT, Plaintiff, vs. STARBUCKS CORP, ET AL., Defendants.	SUPERIOR COURT CASE NO. BC 435759 BC 461182

I, DAVID A. SALYER, Official Pro Tem Reporter of the Superior Court of the State of California, for the County of Los Angeles, do hereby certify that the foregoing pages, 1 through 76, inclusive, comprise a true and correct transcript of the proceedings taken in the above-entitled matter reported by me on September 25, 2017.

DATED: September 25, 2017.

DAVID A. SALYER, CSR, RMR, CRR
Official Pro Tem Court Reporter
CSR No. 4410

EXHIBIT “G”

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT 323 HON. ELIHU M. BERLE, JUDGE

CERT, PLAINTIFF, VS. STARBUCKS CORP, ET AL., DEFENDANTS.	CASE NO. BC 435759 BC 461182

REPORTER'S TRANSCRIPT OF PROCEEDINGS

MONDAY, SEPTEMBER 25, 2017

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M A S T E R I N D E X

September 25, 2017, P.M. Session

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EXHIBITS

PLAINTIFF'S EXHIBIT	MARKED FOR I.D.	RECEIVED IN EVD.	WITH-DRAWN

DEFENDANT'S EXHIBIT	MARKED FOR I.D.	RECEIVED IN EVD.	WITH-DRAWN

JOINT EXHIBITS	MARKED FOR I.D.	RECEIVED IN EVD.	WITH-DRAWN

CASE NUMBER: BC411192/BC435759
CASE NAME: CERT CASES
LOS ANGELES, CALIFORNIA MONDAY, SEPTEMBER 25, 2017
DEPARTMENT 323 ELIHU M. BERLE, JUDGE
REPORTER: MARK SCHWEITZER, CSR 10514
TIME: 1:41 P.M.

-o0o-

THE COURT: Back on the record in the case of CERT versus Starbucks. All counsel are present. Mr. Infante is on the stand, and Mr. Schurz was inquiring.

Counsel may proceed.

PETER INFANTE, PREVIOUSLY SWORN.

CROSS-EXAMINATION (CONTINUED)

BY MR. SCHURZ:

Q. Thank you, your Honor. Good afternoon, Dr. Infante. At the conclusion of our session this morning, you referenced an amicus brief that was filed in the Burst versus Shell Oil Company.

Do you recall that discussion we were having?

A. Yes.

Q. And how did the Fifth Circuit rule?

MR. METZGER: Objection, your Honor. 352, relevance.

THE COURT: The way the question is phrased, the Court is going to sustain the objection unless it has something to do with Dr. Infante's testimony.

Q. BY MR. SCHURZ: Let me move back to the trial court's decision and discussion of the methodology that you used, Dr. Infante.

Do you have that in mind?

A. For that case you're talking about?

Q. Yes.

A. Yes.

Q. And you accused me prior to the lunch break of cherry-picking your testimony.

Do you recall that?

MR. METZGER: Objection. This is argumentative, your Honor.

THE COURT: Objection sustained.

Q. BY MR. SCHURZ: The Court found your methodology unreliable -- correct? -- in the Burst versus Shell Oil company case, correct?

MR. METZGER: Objection. Cumulative and 352.

THE COURT: Overruled.

Q. BY MR. SCHURZ: And further, the Court found that Dr. Infante cherry-picks data from studies in several significant instances and fails to explain contrary results in a manner that belies the reliability of his methodology, right?

MR. METZGER: Objection. Hearsay. 352.

THE COURT: Overruled.

THE WITNESS: That's what the judge ruled, yes.

Q. BY MR. SCHURZ: Take a look, if you would, at DX 73541, which is the last tab in the binder that I gave you

this morning.

A. Okay.

Q. And do you have 73541 in front of you, Dr. Infante?

A. Yes, I do.

Q. All right. And if I could direct your attention to Page 12 of the document that you are looking at here, 73541. And further, if I can direct your attention to the left-hand column at the top where the header reads --

MR. METZGER: Objection. Hearsay. This is hearsay. An out of state --

THE COURT: I haven't heard a question yet.

MR. METZGER: Well, he's reading from -- he's reading from a document.

THE COURT: I assume we'll get to a question. Counsel may continue.

Q. BY MR. SCHURZ: And the header reads, quote, Dr. Infante cherry-picks data and fails to explain contrary results.

Do you see that?

A. Yes.

Q. And the Court explained further that --

THE COURT: Well, hold on. We don't need a recitation. Whatever the Court said, the Court said. Do you have a question for this witness?

MR. SCHURZ: Yes, thank you, your Honor.

Q. Isn't it the case that the same methodological flaws that the Court found in Burst versus Shell Oil Company

were repeated in this analysis?

A. Not that I recall, no.

Q. All right. So again, in Burst -- and if I could turn your attention to Page 14 of the analysis. Under the section that's entitled Summary.

Do you see that?

A. Yes.

Q. And if I could direct your attention to the end of that paragraph, it's the last sentence of that first sentence, the Court states --

MR. METZGER: Objection. Hearsay. He's reading from an out of court --

THE COURT: You don't have to read the opinion. Just ask the question.

Q. BY MR. SCHURZ: All right. So in that case the Court found that you had used evidence and studies in a way that was inconsistent with the author's own discussion, correct?

MR. METZGER: Objection. Hearsay, 352.

THE COURT: Overruled.

THE WITNESS: Where are you -- well, yeah, that would be correct because I don't take summaries from articles. I look at what the actual data say.

Q. BY MR. SCHURZ: Um-hm. So in this case, you've also offered opinions that are inconsistent with the author's own discussion within the very articles that you are relying on, correct?

A. Well, that's incorrect because I based my

conclusions in this case on the totality of the epidemiological evidence, not based on what an author said in one study.

Q. Well, in a number of cases, you make specific findings with respect to specific studies, don't you, Dr. Infante?

A. I make specific what?

Q. You have offered specific opinions with respect to specific studies, correct?

A. Yeah, with respect to the findings in specific studies, yes. And then you -- then you, you know, look at the totality of information for your conclusions.

Q. And in offering your opinions with respect to specific studies, there are a number of instances in which you disagree with the author's own discussion, correct?

A. Are you talking about in this case?

Q. Yes.

A. Well, you'll have to refresh my memory.

Q. Okay. As you sit here today, do you recall any instances in which you came to a conclusion that was directly contrary to the studies that you are citing?

A. Now, wait a minute. Do you mean contrary to what the author's conclusion was or contrary to the data in the study?

Q. Contrary to what the authors concluded.

A. I don't recall. You'll have to show me an example.

Q. All right. Now, you also testified in a case

called Henrickson versus ConocoPhillips, correct?

A. Yes.

Q. And you testified for the plaintiff in that case?

A. Yes.

Q. And your testimony was excluded, correct?

A. Yes.

Q. And your testimony was excluded because the Court found that you conspicuously failed to cite a study that reached a conclusion contrary to your own, correct?

A. You know, I don't recall. That was a number of years ago. And I testified in a bunch of cases since then.

Q. All right. Now, earlier in your discussion with Mr. Metzger, you discussed some of the conclusions or observations and opinions from Dr. Alexander.

Do you recall that discussion you had?

A. I voiced my opinion about the two conclusions regarding liver cancer and endometrial cancer for his opinion, yes.

Q. And at the time of your deposition, you had not read or considered Dr. Alexander's summary notes and opinions, correct?

A. I thought in my deposition I testified I only looked at the summary. I didn't read his entire document. I thought that was my testimony.

Q. So you saw it visually, but you didn't read it, correct?

A. I think I testified -- and you can refresh my

memory -- I think I testified that I only looked at the summary. I didn't read his report in detail.

Q. Showing you now the deposition transcript from your Phase 2 deposition held on Tuesday, July the 18th, 2017.

MR. METZGER: Is there a page and line?

MR. SCHURZ: Page 19, beginning at Line 16, continuing to 23.

THE COURT: All right. 24?

MR. SCHURZ: Line 23.

MR. METZGER: I'm showing Page 19 as entirely different testimony.

THE COURT: Lines 16 to 23? It doesn't have an answer. Is this Page 19?

MR. SCHURZ: Page 19.

MR. METZGER: Your Honor, this is a different transcript than the testimony in this case in July of 2017. I don't know what counsel is showing.

THE COURT: This doesn't look like the transcript that I have here. What's the date of the transcript?

MR. SCHURZ: July 18, 2017, Deposition of Dr. Peter Infante.

MR. METZGER: It's not here.

THE COURT: Can somebody straighten this out?

MR. SCHURZ: Your Honor, did we hand you the right deposition?

THE COURT: Is that Page 19 that you -- what you put on the screen is not the same Page 19 that's in the transcript.

MR. SCHURZ: Could we take a look? I'm afraid we may have given you the --

MR. METZGER: Then I also have the wrong one, and I have my own.

MR. SCHURZ: We can give you another one.

MR. METZGER: I prefer to have mine that's a certified copy than yours.

MR. SCHURZ: So, your Honor, the testimony is the same. The pagination is different. Reading from Page 20, Lines 9 through 16. Page 20, Lines 9 through 16.

THE COURT: All right. Page 20, line what?

MR. SCHURZ: Lines 9 through 16, your Honor.

THE COURT: All right. Any objection?

MR. METZGER: No objection.

THE COURT: All right. You can read it.

MR. SCHURZ: Okay.

"QUESTION: Is that something you read or considered in arriving at your opinions in this case?

"ANSWER: No.

"QUESTION: You didn't read it?

"ANSWER: No. I haven't had a chance to look" --

MR. METZGER: Could I see what you're reading from, please? There's nothing on the screen.

THE COURT: There's no question pending. Please finish reading.

MR. SCHURZ: Thank you.

Q. In fact, in developing your opinions, you did not consider in any way the opinions of Dr. Alexander in

rendering your own opinions, correct?

A. That's correct. I looked at the literature. So I didn't rely on his opinions for my opinions.

Q. Because you didn't look at them prior to your deposition, correct?

A. No, I looked at the summary of his opinion. I think there was a one-page summary.

Q. All right. So I'd like to return to the discussion that you were having with Mr. Metzger relating to the International Agency For Research and Cancer, the IARC recent publication in Lancet relating to coffee consumption. And if I could direct your attention to the second to last tab in the binder that you have, which is Exhibit 60127.

And do you have the Lancet article entitled Carcinogenicity of drinking coffee, mate, and very hot beverages?

A. I have it.

Q. And this is the document that you reviewed and discussed with Mr. Metzger, correct?

A. I have the review of this as part of my report in the case.

Q. Yes. And you testified that you agreed with the conclusions of IARC with respect to the carcinogenicity of drinking coffee, correct?

MR. METZGER: Objection. Misstates his evidence. He said he agreed with the conclusion, not the conclusions.

THE COURT: Overruled.

THE WITNESS: I'm sorry. Is there a question?

Q. BY MR. SCHURZ: You testified that you agreed with the conclusions reached by IARC with respect to the carcinogenicity of drinking coffee, correct?

A. The overall conclusions, yes. In other words, that it was evaluated as unclassifiable as to the carcinogenicity of humans. That was their overall evaluation.

Q. And you disagree, do you not, Dr. Infante, with many of the subsidiary conclusions and observations offered by the working group in this Lancet article?

A. I don't know that I do or not. You'd have to ask me one.

Q. All right.

Let me direct your attention to the first column, fourth paragraph. And here the authors recite, "For this re-evaluation, a much larger database of more than 1,000 observational and experimental studies was available."

Do you see where I am?

A. Yes.

Q. All right. And the authors continue to state that they gave the greatest weight to well-conducted prospective cohort and population-based case-control studies that controlled adequately for important potential confounders, including tobacco and alcohol consumption.

Do you see that?

A. Yes.

Q. And it is your conclusion, Dr. Infante, that there are no epidemiology studies relating to the coffee consumption literature that adequately control for

confounders, correct?

A. That's correct, yes. They are saying they gave the greatest weight to them, right.

Q. But you've concluded that none of those studies adequately adjusted or controlled for those confounders, correct?

A. Yeah, that's correct, yes.

Q. All right. Now, looking to the conclusion that you discussed with Mr. Metzger, which appears in the third column, in the second to last paragraph where it reads, quote, overall coffee drinking was evaluated as unclassifiable as to its carcinogenicity to humans, Group 3.

Do you see that?

A. Yes.

Q. That was a downgrade from how IARC previously graded coffee, correct?

MR. METZGER: Objection. Argumentative. Vague as to downgrade.

THE COURT: Overruled.

THE WITNESS: Um, you know, I don't recall what the earlier evaluation was that you are saying that was a downgrade from. Do you want to refresh my memory?

Q. Well, it was in your materials. Do you recall the IARC monograph in 1991 relating to coffee?

A. I read it. I don't recall everything about it. It's a pretty thick monograph.

Q. Do you recall the conclusion?

A. I don't recall the conclusion.

Q. All right. Thank you. Now, let's turn to a discussion with respect to specifically bladder cancer. And I'll turn your attention back to the first column in which the authors state, quote, for bladder cancer, there was no consistent evidence of an association with drinking coffee or of an exposure-response gradient from ten cohort studies and several population-based case-control studies in Europe, the United States, and Japan, unquote.

Do you see that?

A. Yes.

Q. And the authors do not find that there is an increased risk for bladder cancer associated with drinking coffee, correct?

A. They are saying there is no consistent evidence. What I'm saying is that I don't remember that there were studies that clearly showed significant dose response. And I believe there was even one published subsequent to the IARC review. So it's like you are kind of picking out these little things here, but their overall conclusion -- I think there's some evidence, as I mentioned earlier, for bladder cancer, but I think there's, you know, confounding from cigarette smoking that I thought they really couldn't separate it so that, you know, in my opinion, I'm not saying that coffee consumption causes bladder cancer. And I went on to say I conclude that overall, the evidence is unclassifiable. I agree with that.

So in other words, IARC can't conclude that it does or doesn't cause cancer based on their review.

Q. But your conclusion, Dr. Infante, is that the epidemiology literature shows an increased risk for bladder cancer, correct?

A. In some studies. I'm not saying overall. I said overall I agree with their conclusion, but I think there are some studies that provided evidence of an increased risk, yes. And there are other studies that, you know, that don't show that. So in my opinion, there's some evidence, some evidence, but I'm not saying that -- I'm certainly not saying that coffee consumption causes bladder cancer because I think there's confounding.

Q. So you have no opinion, then, do you, Dr. Infante, with respect to whether coffee consumption is related to an increased risk of bladder cancer, correct?

MR. METZGER: Objection. Argumentative.

THE COURT: Overruled.

THE WITNESS: I do have an opinion. I do have an opinion. I think there is some evidence.

Q. BY MR. SCHURZ: Right. And that is contrary to the opinion that IARC came out here, correct?

A. Yes, that's contrary to their specific opinion about bladder cancer, correct.

Q. Thank you. Now, let's take a look at some of the other opinions that appear to be at odds with the opinions that you are offering in this case.

Turning your attention to the middle column here, and if I can direct your attention, it's about -- it's in the second half, but it's right -- it's all one very long

paragraph, I'm afraid.

It begins, "Similarly, numerous cohort" --

A. I'm sorry. Where are you?

Q. Let's see if we can pull it up. The language I would direct you to, Dr. Infante, is midway down, and it begins, "Similarly, numerous cohort and case-control studies of cancers of the pancreas and prostate consistently indicated no association between these cancers and coffee drinking."

Do you see that?

A. Yes.

Q. You came to a different conclusion, correct?

A. Well, let's see what my conclusion was before I agree with you.

Q. Do you recall what your conclusion was with respect to --

A. No, I would have to look at my report to see what it says.

Q. So I would direct you --

THE COURT: Just a second. Let the witness look.

THE WITNESS: You know, I have a summary in the back.

MR. SCHURZ: That's where I was, actually.

THE WITNESS: It would be the simplest.

Q. BY MR. SCHURZ: Yes. So if you would turn in Exhibit --

MR. METZGER: Let him answer your question.

THE COURT: Let the witness complete the answer.

Anything further, Dr. Infante?

THE WITNESS: Okay. I'm there.

Q. BY MR. SCHURZ: All right. And in your opinions in Exhibit 60072 at Page 84, you conclude: "Epidemiological studies regarding consumption of coffee have reported increased risks for pancreatic cancer and prostate cancer," correct?

A. Yes, and if you look at the summary on Page 82, I indicated there are 12 case-control studies that indicated statistically significant elevated risk of pancreatic cancer. That's taken right out of the literature.

Q. So with respect to your opinions relating to pancreatic cancer and prostate cancer, they are directly at odds with the conclusions offered in the Lancet article at Exhibit 60127, correct?

A. Yeah, I think there's some evidence.

Q. So you disagree with IARC, again, with respect to pancreatic cancer and prostate cancer, correct?

A. I mean specifically, yes.

Q. All right. Now, you've offered further opinions in this case with respect to coffee ingestion and the incidence of childhood leukemia, correct?

A. Yes.

Q. And once again, the IARC working group did not reach the same conclusion, correct?

A. Well, I think they said that there wasn't evidence, and I think actually there's pretty strong evidence. So that would be different. However, I can't really see what -- you know, this is simply a summary, and they don't

have anything in there about which studies they evaluated to come to that conclusion and what they thought of them. So it's really hard for me to say, well, I don't know what that's based on.

THE COURT: All right. Well, Dr. Infante, I understand you may not agree with Mr. Schurz's viewpoints, but please listen to the question and answer only the question. Don't answer something else that you want to talk about.

THE WITNESS: All right. So --

THE COURT: So let's repeat the question.

Q. BY MR. SCHURZ: You came to a different conclusion with respect to the adequacy of the evidence with respect to coffee consumption in childhood leukemia that IARC did last year, correct?

A. Well, just so we understand, I didn't say the evidence was adequate. I said there was evidence of association with maternal coffee consumption and childhood leukemia, which I think is pretty strong. IARC concluded that however they characterized it, they didn't conclude that.

Q. They concluded there was inadequate evidence, did they not?

A. I don't know the exact language they used, but if they concluded that, I think there's some evidence; so there would be a difference of opinion.

Q. I understand that. You just characterized it as some evidence. In your testimony and discussion with Mr. Metzger, you characterized it as very strong evidence. Would you like to amend?

A. No, I don't want to amend that. I think there is strong evidence.

Q. And you would agree with me that IARC did not come to that conclusion with respect to childhood leukemia and maternal consumption of coffee, correct?

A. Correct.

MR. METZGER: Objection, your Honor. I don't even think -- it's lacking in foundation as to whether IARC even mentions that.

THE COURT: All right. Well, the witness is not here to testify or criticize the article written by someone else. So let's just focus on questions about his opinions.

Q. BY MR. SCHURZ: All right. So let me turn, then, to the discussion in the article at the top of the third column that appears on the right-hand side.

Do you see where I am?

A. Yeah.

Q. Where the authors state, quote, the combination of evidence suggesting lack of carcinogenicity for cancers of the female breast, pancreas, prostate, uterine, endometrium, and liver, with inverse associations for the latter two and inadequate evidence for all the other sites reviewed led to the conclusion that there is inadequate evidence in humans for the carcinogenicity of coffee drinking, unquote.

Do you see that?

A. Yes.

Q. And you disagree with that opinion, do you not?

A. Well, there are certain aspects I disagree with

and some I agree with.

Q. All right. Let's see if we can unpack the areas of disagreement.

Here the IARC working group referenced the inverse associations for uterine, endometrium cancer, and liver cancer, correct?

A. Well, wait a minute. Well, they say with inverse associations for the latter two, which would be endometrium and liver. I think you mentioned another cancer in there.

Q. No, I didn't.

A. You didn't?

Q. No.

A. This says with inverse associations for the latter two, which to me would be liver and endometrium, and I agree with that. And I said that in my report also. I think the literature shows inverse associations for those two. But, you know, I have criticisms of that literature. It can be due to confounding. So I don't disagree when it comes to the endometrium and liver.

Q. But IARC didn't say that the inverse associations that are seen in the literature associated with endometrium cancer and liver cancer is due to confounders, did they?

MR. METZGER: Objection. The IARC hasn't published its monograph yet. There's no report.

THE COURT: The question is argumentative. Please restate the question.

Q. BY MR. SCHURZ: Did IARC find -- strike that.

Did the working group of 23 scientists who prepared this, did they find that the inverse associations were attributable to confounding?

A. Well, I would think they did. Or chance or bias. Otherwise -- if they didn't think there was something wrong with the studies that showed that, then why wouldn't they conclude there was a causal association between coffee consumption and the reduction of liver and endometrial cancer? They didn't conclude that even though they pointed out that there are studies that show inverse associations, which I also agree with.

There are studies that show inverse associations. It's a question of what's that -- what's that -- you know, why is that. So I think I'm on the same page with IARC about that.

Q. And they conclude, do they not, that there is inadequate evidence in humans for the carcinogenicity of coffee drinking. Do you agree with that conclusion?

A. I do.

Q. All right, then. So let's discuss, then, some of the specific cancer sites you discussed with Mr. Metzger. And I'll start with the endometrial cancer that you discussed.

Now, this was one in which you observed that there is consistent evidence of an inverse association, correct?

A. Yes.

Q. And you posit, do you not, that that inverse association may be due to confounding, correct?

A. Yes.
Q. All right. Now, as part of your review, you reviewed the meta-analyses, correct?
A. Yes.
Q. And did you make any effort to prioritize studies, giving those studies that were the most recent and had the broadest base greater weight than other studies?
A. Well, I didn't do any ranking system when I evaluated them.
Q. All right. And your exercise here was to review the studies that Mr. Metzger had provided to you and identify and classify those that had found an increased risk and those that had found a decreased risk; is that correct?
A. When you say provided to me, you know, we had this discussion before. I provided some to him and asked him to get them. So we just talked about in terms of the evidence that I evaluated.
Q. Is that an accurate description of the exercise you took, of looking at this -- looking at the individual studies and assessing their results; is that correct?
A. Yes.
Q. You did not purport to perform a critical evaluation prioritizing those studies that were not deemed of greatest significance and may be superior to others, correct?
A. Well, there are hazards with doing that. And I've participated in those types of reviews. And the hazards of doing that is that on the basis of the methodology, you know, initially you say okay. This is a Category 1 study.

This is a good study. But then, when you start to review the results, it's not such a good study because you find out the study may not have had a long enough latency, or the comparison group might not have been done right. Or there could have been confounding of the exposure in the controls.

So just doing this carte blanche thing of just, you know, before you go into debt, when you're selecting the studies for review, saying, you know, this is a Category 1 study. This is a Category 2 study, a Category 3 study. I think when you actually review them, you end up switching those around. So I don't do that.

Q. Just to be clear so the record is clear, because I thought my question was much simpler. You did not perform a critical analysis of the studies by which you prioritized the studies that you believed deserved greater weight, right?

A. I didn't start out my evaluation by saying these studies I give greater weight. These studies I give less weight. I looked at all the studies.

Q. So you indicated again you didn't start out that way. But I'm interested in the totality of the work that you've done.

In this case, Dr. Infante, you did not perform a critical evaluation in which you prioritized studies giving greater weight that you believe to be of superior value, correct?

A. I based my evaluation upon, you know, the studies that have been done and the methodologies that he

used. I didn't first set up some screen and say okay, I'm going to accept this study, and I'm not going to accept -- I think you have to look at the study and then the results and go into the study in more detail before you can do that.

I'm just telling you that I didn't do that kind of a screening analysis and exclude some studies because, well, I thought this wasn't good and this one is a better study.

Nor does IARC do that.

Q. Let's take a look at a couple of the studies that are part of your file, and again, specifically focusing on endometrial cancer.

And let me direct you to -- this one is sort of in the middle. It's Exhibit 56483. The first author is Wang from 2016. Let me know when you've identified that document.

MR. METZGER: We're cherry-picking the one study.

THE WITNESS: Okay.

Q. BY MR. SCHURZ: And do you have Exhibit 56483 in front of you?

A. Yes.

Q. And this was one of the studies in your file, correct?

A. Yes.

Q. And it's one of the studies you reviewed, correct?

A. Yes.

Q. And it was published in 2016?

A. Yes.

Q. And this is the most recent meta-analysis that

assesses coffee and endometrial cancer; is that correct?

A. Well, it's 2016. So I would think it would be fairly recent. Whether, as I sit here, if I can recall this is the most recent, I don't know, but it's 2016. It's not very old.

Q. All right. And based on this recent meta-analysis addressing coffee and endometrial cancer, the authors conclude, do they not, Dr. Infante, that coffee is associated with a statistically significant reduced risk of endometrial cancer, correct?

A. Yes.

Q. All right.

A. I'm not arguing that. I'm not arguing that there are studies that show that.

Q. Now, let's take a look at another of the recent meta-analyses that you cited, and let me direct your attention now to Exhibit 56964. And this is the Zhou study?

A. You left off a number, I think. 569 --

Q. 56964. Do you have Exhibit 56964 in front of you?

A. Yes.

Q. And this is one of the meta-analyses that you reviewed, correct?

A. Yes.

Q. And this was another meta-analysis that addressed coffee consumption and the risk of endometrial cancer, correct?

A. Yes.

Q. And in this specific meta-analysis, it includes a total of 1,534,039 participants, correct?

A. Okay. I don't see where you're reading it. Okay. I'm with you. Right.

Q. And again, the authors conclude that there's a statistically significant reduced risk of endometrial cancer observed by the authors of this study, correct?

A. Yeah, and I've never disagreed that there is epidemiological studies that don't show inverse associations. In fact, I think that was my testimony, that I have, you know, reservations about this just like these authors do.

If you look back on Page 7 of this report, and not limit yourself to the summary, it says there are several limitations of this study as listed below. Coffee intake data were collected using food frequency questionnaires. Number 3, most studies did not distinguish between types of endometrial cancer. Number 4, the possibility of residual confounding due to other risk factors cannot be excluded. You know, and that's my opinion. That's the issue.

5. Publication bias was detected in the total coffee intake and endometrial cancer risk.

So they acknowledge themselves there's publication bias in what they reviewed. And if you look at 6, it says the grade quality of the evidence was moderate to low, which lowers confidence in any subsequent recommendations. So there are limitations that they're now acknowledging to the study, and that's my opinion.

Q. Of course, and they conclude, do they not, that

based upon the evidence that they were reviewing that there was a statistically significant reduced risk of endometrial cancer observed by the authors, correct?

A. Yeah, and I agree with that.

Q. All right. But you, Dr. Infante, attribute that to confounders, correct?

A. Overall, looking at all the literature, yes.

Q. And that opinion, the inverse opinion associated with the injection of coffee and --

A. Excuse me. Let me rephrase it. It's likely due to confounding, and that's why I'm saying that a controlled clinical trial needs to be done to answer the question.

Q. And can you identify for this Court any public agency that shares your opinion that the inverse association associated with coffee consumption and endometrial cancer is due to confounders?

A. Well, I'm saying it's likely due to confounders. I don't know for sure. But it seems to me that, you know, there are, for example, I talked about confounding from cigarette smoking and, you know, other confounding in terms of misclassification.

So that's why I'm saying, as a result of my concern about confounding, that to me, I don't -- you know, I don't think that this study shows a causal effect in the reduction of endometrial cancer, and neither does IARC.

IARC says it's unclassifiable. If IARC thought that there weren't issues of confounding, then why wouldn't they

have, you know, I think they would have concluded that, well, there's some causal effect here in reducing the risk of endometrial cancer. They didn't do that. They do have a Category 4, which says in IARC's classifications, which if you look at IARC's classifications, No. 4 is that the substance or agent is unlikely to be carcinogenic to humans. They didn't --

Q. And how many substances, Dr. Infante, has IARC found to put in your Group 4?

A. It's not my Group 4. It's IARC's Group 4.

Q. IARC's Group 4. How many substances, how many elements have been found to be put in that class in the history of IARC?

A. One.

Q. Thank you.

A. Yeah, and the reason being is that they choose their substances for evaluation on the basis of, you know, evidence that's already indicated some cancer risk. So, you know, they are biased in what they choose to review.

Q. Now, with respect -- the question I asked you, Dr. Infante, was slightly different than the discussion we've just been having.

My question to you was can you identify for this Court any public agency that shares your opinion that the inverse association that's associated with coffee consumption and endometrial cancer is due to confounding?

MR. METZGER: Objection. Assumes --

THE WITNESS: IARC. Otherwise, they would have

concluded there was some causal association. And if you look at the summary, they talk about bias, confounding, and chance, and why they couldn't draw a conclusion one way or the other.

Q. BY MR. SCHURZ: Well, they found the issue of bias not with respect to endometrial cancer, didn't they? It was entirely different, wasn't it?

THE COURT: Let's not get into an argumentative questioning.

THE WITNESS: It could be confounding.

Q. BY MR. SCHURZ: Let's discuss for a moment the discussion you had with Mr. Metzger relating to childhood leukemia.

You are familiar with the Dietary Guidelines Advisory Committee that advises the United States Department of Agriculture with respect to the dietary guidelines for America, correct?

A. I'm aware of them.

Q. Well, in fact, didn't you, after the first phase of this trial, send the advisory committee a letter stating that the link between maternal coffee consumption during pregnancy and childhood acute leukemia is strong?

A. Yes, I did. And I haven't seen the letter for a while. I also advised them that I noticed in their review, they didn't review any studies related to maternal coffee consumption and childhood leukemia. It's not in their bibliography.

Q. And you saw that the advisory committee for the United States Department of Agriculture chose not to warn

against maternal consumption of coffee for risk of childhood acute leukemia, correct?

A. Yes. And to my knowledge, they never reviewed the data on coffee consumption -- maternal coffee consumption and childhood leukemia. So how could they come up with that conclusion? It doesn't seem very scientific to me.

Q. IARC, however, did review the literature relating to childhood leukemia and maternal consumption of coffee, correct?

A. Yes.

Q. And they found that the evidence was inadequate for purposes of determining the carcinogenicity of coffee with respect to childhood acute leukemia, correct?

A. Yes, and as I said earlier, I disagree with that particular sub conclusion.

Q. So in that context, this would be a further disagreement that you have with IARC in this analysis, correct?

A. What do you mean further disagreement? We talked about it earlier, and I said I disagreed with it. I don't know what you mean by further disagreement.

Q. I'm talking about specific cancer sites. We've identified a difference of opinion with respect to pancreatic cancer, prostate cancer, and childhood leukemia, correct?

A. Yes.

Q. All right, now, let's discuss confounding and childhood leukemia. You discussed confounding earlier with respect to the endometrial and liver cancer. You didn't

discuss it with respect to others, correct?

MR. METZGER: Objection. Your Honor, this was all testified to at length during the Phase 1 trial.

THE COURT: Objection overruled. You may answer.

THE WITNESS: Pardon me. I didn't hear you, your Honor.

THE COURT: Read back the question, please.

(Record read.)

THE WITNESS: I think in my earlier report, and I think some is in this report, I talked about confounding with childhood leukemia as I recall.

Q. BY MR. SCHURZ: And you identified in your appendix some such factors for childhood leukemia, correct?

A. Yes.

Q. And those would include benzene, gasoline, ionizing radiation, and petrochemical exposures, correct?

A. Yes.

Q. And these are all potential confounding factors, correct?

A. Yes.

Q. Did any of the studies you relied on control for any of these potential confounders?

A. I don't think directly that I can recall.

Q. So that would be no, correct? They did not address these potential confounding factors, correct?

A. You know, I'd have to look back and see. I can't recall.

Q. And yet you've offered testimony to this Court

that you believe the evidence is very strong with respect to the connection between maternal consumption of coffee during pregnancy and childhood leukemia, correct?

A. Yes.

Q. And you base that opinion without any understanding of whether any of the studies you're relying on controlled for potential confounders, correct?

A. Well, you know, I have to look back at the studies. I mean, these are questionnaire studies of case-control studies, and I would have to look back to see if they control for that. They may not have. I can't recall as I sit here.

Q. All right. As you sit here today, you don't know whether they controlled for any of the potential confounders that you've identified, correct?

A. I don't recall.

Q. All right. So let's turn, then, to childhood brain cancer, another of the cancer sites you addressed. You cite just four studies regarding childhood brain cancer, correct?

A. Right.

Q. And the most recent of those studies is the Bailey study, which you'll find in your binder at 59313. It's towards the back of the binder.

A. Okay.

Q. And do you have Exhibit 59313, the Helen Bailey study of parental smoking, maternal alcohol, coffee and tea consumption, and the risk of childhood brain tumors?

A. Yes.

Q. All right. And would you agree with me, Dr. Infante, that the authors find and conclude that there was no association seen between childhood brain tumors and the mothers drinking coffee during the index pregnancy?

A. Where are you reading from?

Q. Results, Page 1 of the abstract. First sentence, quote, no association was seen between CBT and the mother smoking or drinking alcohol, coffee, or tea during the index pregnancy, unquote.

A. Yes, I see that, but then if you look at Table 4, it shows that for coffee during pregnancy, a regular, more than a cup a day -- wait a minute. I'm sorry. At the bottom it says ESTELLE only. And didn't I cite the ESTELLE aspect of that population? Yes, I did.

Q. Yes, you elected to --

MR. METZGER: Let him finish his answer, please.

Q. BY MR. SCHURZ: I'm sorry, Dr. Infante. Were you finished?

A. No, I'm not, because that was their best data set, according to the authors, was the ESTELLE population. And if you look at that coffee consumption during the first trimester of pregnancy, regular, more than a cup per week, the odds ratio was 1.29, and that's statistically significant.

Q. Yes. And based upon that evidence, these authors still concluded, did they not, Dr. Infante, that there was no association seen between childhood brain tumors and the mother's drinking of coffee during the index pregnancy,

correct?

A. That's what they concluded. But I'm pointing out in their own table it shows a significant increase for --

Q. Yes, and let us discuss for a moment --

MR. METZGER: Let him finish his answer, please.

THE COURT: Just one second. Did you finish your answer?

THE WITNESS: In this, it shows that in fact for the population that they thought was the best, they have a significant increase. I know what they concluded. I saw what they concluded. Nevertheless, this analysis shows there's significant increase in childhood leukemia.

Q. BY MR. SCHURZ: So you disagree with the ultimate conclusion that these authors reach, correct?

A. I disagree with the conclusion there's no evidence because in my opinion it shows a significant increase from the population that they said was the best population to study.

Q. And you offered an opinion in this case, presented an opinion that the Bailey study actually supports your view that there's a statistically significant increase, correct?

A. Yes, that's right. And I indicated, if you look on Page 21 of my report, 6-C, it says any material consumption during the first trimester showed a significant elevated risk of childhood brain tumor, odds ratio 1.29 is significant. Data only available for the ESTELLE study population.

So in this particular study population, there is an increased risk. You know, I look at the data. I'm an epidemiologist. I don't just look at author's conclusions.

Q. Well, in this case your conclusion is at odds with the authors' conclusions, correct?

A. Correct. They are saying no association. That's obviously not borne out by the analysis.

Q. Right. So you believe the authors are wrong?

A. I'm not arguing what they said versus what anyone else says. I'm saying that the data in their own study contradict that.

Q. And isn't it the case that these very authors made a determination that the data upon which you are relying was not reliable?

A. Well, what do you mean by that?

Q. Isn't it the case, Dr. Infante, that the Bailey authors looked at the very data that you were relying on and said it's not a reliable basis for the purpose of rendering the very conclusion that you are offering in this case?

MR. METZGER: Objection. That's argumentative, and it nowhere states that in the article.

THE WITNESS: I don't see where they say that.

Q. BY MR. SCHURZ: Turn to Page 11.

THE COURT: The answer stands.

Q. BY MR. SCHURZ: Right-hand column. Excuse me. Left-hand column.

A. 11. Okay.

Q. Left-hand column, first full paragraph that

begins with in regards. And directing you to the end of that paragraph.

Do you see where I am?

A. Yes.

Q. And here the authors state, quote, although we found some evidence of an association with drinking coffee in the first trimester, this was based on ESTELLE data only with no indication of a trend relationship. As we were the first to specifically investigate this time period, it may be a chance finding, thus replication in other studies is needed, unquote.

Did you consider the authors' analysis of the ESTELLE data?

A. I did consider the authors' analysis of the ESTELLE data, and that's what's in Table 4.

Q. And did you consider that the authors of this very study, upon which you rely, considered that that data, upon which you were relying, may be a chance finding?

A. Well, they considered it may be. And it may be. But my point is that the study shows a significant increase.

Q. And the authors --

A. You can always have a chance finding, but since it was statistically significant, it would be a chance finding but less than five times out of a hundred.

Q. And isn't it the case, Dr. Infante, that these authors, in reviewing the very data that you were relying on, looked at this data and concluded that there was no

association seen between childhood brain tumors and the mothers drinking coffee during the index pregnancy?

A. Well, I mean, that was their conclusion, yes. And likewise, in my opinion, yeah, there are studies that show increases, and I think, as I testified earlier, you need more study because there are only a few, at most four studies. That was my testimony.

Q. So this would be an instance, would it not, Dr. Infante, in which you have reached conclusions that are inconsistent with the authors' own discussion?

MR. METZGER: Objection. Argumentative and cumulative.

THE COURT: Overruled.

THE WITNESS: It's -- it would be inconsistent when you say there's no association because in my opinion, their data shows a statistically significant increase. And like I said, I'm not saying from that that coffee consumption causes brain cancer. I'm merely pointing out that there's a study that shows a significant increase.

So to me, you know, it would provide some evidence. And I also said you need more studies. So, you know, it provides -- you know, it's a significant increase.

Q. BY MR. SCHURZ: So in this respect, isn't it the case, Dr. Infante, that your review of the coffee epidemiology is exactly the very reason that the Court in Burst versus Shell Oil company found the methodology lacking and that you reached conclusions that were inconsistent with the authors' own discussion?

MR. METZGER: Objection. Argumentative, 352.

THE COURT: Overruled.

THE WITNESS: In the Burst case, the Court ruled that, I believe, as I can recall it, that there was evidence that benzene from gasoline could cause leukemia. You know, and in my opinion that's just so -- that's just so wrong to say that I evaluated -- here's the thing. They said well, I evaluated all these studies on gasoline and leukemia when the question was does benzene cause leukemia. Well, benzene is contaminated gasoline. 1 to 2 percent.

So it made no sense epidemiologically for the Court to draw that conclusion, and that is exactly why 45 experts from around the world that are experts in cancer, epidemiology, statistics, occupational health sent a letter to the Court saying that my testimony should be reinstituted or whatever legal word you use for that. I don't know. And that in their opinion, that benzene in gasoline was a cause of acute leukemia.

So because I had 20 single-spaced pages in my report on gasoline and as it relates to acute leukemia, so the Court ruled that, well, but that's not benzene. So I'm reviewing the long literature.

That conclusion of the Court is just totally flawed from an occupational health standpoint. 45 scientists in this area agree with me.

Q. BY MR. SCHURZ: And what did the Fifth Circuit say --

THE COURT: Let's not go over this again.

MR. SCHURZ: Your Honor, this is the second time that Dr. Infante has sought to enlist this amicus brief as authority for the proposition --

THE COURT: Well, you cited it. You can argue from it. Let's move on.

Q. BY MR. SCHURZ: All right. Let's talk about gastric cancer. Another site that you discussed with Mr. Metzger?

And it is your opinion that the epidemiological studies show an increased risk of gastric cancer in relation to drinking coffee, correct?

A. There's some evidence, yes.

Q. And the most recent meta-analysis would disagree with that conclusion, would it not?

MR. METZGER: So now we're cherry-picking the one out of ten that --

THE COURT: All right. Let's not argue. You'll have an opportunity to respond.

MR. METZGER: Excuse me.

THE WITNESS: Well, there were -- I think I had mentioned in my testimony that of ten meta-analyses that I reviewed, nine of them showed an increased risk. Six showed a statistically increased risk of gastric cancer. And I also mentioned that there's one study, except I said one study. So there's one study that didn't report an increased risk. So which study now do you want to discuss with me?

Q. BY MR. SCHURZ: I'd like to discuss the most recent one.

A. All right. What is that one?

Q. It's Xie study from 2016, which you'll find at Exhibit 56130.

A. Okay.

Q. Now, this is the most recent, is it not?

A. It's 2016, but I also have Wang 2016. I don't -- I mean, I don't know which month they were published in in 2016. So I don't know. They were published in the same year. So it's not necessarily the most recent, but it's, you know, it's within the last year.

Q. All right. And in this case, based upon a meta-analysis published just last year that seeks to bring together a group of prior studies, the authors conclude that the meta-analysis suggested that coffee consumption might be associated with a decreased risk of gastric cancer, correct?

A. Yes, that's right. And in my testimony, in my report I stated that all the meta-analysis except one reported increased risks of gastric answer. So I assume this is the one that didn't that you're asking me about.

I'm not disagreeing with their findings. I'm just saying it's, you know, it's like the only one that doesn't show an increase.

Q. And IARC also reviewed the epidemiologic literature with respect to gastric cancer, did they not?

A. Yes.

Q. And they concluded that there was inadequate evidence of any carcinogenicity to show either an increased or decreased risk of cancer associated with coffee ingestion and

gastric cancer, correct?

A. In essence, IARC concluded there was inadequate evidence for every site, either positive or negative.

Q. I'm focusing specifically on gastric cancer.

A. That would include every site of cancer.

Q. So with respect to gastric cancer, your opinion is at odds, is it not, with the IARC conclusion that there is inadequate evidence to show either an increase or a decreased risk of cancer associated with coffee consumption and gastric cancer?

A. Well, I pointed out that nine of the ten meta-analyses showed an increased risk. And overall, I agree with IARC's opinion that you can't make a determination. So you can characterize that, you know, testimony however you want. The bottom line is I'm not saying any cancer site related coffee is causally, you know, causing an increased risk or causing a decreased risk. I think you can't make that determination.

But, you know, within that body of epidemiology, I think there are some -- you know, there are some studies that show an increase. But you know, overall, you know, they are saying it's inadequate to determine causality. And my testimony was that the sites that show an increased risk, in my opinion, there's not evidence of causality for those increased risks. So it's consistent with IARC.

Q. Well, the conclusion is that there was inadequate evidence in humans for the very carcinogenicity of coffee drinking, correct? Not just causality. The conclusion

is that there's inadequate evidence in humans for the carcinogenicity.

MR. METZGER: That means causality.

THE WITNESS: That means the same thing to me.

Q. BY MR. SCHURZ: Okay. Let's talk a little bit about lung cancer. In your discussion with Mr. Metzger, you stated that the studies show that coffee consumption increases the risk of lung cancer in certain studies, correct?

A. Correct.

Q. And you state that the five meta-analyses on coffee consumption and lung cancer, all but one report some significantly increased lung cancer risks, correct?

A. Well, where are you referring to in my report?

Q. Page 58.

A. Okay. Where?

Q. Paragraph 14, Subparagraph C.

A. All right.

Q. And among the studies you cite is the Galarraga meta-analyses from 2016, correct?

A. Yes.

Q. And this was the largest of the meta-analyses relating to the coffee drinking and lung cancer, correct?

A. You know, I don't recall if it's the largest as I sit here.

Q. Let's take a look at it. It's Exhibit 58414. Do you have it? It's a study entitled Coffee Drinking and Risk of Lung Cancer, a Meta-Analysis.

A. Yes, I do.

Q. And this is the largest of the meta-analyses relating to coffee drinking and lung cancers that you reviewed; is that correct?

A. I don't recall, as I sit here, how large they were. Well, this one says data for 19,892 cases.

Q. And the conclusion of the study, Dr. Infante, directing your attention to the top of Page 1 of 58414, is that, quote, the pooled estimates indicated --

A. I'm sorry. Excuse me. Which page are you on?

Q. First page.

A. All right.

Q. I'm reading from the conclusions section that appears there.

Do you have that?

A. Yes.

Q. All right. And the authors conclude, quote, the pooled estimates indicated that when the potential confounding effect from smoking is controlled for, coffee drinking does not appear to be a lung cancer risk factor. Further pooled analyses, with larger non-smokers population size, are encouraged to confirm these results, unquote.

Do you see that?

A. Yes.

Q. So this would be an instance in which your conclusion, again, at page -- to return to your opinions, again, when looking at your conclusions, this was one where you indicated, actually, that the meta-analysis showed an increased risk of lung cancer, correct?

A. I said but not among non-smokers. If you look, it says risk was also increased for each one cup per day increase in consumption. Relative risk 1.04. And that's statistically significant, but not among non-smokers.

Q. Right, and directing your attention --

A. And that would indicate that if the risk isn't increased among non-smokers, then maybe smoking was responsible for the elevated risk of lung cancer that's in the line above that.

Q. So let's --

A. So I'm presenting both.

Q. Let me take you back to Galarraga and the conclusions here. This is a case, Dr. Infante, in which you state except for you, all these reported some significantly increased lung cancer risks with respect to the Galarraga study, whether in fact Galarraga, when it made the appropriate adjustments for smoking, came to the opposite conclusion, did they not?

A. Right. And I think I point that out in Paragraph 4 there that among non-smokers, there's not an elevated risk.

Q. So once again, though, Dr. Infante, is this -- isn't this an instance in which what you chose to put forward in your patterns with respect to the Galarraga is inconsistent with the conclusions that the authors themselves concluded?

MR. METZGER: You mean Dr. Boffetta?

THE COURT: Please rephrase the question.

Q. BY MR. SCHURZ: Okay. Dr. Infante, let me try

this again.

Isn't the Galarraga instance yet another example of where you have drawn an opinion and offered an opinion to this Court that is at odds inconsistent with the very conclusion that the authors made in this study?

A. Not exactly, no. Because I point out that -- you're talking about lung cancer, and in non-smokers there's no elevated risk. I'm simply pointing out that, hey, look, when you look at one day cup increase in consumption, there's an increase that's statistically significant but not among non-smokers, which would tell certainly any epidemiologist that, you know, from this study, you know, could well be due to cigarette smoking.

Q. But that's not what the authors of this study concluded, is it?

A. You know what? I'm presenting the data in a little bit different way. I'm talking about what their results were, and I'm just putting them out there rather than just simply taking their conclusion and saying that, well, we didn't observe any increased risk. That's right. And the non-smokers, there is no increased risk. So I'm not disagreeing with that part of it.

Q. But you are disagreeing with the ultimate conclusion that they have offered, correct?

A. I don't think so.

Q. All right. And once again, IARC found that there was inadequate evidence with respect to any connection between an increased risk of lung cancer, correct?

A. That's correct.

Q. All right. So let's talk a little bit about pancreatic cancer. Yet another site that you appear to be at odds with what IARC --

MR. METZGER: Objection. Argumentative.

THE COURT: Objection sustained. Rephrase the question.

Q. BY MR. SCHURZ: You identified five meta-analyses relating to pancreatic cancer, correct?

A. You'll have to go to my report. What page are you on?

Q. Well, the summary of your pancreatic cancer findings can be found on 82.

A. Okay. Okay.

Q. So with that orientation, I'd like to direct a series of questions relating to the five meta-analyses relating to pancreatic cancer. Okay?

A. Yes.

Q. So three of these meta-analyses were published last year, correct?

A. They may have been. I can't tell from this page.

Q. And as you indicate here, three of these -- well, specifically with respect to those that are most recent, none of them showed a statistically significant increased risk associated with -- strike that. Let me start over.

None of the three meta-analyses published within the last year showed a statistically significant increased risk

associated with drinking coffee and pancreatic cancer, correct?

A. That's what I have in that Paragraph 3, yes.

Q. All right. And you state earlier that one such study reflects a borderline significant increase, correct?

A. Right.

Q. So let's take a look at the Turati opinion that is at 54026. It's the first exhibit, and this is Exhibit 45026. I inverted some numbers here?

A. 45026. I have it.

Q. Okay. And this is one of the studies you relied on in developing your opinions with respect to coffee consumption and pancreatic cancer, correct?

A. It's one that I reviewed, yes.

Q. And is it the case that you state that the Turati paper shows a borderline significant increase in cancer risk?

A. Yes.

Q. So let me direct your attention to the conclusions of the authors, which you'll find on the first page under conclusions, in which the authors offer the conclusion: "This meta-analysis provides quantitative evidence that coffee consumption is not appreciably related to pancreatic cancer risk, even at high intakes," correct?

A. Yeah, and I think the key word there is appreciably. Because when they qualify their studies, if you look on Page 6, they state that the observational studies included in our meta-analysis may have various sources of

bias, an important issue concerns the assessment of coffee intake, which is always based on patient's self-reporting, a reduction in coffee consumption because of early symptoms of pancreatic cancer in cases may weaken a potential positive relationship in case-control studies that consider more recent exposures. And then they go on to say, with reference to confounding, apart from the smoking, other recognized risk factors for pancreatic cancer and diabetes, pancreatitis, and family history.

So they are talking about confounding. So they are saying there's no appreciable increase in risk, and obviously, I don't disagree with that because they characterized it as a borderline significant increase, which means it wasn't statistically significant, but now they are offering reasons for why this study may not have been able to find an elevated risk was because of the exposure misclassification.

Q. Now, in this case, Dr. Infante --

A. And also not just exposure misclassification, but also the fact, as they state, that individual symptoms of pancreatic cancer may have weakened a potential positive relation in case-control studies. They acknowledge that, and I agree with that.

So I'm just saying that in this study there's a borderline significant increase, and they talk about, well, the association may have been weakened because of these biases in the study. And I agree with that too.

Q. So, Dr. Infante --

THE COURT: All right. Well, you can complete the

question.

Q. BY MR. SCHURZ: Dr. Infante, isn't this yet another case in which you've offered an opinion with respect to a specific study but failed to provide the ultimate conclusion that those authors reached?

A. Well, you read the conclusion. I think it's consistent with what I've said. You said -- it says appreciably is what you showed me. That's the key. That would mean there's an increase, but it's not an appreciable increase. You could have a significant increase. They could characterize it even as non-appreciable. They didn't say there's no increase. They said it's not an appreciable increase.

Q. And you used it for the proposition that there was borderline significance, correct?

A. Yeah, and I exactly stated that, right. And right above that, if you'll notice, I mentioned studies that were negative.

Q. All right.

THE COURT: All right. We're going to take a recess at this time. We're going to be in recess for 15 minutes.

(Recess taken.)

THE COURT: We're back on the record in CERT versus Starbucks. All counsel are present.

You've completed your examination?

MR. SCHURZ: I have, your Honor. Thank you.

THE COURT: All right. Okay.

Mr. Metzger.

MR. MARGULIES: Your Honor, I have just a couple of questions.

CROSS-EXAMINATION

BY MR. MARGULIES:

Q. Good afternoon, Dr. Infante. I have just a few follow-up questions from the questions Dr. Schurz asked you with regard to endometrial cancer, your opinion, that is, you believe the inverse association is due to confounding by smoking; is that correct?

A. That's one of the factors. I am not saying that it is. I'm saying that it likely is, and that needs to be investigated further with a clinical trial because of all the, you know, confounding from not only cigarette smoking but the risk of endometrial cancers related to parity, related to the age at which you reach menopause, when you reach menarche, there are a lot of factors related to endometrial cancer that need to be explored in a more detailed study.

Q. In referencing the Zhou article, 56964, you pointed Mr. Schurz to a statement in the Zhou article where the authors reference this issue of confounding, correct?

A. Yes.

Q. With regard to that article, you referred Mr. Schurz to a statement the authors made about the possibility of confounding.

Do you recall that testimony?

A. We talked about so many, I don't remember, but do you have a specific --

Q. So if you'd turn to Page 8, and there's some numbered paragraphs at the bottom, and No. 4 says the possibility of residual confounding due to other risk factors cannot be excluded.

Do you recall reading that to Mr. Schurz on cross-examination a few minutes ago?

A. Yes.

Q. Could you read the rest of that sentence, please?

A. "Although most investigators had adjusted BMI, hormone therapy, and smoking status."

Q. So that indicates that these confounders were addressed in the Zhou meta-analysis, correct?

A. Yes, but there were plenty others that weren't.

Q. The Wang meta-analysis, 56483, this was another study that found -- or another meta-analysis that found an inverse association with endometrial cancer?

A. Yes.

Q. And this was another one in which you felt that they did not address the confounding factors?

A. You know, I acknowledge that these studies with endometrial cancer show inverse associations. The question is are those -- is that reduction in endometrial cancer causal, or is it due to confounding from various sources? My opinion is it could well be due to confounding and further study needs to be done. I acknowledge the studies show the inverse association, but the question is what's it attributable to.

Q. Is it your opinion --

MR. METZGER: Hold it. Have you finished your answer?

THE WITNESS: Yes.

Q. BY MR. MARGULIES: Is it your opinion that the Xu meta-analysis did not address confounding for endometrial cancer?

A. Well, you know, some of these studies they addressed some confounding factors. But, you know, there are a lot of issues in these studies, and they don't always address all the confounding factors, and, you know, there's also issues with misclassification of exposure.

Q. I'm sorry. Is it your opinion that Zhou did not address the confounding factor? Yes or no.

A. Which confounding factors are you speaking about?

Q. Any.

A. Well, I'm sure they addressed some.

Q. Which ones did they address?

A. I'll have to look at it and see. What's the number of the article?

Q. 56483.

MR. METZGER: That's the Wang article, not Zhou.

MR. MARGULIES: I'm sorry. My apologies.

THE WITNESS: I'm not clear which study.

Q. BY MR. MARGULIES: The question is with Wang, 56483. Did it or did it not address confounding factors?

A. You know, I would think it would address some of them, but let me look.

MR. METZGER: Take a moment to answer it.

MR. MARGULIES: Your Honor, I'd object to Mr. Metzger instructing the witness on cross-examination.

THE COURT: Please don't advise the witness from counsel table.

MR. METZGER: I apologize, your Honor. It was improper.

THE WITNESS: It's a meta-analysis. So it's evaluating a bunch of studies pooling the data. So, you know, some of those studies, you know, address confounding, but not all confounding factors. And, you know, others, you know, don't address it. You're pooling data from a bunch of different -- you're pooling not data but actually results in the literature from a bunch of different studies.

So if you're asking me did the Wang meta-analysis consider confounding factors, well, probably there's a varying degree of confounding factors that were considered in these studies that were all study results that were pooled together.

Q. Did Wang conduct subgroup analyses by confounding factors to find no substantial factors influencing the results?

A. Well, I guess I would have to answer that question after I'd say okay, what confounding factors did they evaluate because, I mean, you know, and it's a matter of how well you address those confounding factors, in my opinion, they haven't been adequately addressed. And, you know, in any of these studies.

That's why I'm saying I don't think you can

determine causality one way or the other. There are studies, for example, that I testified to earlier. I said yeah, they show an increased risk. But that doesn't mean that, you know, they cause those cancers. I'm reviewing the data and say yeah, here's some studies that show an increased risk for the same site. Here's some that don't.

But does that mean that let's say the positive studies indicate that coffee causes those cancers. The answer is no. I think you can't make the determination. And I feel the same way about the endometrial cancer and liver cancer and --

MR. MARGULIES: Move to strike as non-responsive. The question was --

THE COURT: The answer will stand. You can rephrase the question.

Q. BY MR. MARGULIES: I'll repeat the question.

Did Wang conduct subgroup analyses by confounding factors to find no substantial factors influencing the results?

A. Well, I'll have to look at the study right now.

Q. So you don't know off the top of your head --

A. No. I'll have to review the study to answer the question.

Q. Why don't you turn to Page 8 in the last full paragraph, please.

A. Page 8, okay.

Q. Would you read the third sentence, please.

A. The one that you have highlighted?

Q. The sentence that starts "however."
A. "However, we conducted subgroup analyses by confounding factors and found no substantial factors influencing the results."
Q. Thank you.
A. That's what they said.
Q. We've been talking about meta-analyses, Dr. Infante. What is a meta-analysis?
A. It's an analysis where you combine the study results from various studies in order to try to increase the precision of the estimate of relative risk.
Q. So you take a number of studies. You pool them together. You look at what the data tell you as a whole where you might find different results from any of the individual studies, right?
A. No. You're pooling the study results, not data from the studies. But, you know, usually from the summary relative risks.
Q. You don't pull -- I'm sorry. Please finish.
A. When you're doing a meta-analysis, you look in the literature, and you take the study results, and you pool the information on the relative risks from the various studies. Sometimes authors only include the overall relative risk. Sometimes and less often they include information on dose response from the various studies.
So there are different ways to combine data in a meta-analysis, depending on which the authors choose to do.
Q. But it's a pooled analysis in the series of

individual studies, correct?

A. Of the results from individual studies, correct.

Q. So you might have a study where you looked at some cases and controls for the type of cancer. You might have a cohort where you're looking at the same type of cancer. You take all of those studies together and try to come up with an overall analysis, right?

A. An overall estimate of relative risk, yes.

Q. In talking about gastric cancer, I think you mentioned there were ten meta-analyses done?

A. Yes.

Q. Did they involve different underlying studies, or were they all on the same studies?

A. I'll have to look back.

Q. You don't know off the top of your head?

A. Correct.

Q. Let's talk about the Xie, 56130. This was the one study that you said found no association; is that right?

A. Correct. I didn't say one study. I said of the 10 meta-analyses that I reviewed, it doesn't show an elevated risk. The opposite.

Q. And you're not aware of any more recent analysis than the one that was published last year, correct?

A. Correct.

Q. And do you know what studies, underlying studies, were included in this meta-analysis regarding coffee and gastric cancer?

A. I'd have to look at it to answer the question.

Q. Do you know if they excluded any of the underlying studies on coffee and gastric cancer?

A. Well, I would assume, when you do a meta-analysis, there's always some criteria for selecting the study. So I would assume that some studies were selected and others were not included.

Q. I'm sorry. Would you turn to the back -- if you look at the abstract, where it says methods and study design. The second sentence after methods and study design states: "All epidemiologic studies regarding coffee consumption and gastric cancer risk were selected."

Do you see that?

A. Yes.

Q. So that indicates that all studies that were available at the time of publication were included in the meta-analysis, correct?

A. Well, that's what they say. I mean, a lot of times authors say that, and you look at and you see studies that they missed.

Q. Can you tell us which studies they missed here?

A. I'm making a general comment. I'm making a general comment. They said that they included all epidemiologic studies regarding coffee consumption and gastric cancer risk were selected. I'm not disputing that. I'm not disputing that at all. I just made the comment that, you know, because -- you know, I would have to look back at this and compare, you know, all the studies to see if they -- it

was complete. It may be, and it may not be. That's all I'm saying. But I'm accepting what they said, and I'll assume that every study they could find they included.

Q. If you assume that they included every study that existed and you assume that it's the most recent meta-analysis, wouldn't that be the most useful piece of information on the issue of whether there's an association between gastric cancer and coffee consumption?

A. You raise an excellent question. And as an epidemiologist, I would say if there's such divergent results, one has to ask, well, what's going on here when you have other meta-analyses that show significant increases, and then you have the one that's the outlier, well, what do they mean by selecting all studies? How can they select, you know, all of the studies?

And, you know, there are other meta-analyses published almost the same year and come up with such divergent results? I would -- I think one would have to look into that a little more closely. So to answer your question, I wouldn't think that, you know -- I wouldn't think that it's, you know, the best study because it's the most recent. It may be. But I don't know that.

Q. Certainly the most comprehensive study, you'd agree.

A. Well, I don't know. Several of these meta-analyses that the authors essentially use the same studies and get very similar results. Now, this one, I guess, in order to answer your question, I would have to look. When

they say they included all studies, which studies did they include and then include that to another meta-analysis where -- and see what studies they included.

You know, I mean, there has to be some difference, and they may have, you know, added a new study that, you know, another meta-analysis didn't have that weighted the results because to go from quite a few showing a significant increase to one, then, that shows a deficit, that should raise a red flag about, you know, what's going on here.

And why is it so divergent from all of the others? Is it the way they selected the studies? You would have to look at that question.

Q. You haven't looked at that, have you?

A. No.

Q. You didn't see that red flag and decide I'd better take a look and see whether this study that's the most recent and the most comprehensive came to a different --

A. Well, I don't know that it's the most comprehensive. That's your characterization of it. Because I don't recall. I'm saying I think one could answer that question by looking at, you know, all the studies that they said they included when they included all the studies and looking at when other people did meta-analyses on gastric cancer, which ones did they -- did they include all the same studies and just came up with a different result.

Q. You haven't done that, correct?

A. I haven't done that, correct.

Q. So let's now take a look at pancreatic cancer.

You were talking with Mr. Schurz about the Turati study, which was 45026.

A. Yes.

Q. And you mentioned that the authors there acknowledged that the study results could have been due to bias; is that correct?

A. Yes.

Q. Did the authors do any analysis to determine whether bias was likely causing the study results that you saw?

A. Not that I'm aware of.

Q. Okay. Let's turn to Page 6, please. In the right column, the third full paragraph that starts with the observational studies included in our meta-analysis may have various sources of bias.

You see that?

A. Yes.

Q. And as you read along, they state, however, the similar estimates in case controlled, (pooled RR equals 1.10) and prospective (pooled RR equals 1.04) studies, where information is collected a long time before pancreatic cancer symptoms are against such --

A. Okay.

Q. More in general, case-control studies may be more subject to selection bias than cohort ones. However, the consistency of the results between hospital- and population-based case-control studies --

A. Okay. I see it.

Q. So they did address whether bias was playing a role --

A. No, they didn't. They are looking in the literature to say well, we don't think that, you know, information bias is an issue here. But, I mean, they don't know for their own study.

Q. Were they looking in the literature, or were they looking in their own data?

A. Well, they cite, however, recall of coffee drinking has been shown to be satisfactorily valid. And they cite three references and should not be different among cases and controls. So they are citing other studies and saying well, it shouldn't be different, but they don't know that it is or not in their own study.

Q. Do you?

A. No.

Q. Have you read those three or four references that are cited?

A. I don't know. I'd have to see what they are.

Q. Do you have an answer?

A. Did you want me to look and see what they are? I'm sorry.

Q. You don't know what they are, right?

A. Well, they are cited there.

Q. And you don't recall reading any articles on coffee recall bias, do you?

A. There are a bunch of articles on recall bias and misclassification of exposure that are discussed, yes. I

thought you were asking me specifically about these three articles that they are relying on. And you say did I read those, and my response was, you know, I don't know. I would have to see what those three studies are. If you want me to do that, I will be happy to do that.

Q. But they also looked at their own data to address other sources of bias, correct?

A. They are saying that, well, we think it's satisfactory, and it's based on someone else's research.

Q. So you talked earlier about reverse causation. Is that the right word?

A. Yes.

Q. And that's where somebody stops drinking coffee because their liver is already sick, and they don't want to drink coffee, or they have been told not to drink it, right?

A. Yes, and it's a question, then, of right where those people go in the study. If they have chronic liver disease and they are not drinking coffee, then they would go into like the zero or very low coffee consumption group selectively, and they would have the highest risk of developing hepatocellular carcinoma.

Q. And does that phenomenon also occur with pancreatic cancer?

A. Well, I don't know the data on pancreatic cancer.

Q. Does this article suggest that that phenomenon occurs with early symptoms of pancreatic cancer?

A. I think there were some that said that could be

the case. But it's more important, I think, in liver cancer because chronic liver disease is, I would say, the major source of individuals -- or a major cause of hepatocellular carcinoma, having liver disease for whatever reason.

Q. The authors rule out information or selection bias from the data in their study in Turati, didn't they?

A. Which study are you referring to?

Q. I'm talking about Turati.

A. Well, they could rule it out if they had information on Hepatitis B and Hepatitis C among the individuals who are part of their study. But since it's a meta-analysis, I know that most studies that they would pool in to analyze don't have data on Hepatitis C or Hepatitis B virus. So they can't rule out reverse causation.

Q. Is Hepatitis B or C related to pancreatic cancer?

A. I'm sorry. I thought you were talking about liver.

Q. We're talking about Turati.

A. Are you saying did they rule out reverse causation?

Q. They ruled out information or selection bias from the data in their study in Turati, didn't they?

A. I don't -- I could see in an individual study how they could attempt to do that. When you're doing a meta-analysis, you're pooling the data that was derived from other investigators. So I really don't know how they could rule that out.

Q. It says, however, the consistency of the results between hospital and population --

A. I'm sorry. Where are you reading?

Q. The bottom of that paragraph. The consistency of the results between hospital- and population-based case-control studies and cohort ones argues against the presence of major information or selection bias, correct?

A. Well, I think they are talking about the difference in selection bias between hospital-based case-control study and a population-based case-control study.

Q. Where do you get that?

A. That's what they say. Now, the consistency of the results between hospital- and population-based case-control studies and cohort studies argues against the presence of major information or selection bias.

Well, they don't know that from their own studies. They are making that assumption.

Q. So you just disagree with what they said?

A. I'm not saying I disagree with it. I don't know if it's true or not. Nor do they. They are just hoping that, you know, that's a reasonable -- and it may be. All I'm saying is they can't verify it. Their discussion of the results saying that, well, we think because of the consistency of the results, it argues against major information or selection bias. It may be the case, but it may not be. It's not verifiable.

Q. What are results based on, Dr. Infante?

A. Well, they are based on analyses of data.

Q. Are results the same as analysis?

A. You come up with estimates of relative risk and so on. You can say those are the results.

Q. So you haven't seen the data. You haven't done the analysis. But you disagree with their conclusion --

MR. METZGER: Objection.

THE WITNESS: You're mischaracterizing my testimony. I'm saying that they -- I see what they have said. I say I'm not disagreeing necessarily with what they said. But I'm saying they can't verify that. They are like hoping that's the case.

Q. BY MR. MARGULIES: Can you verify the opposite?

A. No. I'm not verifying the opposite. It's not my study. All that I'm saying is that he can't verify it. They are like hoping that's the case. Maybe it is. But it's unverifiable.

MR. MARGULIES: Your Honor, I don't have any further questions. Thank you.

THE COURT: All right. Thank you.

Mr. Metzger, anything further?

MR. METZGER: Yes, thank you, your Honor.

REDIRECT EXAMINATION

BY MR. METZGER:

Q. Dr. Infante, I'd like to ask you about -- well, would you turn to Exhibit 56964, the Zhou meta-analysis regarding endometrial cancer. Published in 2015. I'd like to direct your attention to Page 7 towards the bottom. There's

the sentence that says: "There are several limitations of this study as listed below." And then turn to the next page for the last one, which says: "The grade quality of the evidence was moderate or low, which lowers confidence in any subsequent recommendations."

What does that mean to you?

A. Well, it means what it says. It says the quality of the evidence was moderate to low. But whether they say it lowers confidence in any recommendations, to me that means that, you know, they are really not sure about their findings because the evidence was moderate to low quality.

Q. All right. And would you look up two paragraphs above that to Paragraph 4. It says: "The possibility of residual confounding due to other risk factors cannot be excluded," and it goes on.

Do you agree with that --

MR. SCHURZ: I'll interpose an objection. Mischaracterizes the statement.

THE WITNESS: Yes, I agree with it.

Q. BY MR. METZGER: All right. And then is says: "Although most investigators had adjusted BMI, hormone therapy, and smoking status," correct?

A. Yes.

Q. All right.

A. But that's not all the factors related to the cancer.

Q. Let me ask you that, please.

A. Oh, all right.

Q. Well, just do me a favor. Take a look at your report, and just count up in your appendix the number of factors that you found from your review of the literature were significantly associated with increased risk of endometrial cancer.

Dr. Infante, from the appendix that you prepared in your report, you count up the number of factors that you found from your review and study of the epidemiologic literature had been reported to significantly reduce the risk of endometrial cancer.

A. The number of them?

Q. Just the number of them.

A. 16.

Q. Okay. And in this meta-analysis, the authors -- going back to the Zhou meta-analysis, Exhibit 56964, the authors indicate that they -- most of the studies had adjusted for BMI, hormone therapy, and smoking status. Three factors, correct?

A. Yes.

Q. All right. And is BMI a factor that has been associated with reducing the risk of endometrial cancer?

A. I have not seen that.

Q. All right. And is hormone therapy a factor that has been associated with reducing the risk of endometrial cancer?

A. Well, it's possible that, you know, hormone therapy for what. You know, I don't know. It's not on the list of what I've seen.

Q. Well, actually, if you look on Page 87, you have factors reported to increase risk, and there you have estrogen and -- menopausal person, correct?

A. Yes.

Q. So is hormone therapy a factor that has been reported to decrease the risk or increase the risk of endometrial cancer?

MR. SCHURZ: Objection. Leading.

THE COURT: Overruled.

THE WITNESS: To increase the risk.

Q. BY MR. METZGER: So the only factor here that these investigators say have been adjusted in the studies as a confounding factor that has been reported to reduce the risk of endometrial cancer is smoking, correct?

A. Yes.

Q. That leaves 15 factors that have been reported to reduce the risk of endometrial cancer unaddressed in the studies, correct?

A. Correct.

Q. And what do you conclude, based on that in terms of what can be concluded from the meta-analyses or the studies regarding coffee consumption and endometrial cancer?

A. Well, my conclusion is that, you know, while they report in many of these studies an inverse association, they don't rally know what it's due to because there are too many factors that haven't been accounted for.

Q. Is it a significant problem in a study if there's 16 factors that have been reported to significantly

reduce the risk of a cancer and you only address one of them in the study?

A. Yes.

Q. And why is that?

A. Well, because there's other confounding factors that you are not adjusting for which, you know, pretty much makes it impossible, then, for you to get an estimate of what the risk is in that study, what the true risk is of the study.

Q. Okay. Thank you, Dr. Infante.

Within the binder -- oh, I'd like you to take -- do you have the binder that Mr. Schurz has provided you?

A. Yes.

Q. All right. Would you turn to Exhibit 55010.

A. Yes.

Q. This is the Chen meta-analysis regarding laryngeal cancer --

MR. SCHURZ: Objection. Beyond the scope. There was no discussion of laryngeal cancer.

THE COURT: Overruled.

Q. BY MR. METZGER: And what did you observe from your review of this meta-analysis?

MR. SCHURZ: Again, the same objection. Outside the scope. It was not part of the cross-examination or the direct, for that matter.

THE COURT: Well, the way the question is phrased calls for a narrative. It doesn't sound like it's responsive to anything.

Q. BY MR. METZGER: All right. Dr. Infante, from

your review of this meta-analysis, did you conclude that the risk of laryngeal cancer is significantly increased?

A. Yes.

MR. SCHURZ: Objection with respect to scope, your Honor. There was no discussion about laryngeal cancer in the direct. And that's why it didn't show up in the cross.

THE COURT: Mr. Metzger, why are we getting into this?

MR. METZGER: These are the exhibits that Mr. Schurz provided me --

THE COURT: So what? He could have given you a telephone book.

MR. METZGER: Okay. I thought it was discussed. If it wasn't, I will just say that I'm done.

THE COURT: All right. Thank you.

Anything further, Mr. Schurz? May the witness be excused?

MR. SCHURZ: Yes, no further questions, your Honor. The witness may be excused.

THE COURT: All right. Dr. Infante will be excused.

Do we have another witness today?

MR. METZGER: Tomorrow morning, your Honor.

MR. SCHURZ: Your Honor, at this time I would move to exclude and strike the testimony of Dr. Peter Infante on the grounds that Dr. Infante lacks the requisite expertise in the field of nutritional epidemiology, and further, the methodology or the absence of methodology he applied in this case is unreliable for each of the reasons that the District

Court and the Fifth Circuit found in Burst versus Shell Oil, that it should be excluded. And we'd be happy to provide your Honor with briefing on that.

THE COURT: All right. The Court will allow the parties to brief the issue.

Do you have the brief now?

MR. SCHURZ: No, I wanted to get the testimony. So we'll get it for you.

THE COURT: All right. So the Court will defer ruling until after submission of the appropriate briefs.

Anything else anyone wishes to address?

All right. We'll be in recess until tomorrow morning at 9:00 o'clock.

(Proceedings concluded at 4:02 P.M.)

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

DEPARTMENT 323 HON. ELIHU M. BERLE, JUDGE

CERT, PLAINTIFF, VS. STARBUCKS CORP, ET AL., DEFENDANTS.	CASE NO. BC 435759 BC 461182

I, MARK SCHWEITZER, OFFICIAL COURT REPORTER PRO TEM OF THE SUPERIOR COURT OF THE STATE OF CALIFORNIA, COUNTY OF LOS ANGELES, DO HEREBY CERTIFY THAT THE FOREGOING TRANSCRIPT, DATED SEPTEMBER 25, 2017, P.M. SESSION, COMPRISES A FULL, TRUE, AND CORRECT TRANSCRIPT OF THE PROCEEDINGS HELD IN THE ABOVE-ENTITLED CAUSE.

DATED THIS 25TH DAY OF SEPTEMBER, 2017.

Mark Schweitzer

MARK SCHWEITZER, RPR, CRR, CSR NO. 10514

EXHIBIT “H”

CURRICULUM VITAE

Name: **Peter Francis Infante**

Business Address: Managing Member
Peter F. Infante Consulting, L.L.C.
[redacted]
[redacted] Virginia [redacted]
(571) [redacted]
e-mail: pinfante@starpower.net

Home Address: [redacted]
[redacted], VA [redacted]
(703) [redacted]

Date of Birth: February 23, 1941
Place of Birth: Lima, Ohio
Marital Status: Married
Children: Two

Education:

Year:	Degree:	Institution:
1971-73	Dr.P.H.	Department of Epidemiology School of Public Health University of Michigan
1970-71	M.P.H.	School of Public Health University of Michigan
1968 (6 months)		Graduate Studies Pediatrics & Nutrition College of Medicine Ohio State University
1967-68	Certificate of Residency	Pediatric Dentistry Children's Hospital Ohio State University
1966-67	Certificate of Internship	Pediatric Dentistry Children's Hospital Ohio State University
1962-66	D.D.S.	College of Dentistry Ohio State University
1959-62		St. Joseph's College Rensselaer, Indiana

Present Positions:

June 1, 2002 to present: Managing Member, Peter F. Infante Consulting, L.L.C. Consulting in occupational and environmental health.

Past Positions:

August 1, 2002 to January 1, 2011: Adjunct Professor and Professorial Lecturer of Environmental and Occupational Health, The George Washington University, School of Public Health and Health Services, Washington, D.C.

1983 to May 2002: Director, Office of Standards Review, Health Standards Program, Occupational Safety and Health Administration, U.S. Department of Labor, Washington, D.C.

Work description: Primary Agency responsibility for reviewing existing OSHA health standards and making recommendations for modifications based on risk assessments and epidemiologic, toxicologic and industrial hygiene data. Office responsible for regulation of toxic substances in the workplace.

Past Positions:

1978-83: Director, Office of Carcinogen Identification and Classification, Health Standards Programs, OSHA, Department of Labor, Washington, D.C.

Work description: Responsibility for identification and classification of carcinogenic substances and establishing priority for their regulation.

1975-78 -- Epidemiologist, Biometry Section, Industry-wide Studies Branch, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Center for Disease Control, Cincinnati, Ohio

Work description: Conducted epidemiological investigations to determine associations between exposure to toxic substances and cancer, pregnancy outcome and other chronic disabling conditions.

1976-77 -- Acting Chief, Biometry Section, Industry-wide Studies Branch, National Institute for Occupational Safety and Health, Center for Disease Control, Cincinnati, Ohio

Work description: Responsibility for the conduct of all occupational epidemiological studies being carried out by the Biometry Section

1974-75 -- Epidemiologist, Division of Chronic Disease, Ohio Department of Health, Columbus, Ohio

Work description: Responsibility for establishing a central data base for the occurrence of cancer in Ohio children and also for investigating secular trends in cancer mortality. I also worked with members of other State and Federal Institutions investigating possible relations between polyvinyl chloride manufacture, other industrial factors and increased risk of congenital malformations and cancer. I also advised the Division in methodology and statistical analyses for the selection of population groups for health screening and for follow-up evaluation of treatment.

1973 -- (April-December) -- Epidemiologic Consultant for World Health Organization, Pan American Health Organization, Washington, D.C.

Work description: Scientific responsibility for determining the dental epidemiologic aspects of multi-disciplinary field research to investigate fluoride metabolism for the individual child and its relation to eventual caries experience in children of rural Guatemala. This included evaluation of field procedures and statistical analyses of data available. During this period, I also examined several hundred children to obtain baseline data for oral conditions. Analyses and reports pertaining to this investigation were submitted to Pan American Health Organization, World Health Organization and to the National Institute of Dental Research.

1973 -- Research Associate, Center for Human Growth and Development, University of Michigan

Work description: Analyses of data from the National Preschool Nutritional Survey of 1969 and 1970.

1972-73 -- Research in Child Growth and Dental Development

Work Description: Conducted an epidemiologic study of dental development in relation to growth in black and white preschool children of the lower socioeconomic level from southeastern Michigan. This investigation was completed in partial fulfillment for the degree of Doctor of Public Health from the Department of Epidemiology, School of Public Health, University of Michigan.

1969-70 -- Dental Epidemiologist for the National Preschool Nutritional Survey, 1968-70

Work description: Conducted the dental aspects of this survey, which was supported by Maternal and Child Health Services, Department of Health, Education and Welfare. This included the examination of preschool children in approximately 36 states, plus children of the White Mountain Apache Indian Reservation. Some of these findings were reported in "A Study of Nutritional Status of Preschool Children in the United States, 1968-70," Suppl., Pediat., 53:597-646, 1974. Several others have been reported elsewhere.

Consultant or Advisory Positions:

Ohio Department of Health, Columbus, Ohio
* Consultant to Division of Chronic Diseases, 1974-75

American Public Health Association.
* Health Hazards Project, 1975

Department of Health, Education and Welfare Subcommittee on Environmental Mutagenesis.
* NIOSH representative, 1975-78
* OSHA representative, 1978-85

World Health Organization, International Agency for Research on Cancer, Lyon, France.
* Member of the Expert Committee on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, 1977-79

International Workshop/Conference on the Toxicology of Metals, 1980
* Member of Epidemiology Workgroup

Consensus Workshop on Formaldehyde, 1983
* Member of Epidemiology Panel

Federal Asbestos Taskforce
* Chairman, Epidemiology Panel, 1982-87

National Academy of Sciences, National Research Council
* Subcommittee to revise Emergency Exposure Guidance Levels for Benzene and Ethylene Oxide, 1985

National Cancer Institute
* Advisory Panel for Occupational Mortality Study of Workers Exposed to Methylene Chloride, OSHA representative, 1987-90

National Cancer Institute
* Advisory Panel for Occupational Mortality Study of Workers Exposed to Acrylonitrile, OSHA representative, 1988-90

World Health Organization, International Program on Chemical Safety
* Member of Task Group on Environmental Health Criteria, 1989-1990

National Academy of Sciences, National Research Council
* Committee on Environmental Epidemiology, Federal liaison member, 1990-1992

National Academy of Sciences, National Research Council
* Committee on Risk Assessment Methodology, Federal liaison member, 1990-1993

Teratogenesis, Carcinogenesis, and Mutagenesis
* Associate Editor, 1989-90

National Safety Council
* Planning Committee for Conference on Risk, 1990-91

World Health Organization, International Agency for Research on Cancer, Lyon, France.
* Expert Committee on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, February, 1993--participant

World Health Organization, International Agency for Research on Cancer, Lyon, France.
* IARC Meeting of European Investigators on Cancer Risk Among Service Station Attendants and Related Occupations, December, 1993--participant

National Institute of Environmental Health Sciences
* ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods (e.g., evaluation of alternate toxicologic testing methods that can be used for regulatory purposes)
--principal OSHA representative, 1994-2002

Department of Health and Human Services, Office of Women's Health,
* Interagency Working Group on the Environment and Women's Health--OSHA representative, 1994-2002

World Trade Organization (WTO) 2000;
*Selected as one of only four experts world-wide to provide opinions to a panel of judges at the WTO in Geneva, Switzerland regarding the relative toxicity of chrysotile asbestos in relation

to other forms of asbestos and asbestos substitutes for a case on whether the WTO should allow the European Community countries to ban the importation of chrysotile asbestos from Canada.

New York State Department of Health, Center for Environmental Health, Bureau of Toxic Substance Assessment--Trichloroethylene Air Criteria Document 2006;

* Member of Review Panel-Purpose of document is to determine the atmospheric concentration to be used as a guide for decisions about the nature of the efforts to manage and reduce TCE exposure in the general environment in the State of New York.

National Toxicology Program 2008;

*Served on Styrene Expert Panel; evaluated epidemiological and toxicological data to make recommendation for listing of styrene in the 12th Report on Carcinogens

World Health Organization, International Agency for Research on Cancer, Lyon, France 2009;

* Member of the Monograph Working Group on IARC Monographs on the Evaluation of the Carcinogenic Risks Humans; Arsenic, Metals, Fibers, and Dusts. Volume 100 C; A Review of Human Carcinogens 2012

Environmental Protection Agency (EPA) 2014;

***** Appointed to the EPA Science Advisory Board (SAB) Chemical Assessment Augmented for Ethylene Oxide. The document develops an estimate of cancer risk to humans exposed to ethylene oxide.

Awards:

U.S. Public Health Service Traineeship, 1970-73

* Award to study Public Health and Epidemiology at University of Michigan, School of Public Health

U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health

* Special Commendation for Research Contributions Toward Understanding the Toxicology of Benzene and Beryllium, 1978

U.S. Department of Labor, Secretary's Exceptional Achievement Award, 1993

U.S. Department of Labor, Special Achievement Award, 1993

Past Clinical Activities:

The Children's Hospital, Columbus, Ohio, July 1966 to June 1968. Children and Youth clinical practice while completing Internship and Residency in Pediatric Dentistry

Martin Memorial Hospital, Mt. Vernon, Ohio, summer of 1968. Outpatient clinical practice while attending graduate school.

Children and Youth Program, Columbus, Ohio. Clinical Pediatric Dental Practice, 1974.

Dental License:

Ohio, 1966
District of Columbia, 1981
Northeast Regional Dental Boards, 1980

Professional Organizations:

American College of Epidemiology (Fellow)
American Conference of Governmental Industrial Hygienists
American Public Health Association (Occupational Health and Safety)
Collegium Ramazzini (Fellow)

Publications:

Infante, P.F. Epidemiologic studies of the relation between deciduous tooth eruption and child growth. Ann Arbor, University of Michigan, School of Public Health, 1973. VIII + 100 p. typed dissertation.

Infante, P.F. and Owen, G.M. Relation of the chronology of deciduous tooth emergence to height, weight and head circumference in children. Arch. Oral Biol., 18:1411-1417, November, 1973.

Infante, P.F. Sex differences in the chronology of deciduous tooth emergence in white and black children. J. Dent. Res., 53:418-421, March-April, 1974.

Infante, P.F. and Russell, A.L. An epidemiologic study of dental caries in preschool children in the United States by race and socioeconomic level. J. Dent. Res., 53:393-396, March-April, 1974.

Infante, P.F. Enamel hypoplasia in Apache Indian children. Ecology of Food and Nutrition, 3:155-156, No. 2, 1974.

Infante, P.F. and Gillespie, G.M. An epidemiologic study of linear enamel hypoplasia of deciduous anterior teeth in Guatemalan children. Arch. Oral Biol., 19:1055-1061, November, 1974.

Infante, P.F. An epidemiologic study of deciduous tooth emergence and growth in white and black children of southeastern Michigan. Ecology of Food and Nutrition, 4:117-124, 1975.

Infante, P.F. Estimates of dietary fluoride intake from supplements and communal water supplies. Am. J. Dis. Child., 129:835-837, 1975.

Infante, P.F., Owen, G.M. and Russell, A.L. Dental caries in preschool Apache Indian children. J. Dent. Res., 54:915, 1975.

Infante, P.F. Malocclusion in the deciduous dentition in white, black and Apache Indian children. Angle Orthodont., 45:213-218, 1975.

Infante, P.F. and Owen, G.M. Dental caries and levels of treatment for preschool children by geographical region, social class, race and size of community. Pub. Health Dent., 35:19-27, Winter, 1975.

Infante, P.F. An epidemiologic study of deciduous molar relations in preschool children. J. Dent. Res., 54:723-272, July-August, 1975.

Infante, P.F., Ackerman, J.A. and MacKenzie, A.L. Secular trends in leukaemia mortality. Lancet, ii, 720-721, September 21, 1974.

Infante, P.F. Oncogenic and mutagenic risks in communities with polyvinyl chloride production facilities. Ann. N.Y. Acad. Sci., 271:49-57, 1976.

Infante, P.F. and Gillespie, G.M. Dental caries experience in the deciduous dentition in rural Guatemalan children, ages six months to seven years. J. Dent. Res., 55:951-952, November-December, 1976.

Infante, P.F. An epidemiologic study of finger habits in preschool children as related to malocclusion, socioeconomic

status, race, sex and size of community. J. Dent. Child., 43:33-38, January-February, 1976.

Infante, P.F. and Gillespie, G.M. Enamel hypoplasia in relation to caries in Guatemalan children. J. Dent. Res., 56:493-498, May-June, 1977.

Infante, P.F. and Newton, Jr., W.A. Prenatal chlordane exposure and neuroblastoma. New Engl. J. Med., 293:308, August 7, 1975.

Infante, P.F., Wagoner, J.K. and Waxweiler, R.J. Carcinogenic, mutagenic and teratogenic risks associated with vinyl chloride. Mutation Res., 41:(1) 131-142, November, 1976.

Infante, P.F., and Wagoner, J.K. Evidence for the carcinogenicity of beryllium. International Conference on Heavy Metals in the Environment, Toronto, Canada, October 27-31, 1975. (Proceedings from Conference, pp. 329-338).

Infante, P.F. and Lemen, R.A. Hazards of asbestos in dentistry. Am. Dent. Assoc. J., 93:221-222, August, 1976.

Infante, P.F., Wagoner, J.K., McMichael, A.J., Waxweiler, R.J. and Falk, H. Genetic risks of vinyl chloride. Lancet, i:734-735, April 3, 1976.

Infante, P.F., Wagoner, J.K., McMichael, A.J., Waxweiler, R.J. and Falk, H. Genetic risks of vinyl chloride. Lancet, i:1289-1290, June 12, 1976.

Wagoner, J.K., Infante, P.F., and Saracci, R. Vinyl chloride and mortality? Lancet, ii:194-195, July 24, 1976.

Infante, P.F. and Epstein, S.S. Blood disease, childhood tumors and exposure to chlorinated hydrocarbon pesticides. Conference on Women in the Workplace, Society for Occupational and Environmental Health, Washington, D.C., (p. 51-69) April, 1977.

Infante, P.F. and Wagoner, J.K. The effect of lead on reproduction. Conference on Women and the Workplace. Society for Occupational and Environmental Health, Washington, D.C., (p. 232-242) April, 1977.

Wagoner, J.K., Infante, P.F. and Brown, D.P. Genetic effects associated with industrial chemicals. Conference on Women and the Workplace, Society for Occupational and Environmental Health, Washington, D.C., (p. 100-113) April, 1977.

Infante, P.F. and Wagoner, J.K. Chloroprene: Observations of carcinogenesis and mutagenesis. In Hiatt, H.H., Watson, J.D. and Winsten, J.A., eds., Origins of Human Cancer, Cold Spring Harbor Laboratories, Cold Springs, New York, 1977.

Wagoner, J.K. and Infante, P.F. Vinyl chloride: A case for the use of laboratory bioassay in the regulatory control procedure. (In Hiatt H.H., Watson, J.D. and Winsten J.A., eds., Origins of Human Cancer, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, c1977) pp. 755-758

Infante, P.F., Rinsky, R., Wagoner, J.K. and Young, R.J. Leukemia in benzene workers. Lancet, ii:76-78, July 9, 1977.

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Infante, P.F. Carcinogenic and mutagenic risks associated with halogenated olefins. Env. Health Perspect. 21:251-254, 1977.

Infante, P.F. Health hazards to working women - The plastics and rubber industries. Women in the Workplace, A Symposium, N. Calif. Am. Ind. Hyg. Assoc., 1977, pp. 65-69.

Infante,P.F. Epidemiologic approaches for surveillance of genetic hazards with particular reference to anesthetic gases. Expert Conference on Genetic Damage in Man Caused by Environmental Agents, Academic Press, c1979, pp. 289-300.

Bahlman, J., Alexander, V., Infante, P.F., Wagoner, J.K., Lane, M. and Bingham, E. Vinyl halides: Carcinogenicity -- Vinyl bromide, Vinyl chloride, and Vinylidene chloride. Am. Ind. Hyg. Assoc. J., 40:A30-A40, 1979.

Infante, P.F., Rinsky, R.A., Wagoner, J.K. and Young, R.J. Benzene and leukemia. Lancet, ii:867-868, October 22, 1977.

Infante, P.F., Leukemia among workers exposed to benzene. Environmental Cancer: A report to the public, Texas Reports on Biology and Medicine, 37:153-161, 1978.

Young, R.J., Rinsky, R.A. and Infante, P.F. Benzene in consumer products. Science, 199:248, 1978.

Wagoner, J.K. and Infante, P.F., Beryllium: Carcinogenicity studies. Science, 201:298-303, 1978.

Infante, P.F., Epstein, S.S., and Newton, W.A. Blood dyscrasias and childhood tumors and exposure to chlordane and heptachlor. Scand. J. Work Environ. Health, 4:137-150, 1978.

Infante, P.F., Wagoner, J.K. and Sprince, N.L. Mortality patterns from lung cancer and non-neoplastic respiratory disease among white males in the Beryllium Case Registry. Env. Res., 21:35-43, 1980.

Wagoner, J.K., Infante, P.F. and Bayliss, D.L. Beryllium: An etiologic agent in the induction of lung cancer, non-neoplastic respiratory disease and heart disease among industrially exposed workers. Env. Res., 21:15-34, 1980.

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Kang, H.K., Infante, P.F. and Carra, J.S. Occupational lead exposure and cancer. Science, 207:935-936, 1980.

Braver, E.R. and Infante, P.F. Probability window analysis and lung cancer in chromate workers. J. Occup. Med., 22:302-304, 1980.

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Infante, P.F. and Marlow, P.B. Evidence for the carcinogenicity of selected halogenated hydrocarbons including ethylene dichloride. (In Ames, B., Infante, P.F. and Reitz, R. Eds. Ethylene dichloride: A potential health risk? Banbury Report 5, Cold Spring Harbor Lab., c1980) pp. 287-308.

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Wagoner, J.K., Infante, P.F. and Apfeldorf, R.B. Toxicity of vinyl chloride and polyvinyl chloride as seen through epidemiologic observations. J. Tox. Env. Health, 6:1101-1107, 1980.

White, M.C., Infante, P.F. and Walker, B. Occupational exposure to benzene: A review of carcinogenic and related health effects following the U.S. Supreme Court Decision. Am. J. Ind. Med., 1:233-243, 1980.

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Beall JR, Alexander V, Bien CT, Infante P., et al. Health Hazard Alert-2-Nitropropane (2-NP). DHHS (NIOSH) Pub. No. 80-142, 1980.

Apfeldorf, R. and Infante, P.F. Review of epidemiologic study results of vinyl chloride related compounds. Env. Health Perspect., 41:221-226. 1981.

Infante, P.F. Observations of the site specific carcinogenicity of vinyl chloride to humans. Env. Health Perspect., 41:89-94, 1981.

Blackwell, M, Kang, H., Thomas, A. and Infante, P. Formaldehyde: Evidence of Carcinogenicity. NIOSH Current Intelligence Bulletin #34. Am. Ind. Hyg. Assoc. J., A34-A45, 1981.

Infante, P.F., Ulsamer, A.G., Groth, D., Chu, K., and Ward, J. Health hazards of formaldehyde. Lancet, ii:980-981, 1981.

Infante, P.F., and Tsongas, T.A. Mutagenic and oncogenic effects of chloromethanes, chloroethanes and halogenated analogues of vinyl chloride. (In Tice, R.R., Costa, D. and Schaich, K.M., Eds. Genotoxic Effects of Airborne Agents, Plenum Press, New York, 1982), pp. 301-327.

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Tsongas, T.A. and Infante, P.F. Occupational reproductive hazards: Regulatory concerns.. In Lockey, J.E., Lemasters, G.K. and Keye, W.R. Eds. Reproduction: The New Frontier in Occupational and Environmental Health Research, Alan R. Liss, Inc New York, 1984, pp. 533-539.

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effects. (In Stich, H.F. ed. Carcinogens and Mutagens in the Environment. Volume IV, The Workplace: Monitoring and Prevention of Occupational Hazards. CRC Press, Boca Raton c 1985.) Ch. 9, pp. 75-81.

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Infante, P.F. Exposure assessment and dose response in the evaluation of occupational cancer mortality studies. (In Hogstedt, C. and Reuterwall, C. eds. Progress in Occupational Epidemiology, Proceedings from Sixth International Symposium on Epidemiology in Occupational Health, Stockholm, Sweden, 16-19 August 1988. Excerpta Medica, Amsterdam, c 1988) pp. 383-386.

Sandler, B.H., Harwood, S.E., Thurber, C.H. and Infante, P.F. Development of the Occupational Safety and Health Administration's proposed standard to protect workers from contracting bloodborne diseases in the workplace. J Pub Health Dent, 49:87-89, 1989.

Infante, P.F., Schwartz, E. and Cahill, R. Benzene in petrol: A continuing hazard. Lancet, 336:814-815, 1990.

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Case studies of agents associated with adverse effects on reproduction: Chloroprene. Workshop on Methodology for Assessing Reproductive Hazards in the Workplace, National Institute for Occupational Safety and Health and Society for Occupational and Environmental Health, April 9-22, 1978, Washington, D.C.

Principles and methods for detecting chemical mutagens -- Epidemiologic approaches. First Industrial Workshop in Chemical Mutagens, Environmental Mutagen Society, May 22-25, Hunt Valley, Maryland, 1978.

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An evaluation of the epidemiologic studies related to beryllium exposures. Course on Environmental Epidemiology, Columbia University, March 28, 1984.

Regulation of benzene. Course on Toxic Substances Policy, NIH Graduate School, December 18, 1984.

Adverse health effects of some toxic air pollutants at chemical plants in the Kanawha Valley. Testimony before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States Congress. Institute, W.Va., December 14, 1984.

Risk assessment on benzene. Collegium Ramazzini meeting on Risk Assessment of Benzene, New York, March 12-13, 1985.

Toxic effects of poison gases and other hazardous air pollutants from chemical plants. Testimony at joint hearing: Subcommittee on Health and the Environment and Subcommittee on Commerce, Transportation and Tourism. United States Congress, Washington, D.C. March 26, 1985.

Assessment of Risk Associated with Occupational Exposure to Benzene. Medical College of Virginia, Richmond, November 20, 1985.

Recent Laboratory Studies in Chemical Carcinogenesis: Benzene. Collegium Ramazzini Meeting on Living in a Chemical World, Bologna, Italy, October, 1985.

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Meeting of the American College of Toxicology, "Frontiers in Toxicology" Philadelphia, Pa., November 16-19, 1986.

Occupational Cancer. Uniformed Services University of the Health Sciences, Naval Medical Command, Bethesda, Md., December 8, 1986.

Occupational Cancer and Regulation. Department of Epidemiology, Johns Hopkins University, March 16, 1987.

Living in a Chemical World. Plenary Session: Pathology in a Changing World; 25th Anniversary, The Royal College of Pathologists, London, England, Sept., 8-11, 1987.

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Testimony on OSHA Standard Setting. Committee on Labor and Human Resources, United States Senate, April 19, 1988.

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Exposure Assessment and Dose Response in the Evaluation of Occupational Mortality Studies. 6th International Symposium on Epidemiology in Occupational Health, Stockholm, Sweden, Aug. 15-18, 1988.

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Animal Cancer Testing. The Diane Rehm Show on 88.5 FM, The American University, September 28, 1990.

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The 0.1 ppm ACGIH proposed TLV for benzene. Presented before the ACGIH Committee, Cincinnati, Ohio, March 21, 1991.

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Risk assessment and regulation, Johns Hopkins University, School of Public Health, Baltimore, Md., June 27, 1991.

Panel on state of the science on epidemiologic studies related to workers exposed to gasoline vapors. At International Symposium on the Health Effects of Gasoline, Miami, Fla., November 5-8, 1991.

Prevention or chemophobia: Use of rodent studies for identifying carcinogens and estimating cancer risk. American Public Health Association Annual Meeting, Atlanta, Ga., November 10-14, 1991.

Use of cell proliferation data in cancer risk assessment: U.S regulatory views: OSHA. Presented at An International Symposium

on Cell Proliferation and Chemical Carcinogenesis, National Institutes of Environmental Health Sciences, Research Triangle Park, N. Carolina, January 14-16, 1992,

Panel discussion on implications of using alternative methods of assessing exposures for risk assessments, Committee on Risk Assessment Methodology, Workshop on Single Scenario and Population Distribution Estimates of Exposure: Applications and Implications in Risk Assessments, National Academy of Sciences, Washington, D.C., February 10-11, 1992.

Seminar on scientific basis for occupational regulations, University of Lowell, Lowell Massachusetts, May 8, 1992.

How does exposure information in epidemiologic studies contribute to the process of regulation or risk assessment? Workshop on Retrospective Exposure Assessment in Occupational Epidemiology. National Institute for Occupational Safety and Health, Cincinnati, Ohio, September 22, 1992.

Seminar on the development of OSHA standards for toxic substances in the workplace. Harvard University, Boston, January 22, 1993.

Estimates of cancer risk related to occupational cadmium exposure. American Industrial Hygiene Conference & Exposition, New Orleans, Louisiana, May 15-21, 1993.

OSHA evaluation of carcinogenic risk among workers exposed to formaldehyde. Eighth Annual Toxicology Symposium, Ashville, NC, August 3, 1993.

A historical perspective of some occupationally related diseases of women. Women's Health:Occupation and Cancer Conference sponsored by the National Cancer Institute, Baltimore, Maryland, November 1, 1993.

Issues related to lung cancer and other cancers among industrially exposed workers. Presented before the President's Cancer Panel, Tysons Corner, Virginia, October 5, 1994.

Evaluation of carcinogenicity studies of workers exposed to beryllium. Conference on beryllium related diseases. National Institute of Environmental Health Sciences, Research Triangle Park, N.C., November 8-10, 1994.

Medical and ethical issues related to chronic beryllium disease--OSHA's view of genetic screening. National Institute of Environmental Health Sciences, Research Triangle Park, N.C.,

November 8-10, 1994.

Need for study of occupation and cancer through Cancer Registries. National Program of Cancer Registries Meeting on Occupation, Industry and Cancer Registration, Miami, Fla., June 18, 1995.

Fire Fighters' Occupational Health: Who does care? Presented at 13th Symposium on the Occupational Health and Hazards of the Fire Service, San Francisco, Calif., August 31, 1995.

OSHA's Regulatory Agenda. Harvard School of Public Health, Boston, January 5, 1996.

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Childhood leukemia and low level atmospheric exposure to benzene and other aromatic hydrocarbons. Presented at meeting on Benzene, Childhood Leukemias and Hematopoietic and Lymphoreticular Cancers sponsored by the Collegium Ramazzini and Mount Sinai School of Medicine, New York, NY, June 28, 2012.