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

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Post date:
08/30/2018 - 12:18pm

Comment:
Please accept the report of Dr. Peter F. Infante, including 4 attachments. Thank you.

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August 30, 2018

Ms. Monique Vela
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P.O. Box 4010
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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

Dear Ms. Vela:

I wish to comment on the above-mentioned document in reference to OEHHA's interpretation of the International Agency for Research on Cancer (IARC) 2016 review of drinking coffee as related to cancer risk that was published as IARC Monograph 116 in 2018 **(IARC 2018)**. I will focus my comments on the relationship of maternal coffee consumption and risk of childhood leukemia.

First, I would like to present you with an overview of my credentials and qualifications. I have 49 years of experience as an epidemiologist. My work includes employment as a senior epidemiologist with various governmental agencies, including three years with the National Institute for Occupational Safety and Health (NIOSH) and 24 years with the Occupational Safety and Health Administration (OSHA). During my time at NIOSH, I conducted epidemiological studies related to a number of carcinogens found in the workplace, including benzene, beryllium and vinyl chloride. I was the lead author on the first cohort study to demonstrate a significant association between benzene exposure and leukemia. The findings of this study led OSHA in 1977 to promulgate an Emergency Temporary Standard (ETS) to reduce occupational exposure to benzene. During my 24 years at OSHA, I played a major role in determining cancer risks to workers during the development of standards for a number of toxic substances, including asbestos, arsenic, benzene, 1,3-butadiene, cadmium, ethylene oxide, formaldehyde, and methylenedianiline (MDA). I have served as an expert consultant in epidemiology for: the National Toxicology Program's (NTP) Report on Carcinogens

(RoC); for Working Groups of IARC; the EPA Science Advisory Board (SAB) Chemical Assessment Advisory Committee; and as an expert on cancer risk from exposure to asbestos and asbestos substitutes for the World Trade Organization (WTO) in Geneva, Switzerland. I have testified before the U.S. Congress on numerous occasions about chemical pollution and the causes of cancer. I have over 100 publications in peer reviewed scientific journals, and have published specifically on the subjects of adult and childhood leukemia, dietary supplements and child growth and development. I am currently the Managing Member of Peter F. Infante Consulting, LLC, an organization dedicated to occupational and environmental health. I am a Fellow of the American College of Epidemiology and the Collegium Ramazzini. My *Curriculum Vitae* is attached and provides additional information about my training, education, publications, presentations, experience and advisory positions related to my occupational and environmental health activities.

I also wish to disclose that I have provided expert consultation and testimony at the request of the Council for Education and Research on Toxics (CERT) in the Proposition 65 case related to coffee consumption and risk of cancer.

OVERVIEW OF THE IARC EVALUATION OF MATERNAL COFFEE CONSUMPTION AND RISK OF CHILDHOOD LEUKEMIA

The **OEHHA Initial Statement of Reasons (June 2018, page 11**) states that "coffee .... has not been found to increase the risk of any cancers" based on the **IARC (2018)** review. This statement is clearly contradicted by the IARC review of studies related to maternal coffee consumption and childhood leukemia. It is also contradicted by the results of a large study published subsequent to the IARC review.

In its review of the five studies it ultimately relied upon to evaluate the relationship between maternal coffee consumption and childhood leukemia, **IARC (2018)** reported statistically significant elevated risks for three studies **(Bonaventure et al. 2013; Orsi et al. 2015; Menegaux et al. 2005)** and a non-statistically significant elevated risk for ALL (OR = 1.4) and AML (OR = 1.4) in a fourth study **(Menegaux et al. 2007)**, but for which IARC noted a limitation in sample size related to AML. **See Table 1 (attached)**. Only the fifth study **(Milne et al. 2011)** did not demonstrate an "overall" elevated risk of childhood leukemia, but it did demonstrate a significantly elevated risk of ALL with chromosomal translocations among mothers who consumed > 2 cups/day. This latter observation was not pointed out by IARC.

As shown in Table 1, several strengths and no limitations were reported for the **Bonaventure et al. 2013** and **Orsi et al. 2015** studies; for a third French study (**Menegaux et al. 2005**), several strengths and only a single limitation was mentioned, e.g., use of hospital controls, with no further comment on how this controls selection may have biased the results [Note: In my opinion hospital controls are not an issue in this study; if OEHHA accepts the IARC comment regarding hospital controls as a potential weakness, it should offer an explanation to support this opinion.] The fourth study (**Menegaux et al. 2007**), demonstrated ORs of 1.4 (non-significant) for both ALL and AML in the presence of several study strengths and according to IARC only a single study limitation, e.g., small sample size for AML cases. This IARC comment is suggesting the study shows increased risk but lacked adequate statistical power to evaluate statistical significance for AML. Only the fifth study **(Milne et al. 2011)** could be considered null for overall results, but even this study demonstrated a statistically significant association with ALL cases accompanied with chromosomal translocations. Therefore, the IARC review of individual studies indicates that 3/5 studies demonstrate statistically significant associations between maternal coffee consumption and childhood leukemia, the fourth study indicates elevated risks (ORs = 1.4) for both ALL and AML that were not statistically significant, with the fifth study being null for overall results, but not for children with ALL accompanied with chromosomal translocations. In its conclusion, however, **IARC (2018**, p. 418) states that there was a

> "lack of consistency among the findings of the studies, particularly for those conducted within the same country by the same group, led the Working Group to evaluate the evidence for this site as inconclusive."

This conclusion belies the IARC evaluation based on individual studies as presented in **IARC 2018**, pp 293-296). The first four studies relied upon by IARC were conducted in France. Three demonstrate statistically significant results (**Menegaux et al. 2005; Bonaventure et al. 2013; Orsi et al. 2015)**, with two demonstrating significant dose-response relationships **(Menegaux et al. 2005; Bonaventure et al. 2013)**. The fourth French study **(Menegaux et al. 2007)** indicated an elevated risk of childhood AL and an increase in risk by maternal coffee consumption that did not achieve statistical significance. See Table 1. I fail to understand how the results from the four French studies represent "inconsistent results," nor does **IARC (2018)** offer an explanation. **It is clear that IARC has not correctly summarized its own evaluation of the individual study results**. The studies

clearly demonstrate an elevated risk of childhood leukemia that is a reflection of ALL which comprises approximately 80% of childhood leukemia **(Belson 2007).**

In spite of the contradiction in evidence between the review of individual studies and its summary of the results for maternal coffee consumption and child leukemia, IARC placed coffee consumption in "category #3, e.g., "not classifiable as to its carcinogenicity to humans." If IARC was convinced that coffee consumption had a protective effect against cancer, it would have placed coffee consumption into Category #4, e.g., "probably not carcinogenic to humans."

Subsequent to the IARC 2016 review, a study on coffee consumption and childhood leukemia was published that included data pooled from all of the previously published studies, plus two studies not previously published **(Milne et al. 2018).** This study demonstrates a statistically significant increase in the risk of childhood ALL associated with maternal coffee consumption of >2 cups/day. The study also demonstrated a significant dose-response relationship. See bottom entry to Table 1. The authors concluded that the findings were unlikely due to selection or recall bias, or chance. Dose-response analyses also indicate that any major exposure confounding was unlikely to have affected the results. There are no other data that contradict the findings from this study because the analyses pooled data from all previous studies. Information, not reviewed by IARC, on biological plausibility for maternal coffee consumption to cause childhood leukemia supports the association.

Results of quantitative cancer risk assessment (QRA) indicate a childhood leukemia risk level associated with maternal consumption of 1-2 cups/day that is considered unacceptable to the State of California. Thus, the epidemiological literature provides evidence of a strong association and significant dose-response between maternal coffee consumption and childhood leukemia that is biologically plausible, as discussed below, with a risk level considered significant by the State of California.

A. EPIDEMIOLOGICAL STUDY RESULTS

IARC noted increased risks of childhood leukemia in association with maternal coffee consumption during pregnancy. In its review, IARC identified seven case-control studies reporting results of the association between maternal coffee consumption during pregnancy and risk of childhood leukemia in the offspring **(IARC 2018,** p. 294). "The Working Group considered that the earliest two studies **(Ross et al. 1996; Petridou et al.**

1997) were of limited quality due to low participation rate and uninformative coffee consumption categories" **(IARC 2018**, p. 418). Of the five studies that IARC considered to be of sufficient quality for analysis **(Menegaux 2005**, **Menegaux 2007**, **Milne 2011**, **Bonaventure 2013**, **Orsi 2015)**, all reported statistically significant increased risks of childhood leukemia in association with maternal coffee consumption during pregnancy (Table 1). 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.

The largest case-control study evaluated by IARC **(Bonaventure et al. 2013)** that included 764 children diagnosed with acute leukemia (648 cases of ALL and 101 cases of AML), demonstrates a significant dose-response for childhood ALL and AML separately by maternal coffee consumption during pregnancy. No association was observed between alcohol consumption, nor with cigarette smoking and childhood acute leukemia (AL), both of which are recognized to have adverse consequences to the developing fetus. As pointed out by **IARC (2018):**

> "The adjusted odds ratios (95% CI) for > 2 cups/day for AL, ALL, and AML were 1.6 (1.2–2.1), 1.5 (1.1–2.0), and 2.4 (1.3–4.3), respectively, with *P* values for trend of < 0.001, 0.0027, and 0.002, respectively. "[Strengths included the use of population-based controls, standardized questionnaires, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of an exposure–response relationship.]"

No limitations to the study methodology and analyses were identified. Thus, **IARC (2018)** pointed out the strengths of the study demonstrating an elevated risk of both ALL and AML and significant dose-responses for both types of childhood leukemia separately, and did not list a single limitation.

Orsi et al. (2015) reported results from the ESTELLE study, a nation-wide French population-based case–control study of childhood malignancies. In this study, 747 children newly diagnosed with leukemia in 2010 and 2011 (including 636 ALL, 100 AML, and 11 unspecified) were identified by the investigators. Controls (*n* = 1,421) were children free from cancer selected using random digit dialing (RDD) and a quota sampling method; the latter was applied to ensure their age and sex distributions were comparable to the case group and the French population. Data on maternal coffee intake, and other factors recognized to have adverse consequences on the developing fetus during pregnancy

were collected during a standardized telephone interview. No association was observed between alcohol consumption, nor with cigarette smoking and childhood acute leukemia (AL). As stated by **IARC (2018):**

> "Maternal coffee consumption was not found to be associated with AL overall .... while for ALL, the OR for > 2 cups/day was 1.3 (95% CI: 1.0–1.7). [Strengths included the use of population-based controls, a standardized CATI interview, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of the exposure–response relationship. *P* values for trend were not provided, however.]"

No limitations to the study methodology and analyses were identified. Thus, **IARC (2018)** pointed out the strengths, and again did not point out a single limitation to a study demonstrating a statistically significant elevated risk of childhood ALL in relation to maternal coffee consumption.

Menegaux et al. (2005) conducted a study including 280 incident cases of childhood AL from hospitals in Paris, Lille, Lyon, and Nancy. Controls comprised 288 children admitted to the same hospitals as the cases, mainly with orthopaedic conditions. Recruitment was stratified by age, sex, hospital, and ethnic origin. Maternal coffee intake during pregnancy was assessed by face-to-face interview using a standardized questionnaire. As stated by **IARC (2018)**, the adjusted odds ratios (95% CI) for ≤ 3 cups/day, 4–8 cups/day, and > 8 cups/day for acute leukemia (AL) were 1.0 (0.7–1.5), 2.1 (1.2–3.8), and 2.8 (0.9–8.1), respectively, compared with non-drinkers (*P*-value for trend, < 0.05). Positive associations were also seen for both ALL and ANLL (acute non-lymphocytic leukemia), although results for the latter were imprecise. As stated by **IARC (2018):**

> "For ALL, the corresponding odds ratios and 95% CIs were 1.1 (0.7–1.8), 2.4 (1.3–4.7), and 3.1; for ANLL they were 1.6 (0.6–4.3), 2.8 (0.7–10.4), and 3.0 (0.3–35.1). [Strengths included standardized interviews, adjustment for a range of confounders, presentation of results for ALL and ANLL separately, and assessment of exposure–response relationship. The study was however limited by the use of hospital-based controls and the modest sample size for ANLL.]"

Thus, in the presence of many strengths and a limited sample size, **IARC (2018)** again acknowledged the significant dose response between maternal coffee consumption and childhood leukemia. [Note: In my

opinion, the use of hospital controls is not a limitation in this study. The selection of patients from the orthopaedic department for controls, e.g., they were not admitted for a condition that could be related to leukemia, makes it less likely that there may have been bias in the controls selection.]

Menegaux et al. (2007) conducted a second study of 470 incident cases of childhood acute leukemia (AL) including 470 cases of ALL and 62 cases of AML and 567 controls. Cases were diagnosed between 1995 and 1998 in 14 regions of France, and identified through the National Registry of Childhood Blood Malignancies (NRCL). Controls were recruited by RDD and frequency-matched to cases on age, sex, and region. Mothers completed a standardized self-administered questionnaire that asked about a range of exposures, including coffee consumption, during pregnancy. The overall AL OR = 1.5 (95% CI = 0.9-2.4), the ALL OR = 1.4 (95% CI = 0.9-2.4) and the AML OR = 1.4 (95% CI = 0.5-4.4). Though elevated, none of these results achieved a level of statistical significance. However, maternal coffee consumption of > 3 cups/day during pregnancy was associated with a significantly elevated risk of AL for in children whose mothers were non-smokers, AL OR = 1.9 (95% CI = 1.0-3.5). [Note: This latter observation was highlighted by the authors of the study, but not cited in the **IARC (2018)** review.] Regarding strengths and limitations to the study, IARC stated:

> "Strengths included use of population-based controls, standardized questionnaires, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of the exposure-response relationship. The modest sample size for AML was a limitation.]"

Thus, **IARC (2018)** mentioned several strengths of the study and only a single limitation related to sample size for AML. [Note: consideration of sample size is related to type II error, e.g., the ability of a study to demonstrate an association if in fact one exists. Therefore, IARC seems to be implying that the lack of an association between coffee consumption and AML in the study may be due to the small sample size.]

Milne et al. (2011) conducted a population-based case-control study in Australia that included 337 incident cases of childhood ALL and 697 controls recruited by nationwide RDD. Controls were frequency-matched to the cases on age, sex, and state of residence. Maternal coffee intake during the last 6 months of the index pregnancy was assessed by FFQ, and reported in cups/day. As reviewed by **IARC (2018)**, no overall association between maternal coffee consumption and risk of ALL was observed. See Table 1. [Note: not

pointed out in the IARC review was the observation that among mothers who consumed > 2 cups of coffee per day whose children had ALL with chromosomal translocations, the OR = 2.55 (95% CI 1.04 - 6.22).

B. IARC DID NOT FOLLOW ITS OWN PROCEDURE IN ITS REVIEW OF META-ANALYSES OF MATERNAL COFFEE CONSUMPTION AND CHILDHOOD LEUKEMIA

IARC (2018, p. 296**)** noted that "three meta-analyses of the association between maternal coffee consumption and childhood leukemia have been conducted, and all reported elevated risks with higher levels of maternal coffee intake **(Milne et al. 2001; Cheng et al. 2014; Thomopoulos et al. 2015**.)." IARC then reported results only for the most recent meta-analysis (**Thomopoulos et al. 2015**) and noted that it "included all studies published to date" and further stated:

> "high maternal coffee intake during pregnancy was positively associated with AL (acute leukemia) overall, ALL and AML, with summary odds ratios (95% CI) of 1.57 (1.16 - 2.11), 1.42 (1.22 - 1.68), and 1.81 (0.93 - 3.53), respectively" (**IARC 2018**, p. 296).

Thus, the IARC review of meta-analyses clearly acknowledges that the relationship between maternal coffee consumption and childhood leukemia is statistically significant for both ALL and AML in the **Thomopoulos et al. (2015)** study. However, IARC then offers the following comment on the **Thomopoulos et al. (2015)** study:

> "The most recent meta-analysis of this association reported an overall increased risk for high levels of coffee consumption, but was limited by the fact that the highest exposure level varied widely across studies (from ≥ 4 times per week to ≥ 8 times per day)" **(IARC 2018**, p 418).

IARC was wrong to reject the study results because the high maternal coffee consumption category combined data from two studies that defined high intake as either > 4, or more > 8 cups per day. In its classifications of carcinogens, IARC determines cancer hazard identification, not quantitative cancer risk. As recently explained by IARC:

> "The IARC Monographs program is explicit about the difference between hazard identification and risk assessment on its website" **(IARC January 2018).**

Therefore, the combination of high coffee consumption categories in

the **Thomopoulos et al. (2015)** meta-analysis indicates an increase in risk of childhood ALL with high coffee intake compared to no coffee intake. This qualitative exposure-response does not need to account for the amount of coffee consumed for those categorized in the high coffee consumption category in order to determine cancer hazard. It is only important when determining childhood leukemia "risk." Further, as stated by the authors,

> "the association with ALL was also linear (P for non-linearity = 0.24) (Fig. 3b) and the following frequencies of consumption yielded statistically significant results when compared to non-drinkers: 1-2 cups/day, 2-3 cups/day, 3-4 cups/day, 4-8 cups/day" (**Thomopoulos et al. 2015).**

The study demonstrates a linear relationship between the amount of maternal coffee consumption and childhood ALL. Thus, IARC is wrong on two accounts; first, it did not follow its own procedures for cancer hazard identification; second, it did not mention, or discuss, the linear relationship between maternal coffee consumption and childhood ALL that was demonstrated in the **Thomopoulos et al. (2015)** meta-analysis.

C. THE MILNE ET AL. 2018 POOLED DATA ANALYSIS STUDY SUPERCEDES META-ANALYSIS RESULTS

The recently published **Milne et al. (2018)** study using underlying data from all of the previously published studies, as discussed in detail below ("Section E"), may be considered preferable to meta-analysis based on previously-published results, because it refined maternal coffee consumption categories from some earlier studies and contains more cases (N = 2,552) than all previous studies combined. It clearly demonstrates a significant dose-response between maternal coffee consumption and childhood ALL.

D. RESULTS OF FOUR META-ANALYSES ON MATERNAL COFFEE CONSUMPTION AND CHILDHOOD LEUKEMIA

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

The earliest meta-analysis **(Milne et al. 2011)** based on three case-control studies, reported a statistically significant increased risk of childhood leukemia from maternal consumption of more than 3 cups of coffee per day, OR = 1.67 (95% CI = 1.2-2.33). Among nonsmoking mothers who consumed > 3 cups/day, the risk was even higher, OR = 2.32 (95% CI 1.51-3.57), with a dose-response

relationship. Interestingly, the authors observed no change in risk for equivalent consumption of coffee among mothers who smoked cigarettes, OR = 1.01 (95% CI 0.77-1.33), indicating that the greater than doubling of the risk of childhood leukemia from high maternal consumption of coffee during pregnancy is unlikely the result of confounded by smoking.

A meta-analysis published by Chinese investigators in 2014, **(Cheng et al. 2014)** based on seven case-control studies, also reported an increased risk of childhood leukemia in association with high maternal coffee consumption, OR = 1.72 (95% CI 1.37-2.16). Comparing the highest level of consumption with non-lowest consumption of coffee, significantly increased risks were observed for both childhood ALL, OR = 1.65 (95% CI 1.28-2.12) and AML, OR = 1.58 (95% CI 1.20- 2.08).

A meta-analysis published in 2015 by Greek researchers (**Thomopoulos et al. 2015)** based on eight case-control studies, reported a greater than 50% increased risk of childhood leukemia comparing highest verses never-lowest maternal consumption of coffee during pregnancy (OR 1.57 (95% CI = 1.16-2.11). The authors' concluded:

> "Our findings confirm the detrimental association between maternal coffee consumption and childhood leukemia risk...."

The most recent meta-analysis, published by Chinese researchers **(Yan et al. 2015; 2016)** reported an increased risk of childhood acute lymphoblastic leukemia in association with maternal consumption of coffee during pregnancy (OR 1.44, 95% CI 1.07-1.92).

E. EPIDEMIOLOGICAL STUDY RESULTS PUBLISHED SUBSEQUENT TO IARC 2016 REVIEW PROVIDE STRONG EVIDENCE OF AN ASSOCIATION BETWEEN MATERNAL COFFEE CONSUMPTION AND CHILDHOOD LEUKEMIA

Since the IARC 2016 review of studies regarding maternal consumption of coffee during pregnancy and childhood leukemia, an important study regarding the association has been published. In 2018 **(Milne et al. 2018)**, researchers from the Childhood Leukemia International Consortium, published a study in which they investigated the effects of maternal consumption of coffee (and tea) during pregnancy on childhood acute lymphoblastic leukemia. The investigators pooled individual data (published and unpublished) from eight case-control studies that had been conducted in four countries, e.g., Australia, France, Greece and the United States. The investigators were provided with the original data which allowed

them to convert coffee consumption data that had been analyzed in various formats into cups per day, resulting in fractions of cups per day for all studies. For purposes of analysis, coffee consumption was then categorized into 0, >0-1, >1-2, and >2 cups per day. Data were checked in collaboration with study investigators before pooling.

Participating studies also provided data on maternal smoking during pregnancy and a range of variables that were considered potential confounders: sex, age (at diagnosis for cases and at enrollment/interview for controls), child's ethnicity, mother's age at child's birth, maternal education level, household socioeconomic status (SES), birth order, maternal smoking during pregnancy, maternal alcohol during pregnancy, breastfeeding, birth year, diagnosis or recruitment year, birth weight, and birth defects. Thus, data on maternal coffee intake were available for 2,552 cases and 4,876 controls. Data on genetic variants in *NAT2, CYP1A1,* and *NQO1* were also available in a subset. Pooled odds ratios and 95% confidence intervals were estimated using unconditional logistic regression and linear trends across categories were assessed.

The investigators found no association with "any versus no" maternal coffee consumption, but there was evidence of a positive exposure-response relationship. The pooled odds ratio for consumption of coffee of more than 2 cups/day versus none was 1.27 (95% CI 1.09-1.43), with a highly significant dose-response (p trend = 0.005). For analyses comparing the risk of childhood leukemia for mothers drinking >2 cups/day versus no coffee consumption, the OR = 1.32 (95% CI = 1.12-1.54) and was similar to the overall pooled OR of 1.27 with no evidence of heterogeneity among studies.

No associations were observed with tea consumption. No interactions were seen between coffee or tea intake and age, maternal cigarette smoking, or genotype, and there was little or no evidence that associations with coffee or tea differed among cases with and without the chromosomal translocations evaluated in the study. The investigators repeated the dose-response analyses separately by SES (high, medium, and low), and a positive trend of similar magnitude to the main results was observed for coffee in each SES group, e.g., in the group consuming >2 cups/day, the ORs were 1.28, 1.31 and 1.27 for low, medium and high SES, respectively as compared to an OR of 1.27 with SES combined. Sensitivity analyses in which each study was excluded in turn showed that there was little variation in the pooled ORs for >2 cups/day.

Since the analyses were all based on case-control studies, the

authors evaluated their data to determine whether selection and recall bias may have affected the original data sets and thus the findings in the study. Because dose-response associations were similar for low, medium and high SES, the authors opined that their findings were unlikely affected by selection bias. Regarding recall bias, the authors stated that maternal coffee intake and childhood cancer had not been linked in the public domain and women would not have paid undue attention to the questions related to this association. I also note that the study did not identify an association between childhood leukemia and tea consumption and also that the observation of a dose response for coffee and childhood leukemia was of similar magnitude in all populations studied. These observations make it less likely that selection, or differential recall bias affected the results. [Note: the observation of a consistent dose-response in multiple analyses makes it unlikely that any meaningful confounding of exposure occurred.] Misclassification of coffee exposure is likely to have occurred to some extent. As pointed out by the authors, however, misclassification is likely to have been similar among both cases and controls, which would lead to the pooled OR being biased toward the null, e.g., no association.

Finally, because the authors estimated multiple pooled ORs, they entertained the possibility that some of the observed associations occurred due to chance. They were of the opinion, however, that the main finding of a dose-response with maternal coffee intake and risk of childhood leukemia being consistent across the study populations made this unlikely.

The investigators of this large study concluded that their "findings suggest that high coffee intake during pregnancy may increase risk of childhood ALL." The researchers further concluded that "current advice to limit caffeine intake during pregnancy to reduce risk of preterm birth may have additional benefits," e.g., reduction in risk of childhood leukemia. Thus, a large well-designed and well-conducted international study adds strong evidence to the evaluation of IARC "based on individual study review," that maternal consumption of coffee during pregnancy increases the risk of childhood leukemia. The Milne et al. (2018) study results run counter to OEHHA's statement that coffee "has not been found to increase the risk of any cancers."

F. IMPACT OF NEW EPIDEMIOLOGICAL STUDY RESULTS ON CONCLUSION RELATED TO COFFEE CONSUMPTION AND CANCER

As reviewed directly above, the most recent study by **Milne et al. (2018)** demonstrates a statistically significant association, and

a consistent dose response between maternal coffee consumption and childhood leukemia. The investigators were of the opinion that the positive findings were unlikely due to chance, selection bias, recall bias, and confounding. The investigators used individual data pooled from six populations studied in four countries. Having been provided with individual data, they were able to convert coffee consumption into cups per day for all studies. This procedure improved the categorization of coffee consumption for use in dose response analyses. Thus, the data on consumption in general are of relatively better quality for estimating dose response as compared to previous studies on childhood leukemia. Further, I am not aware of any data set that contradicts the findings of **Milne et al. (2018).** THIS APPEARS TO BE THE UNIVERSE OF DATA AVAILABLE UPON WHICH TO EVALUATE THE ASSOCIATION BETWEEN MATERNAL COFFEE CONSUMPTION AND CHILDHOOD CANCER. The pooling of data from eight case-control studies, and the rigorousness in the study design and analyses add considerable weight to the data that were available at the time of the IARC 2016 review.

Having served on IARC Working Groups since 1977, I am of the opinion that the data currently available on maternal coffee consumption and childhood leukemia would "minimally" meet an IARC classification of "limited evidence of carcinogenicity to humans" because chance, bias and confounding are unlikely to have been responsible for the significant association. The epidemiological data on coffee consumption and childhood leukemia do not support the claim by OEHHA that coffee "has not been found to increase the risk of any cancers."

G. QUANTITATIVE RISK OF CHILDHOOD LEUKEMIA IN RELATION TO MATERNAL COFFEE CONSUMPTION

Based upon the studies available prior to the recent **Milne et al. (2018)** study, a quantitative estimate of childhood leukemia in relation to maternal coffee consumption during pregnancy based on the **Bonaventure et al. (2013)** study was calculated by Dr. Steven P. Bayard at the request of CERT. Dr. Bayard was formerly Director of the Office of Risk Assessment in the Directorate of Health Standards Programs within the U.S. Occupational Safety and Health Administration and a quantitative risk assessment expert at the U.S. Environmental Protection Agency and U.S. Consumer Product Safety Commission. Dr. Bayard estimated an increased risk of childhood leukemia (< 14 years of age) from maternal consumption of 1-2 cups of coffee per day during pregnancy of 19.5 cases per 100,000 births--a substantial risk of childhood leukemia. This increased risk level clearly exceeds the *de minimis* risk level of the Prop 65

Law. (See attachment of Dr. Bayard's "Calculation for the Increased Risk of Two Acute Childhood Leukemias Due to Maternal Coffee Drinking During Pregnancy.")

H. BIOLOGICAL PLAUSIBILITY FOR MATERNAL COFFEE CONSUMPTION AS A CAUSE OF CHILDHOOD LEUKEMIA

In its Monograph on Coffee IARC does not discuss the biological mechanisms that would explain the association between maternal consumption of coffee and childhood leukemia. However, biologically plausible mechanisms for the development of childhood leukemia from maternal consumption of coffee during pregnancy are available in the published literature. During the Phase 1 trial in *CERT v. Starbucks,* Professor Martyn T. Smith, one of the world's leading researchers regarding the causes of childhood leukemia, testified that "the most probable mechanism to explain [the association] is that the clastogenic chemicals within coffee, including acrylamide, cross into the fetus and cause genetic damage in the fetus of the type where there's chromosome breakage, which leads to chromosome translocations, which then develops into leukemia." (See testimony of Dr. Martyn Smith, October 14, 2014 at 42:23-28; report of Dr. Peter Infante regarding maternal consumption of coffee and childhood leukemia); See also **Milne et al. (2011); Sörgel et al. (2002); Annola et al. (2008).**

Sincerely,

Peter F. Infante, M.P.H., Dr.P.H., F.A.C.E.
Peter F. Infante Consulting, L.L.C.
[redacted]
[redacted], VA [redacted]

(Formerly, between 1978-2002))
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Yan K, Xu X, Liu X, Wang X, Hua S, Wang C, Liu X. (2015) The Associations Between Maternal Factors During Pregnancy and the Risk of Childhood Acute Lymphoblastic Leukemia: A Meta-Analysis. Pediatr Blood Cancer 62, 1162-1170, Corrigendum, Pediatr. Blood Cancer (2016) 63, 953-954.

Table 1 Studies Used by IARC to Evaluate Maternal Coffee Drinking During Pregnancy and Risk of Childhood Leukemia

Authors/ Country	**Total Cases/ Controls**	**Maternal Coffee Cups/da**	**Child Acute Leukemia (AL) OR(95% C.I.)**	**Acute lymphocytic Leukemia (ALL) OR(95% C.I.)**	**Acute Myelogenous Leukemia (AML) OR(95% C.I.)**	**IARC Comments**
Menegaux (2005) France	280/288	< 3 4-8 > 8	1.0 (0.7 – 1.5) 2.1 (1.2 – 3.8) 2.8 (0.9 – 8.1) P trend < 0.05	1.1 (0.7 – 1.8) 2.4 (1.3 – 4.7) 3.1 (1.0 – 9.5) Trend not calc.	1.6 (0.6 – 4.3) 2.8 (0.7 – 10.4) 3.0 (0.3 – 35.1) Trend not calc.	[Strengths included standardized interviews, adjustment for a range of confounders, presentation of results for ALL and ANLL separately, and assessment of exposure–response relationship. The study was however limited by the use of hospital-based controls and the modest sample size for ANLL.]
Menegaux (2007) France	470/567	<3 >3	1.1 (0.8 – 1.4) 1.5 (0.9 – 2.4)	1.1 (0.8 – 1.4) 1.4 (0.9 – 2.4) Non-smoking mothers 1.9 (1.0-3.5)	1.6 (0.8 – 3.0) 1.4 (0.5 – 4.4)	[Strengths included use of population-based controls, standardized questionnaires, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of the exposure–response relationship. The modest sample size for AML was a limitation.]
Boneventure (2013) France	764/1,681	< 1 1 – 2 >2	1.0 (0.8 – 1.3) 1.3 (1.0 – 1.7) 1.6 (0.1.2 – 2.1) P trend < 0.001	1.0 (0.8 – 1.3) 1.3 (1.0 – 1.7) 1.5 (1.1 – 2.0) P trend =0.0027	1.3 (0.7 – 2.1) 1.8 (1.0 – 3.3) 2.4 (1.3 – 4.3) P trend =0.002	[Strengths included the use of population-based controls, standardized questionnaires, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of an exposure– response relationship.]
Orsi (2015) France	747/1,421	< 1 1 – 2 > 2	0.8 (0.7 – 1.0) 1.0 (0.7 – 1.3) 1.1 (0.9 – 1.5)	0.8 (0.6 – 1.1) 1.0 (0.7 – 1.3) 1.3 (1.0 – 1.8)	0.9 (0.6 – 1.5) 1.1 (0.6 – 1.9) 0.5 (0.2 – 1.1)	[Strengths included the use of population-based controls, a standardized CATI interview, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of the exposure–response relationship. P values for trend were not provided, however.]
Milne (2011) Australia	337/697	0 - <2 2 +		0.77 (0.51 – 1.16) 1.12 (0.72 – 1.74) P trend = 0.50		[Strengths included the use of population-based cases and controls, standardized questionnaires, adjustment for a range of confounders, and assessment of exposure–response relationship. The study was however limited by the low participation rate.]
		0 - <2 2 +	Non-smoking Mothers, children ALL/CT 1.2 (0.53 – 2.71) 2.6 (1.04 – 6.22) P trend = 0.03			
Milne (2018) ** France, Australia, Greece, USA	2,552/ 4,874	> 0 -1 > 1 -2 > 2		0.95 (0.84 -1.07) 1.07 (0.92 – 1.25) 1.27 (1.09 – 1.48) P trend = 0.005		Published after IARC review

Footnote: ** Study not relied upon by IARC because it was published subsequent to Working Group review.

CURRICULUM VITAE

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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. 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.

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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.

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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.

Infante, P.F. and Legator, M. Workshop on Methodology for Assessing Reproductive Hazards in the Workplace: Recommendations for Future Research. Env. Res., 20:217-223, 1979.

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Wagoner, J.K. and Infante, P.F. A review of the methodologic approaches in the assessment of an association between vinyl chloride exposure and reproductive hazards. (In Infante, P.F. and Legator, M. Eds. Proceedings of a Workshop on Methodology for Assessing Reproductive Hazards in the Workplace. DHHS (NIOSH) Pub. No. 81-100, U.S. Gov. Printing Office, 1980) pp. 43-52.

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.

Ames, B., Infante, P.F. and Reitz, R. Eds. Ethylene dichloride: A potential health risk? Banbury Report 5, Cold Spring Harbor Lab. 1980, XI + 350 p.

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.

White, M.C., Infante, P.F. and Chu, K.C. A quantitative estimate of leukemia mortality associated with occupational exposure to benzene. Risk Analysis, 2:199-203, 1982.

Kang, H.K., Infante, P.F. and Carra, J.S. Determination of blood lead elimination patterns of primary lead smelter workers. J. Tox. Env Health, 11:199-210, 1983.

Infante, P.F. and White , M.C. Benzene: Epidemiologic observations of leukemia by cell type, related blood abnormalities and adverse effects from low-level exposure. Env. Health Perspect. 52:75-82, 1983.

Infante, P.F. and Tsongas, T.A. Occupational reproductive hazards: Necessary steps to prevention. Am. J. Ind. Med., 4:383-390, 1983.

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.

Infante, P.F., White, M.C. and Chu, K,C, Assessment of leukemia mortality associated with occupational exposure to benzene. Risk Analysis, 4:9-13, 1984.

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Occupational factors in embryotoxicity and teratogenicity.
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Vinyl chloride. Canadian Cancer Society International Conference on Cancer in the Workplace, May 16-18, 1983, Vancouver, B.C.

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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.

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Dose Response in Occupational Mortality Studies. American Public Health Association Meeting, New Orleans, La., Oct. 18-22, 1987.

Testimony on OSHA Standard Setting. Committee on Labor and Human Resources, United States Senate, April 19, 1988.

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The 0.1 ppm ACGIH proposed TLV for benzene. Presented before the ACGIH Committee, Cincinnati, Ohio, March 21, 1991.

Prevention versus chemophobia: Testing for carcinogens with rodents. American Industrial Hygiene Conference and Exposition, Salt Lake City, May 21, 1991.

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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.

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Exposure assessment and dose response for industrial carcinogens. Meeting of the Association of Brazilian Industrial Hygienists, Sao Paulo, Brazil, September 2-5, 1996.

Cancer risk to blue collar workers. Meeting of the Association of Brazilian Industrial Hygienists, Sao Paulo, Brazil, September 2-5, 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.

Glyphosate and Cancer: A review of the epidemiological literature related to the development of Non-Hodgkin lymphoma. Presented

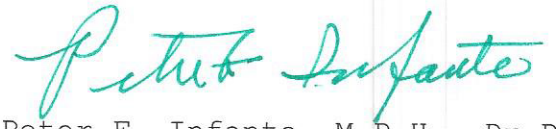
before the FIFRA, US Environmental Protection Agency Scientific Advisory Panel regarding EPA’s evaluation of the carcinogenic potential of glyphosate. Arlington, VA December 15, 2016.

Law. (See attachment of Dr. Bayard's "Calculation for the Increased Risk of Two Acute Childhood Leukemias Due to Maternal Coffee Drinking During Pregnancy.")

H. BIOLOGICAL PLAUSIBILITY FOR MATERNAL COFFEE CONSUMPTION AS A CAUSE OF CHILDHOOD LEUKEMIA

In its Monograph on Coffee IARC does not discuss the biological mechanisms that would explain the association between maternal consumption of coffee and childhood leukemia. However, biologically plausible mechanisms for the development of childhood leukemia from maternal consumption of coffee during pregnancy are available in the published literature. During the Phase 1 trial in *CERT v. Starbucks*, Professor Martyn T. Smith, one of the world's leading researchers regarding the causes of childhood leukemia, testified that "the most probable mechanism to explain [the association] is that the clastogenic chemicals within coffee, including acrylamide, cross into the fetus and cause genetic damage in the fetus of the type where there's chromosome breakage, which leads to chromosome translocations, which then develops into leukemia." (See testimony of Dr. Martyn Smith, October 14, 2014 at 42:23-28; report of Dr. Peter Infante regarding maternal consumption of coffee and childhood leukemia); See also **Milne et al. (2011); Sörgel et al. (2002); Annola et al. (2008)**.

Sincerely,



Peter F. Infante, M.P.H., Dr.P.H., F.A.C.E.
Peter F. Infante Consulting, L.L.C.
[redacted] VA [redacted]

(Formerly, between 1978-2002))
Director, Office of Carcinogen Identification and Classification
Director, Office of Standards Review
Health Standards Program
Occupational Safety and Health Administration
Washington, D.C.

Statement of Steven Bayard

Calculation for the Increased Risk of Two Acute Childhood Leukemias Due to Maternal Coffee Drinking During Pregnancy

I. Introduction:

I have been asked by Raphael Metzger to provide comments on a meta-analysis on maternal coffee consumption and the risk of childhood leukemia (Cheng et al. (2013; Plaintiff's Exhibit #51781), I have also been asked to calculate, if appropriate, a quantitative estimate of the increased risk of childhood leukemia (cases< 15 years of age) from maternal coffee drinking during pregnancy**. I have calculated that increased lifetime childhood acute leukemia risk due to maternal coffee drinking of 1-2 cups per day during pregnancy as 19 per 100,000.**

Below I refer to papers by Cheng et al. and Bonaventure et al. (2013; Plaintiff's Exhibit #48823). My purpose is not to do a hazard identification analysis for maternal coffee drinking as a cause of childhood leukemia, but to calculate the increased cancer risk estimates if others judge there to be sufficient cause to do so.

II. Discussion of Cheng et al. Meta-Analysis

Cheng et al. rely on seven studies of maternal coffee drinking and childhood leukemias: 4 from France, 1 each from Australia and Greece, and one from combined U.S. and Canada. This North American study analyzed only 84 infant (< 12.5 months) leukemias; the remaining studies all considered the age range up to 14-15 years. Although the North American study had the advantage of more recent recall of coffee drinking (and, therefore, may be the best quality as well as the most pertinent study), it was small, and will not be considered further here as part of the larger more homogeneous response group. For the remaining six studies, the total number of acute leukemia (AL) cases was 2,225 (3,638 controls). Most of these came from the four French studies (1735 cases; 2641 controls). In a

further breakdown (where specified; Cheng, Table 1), of AL to acute lymphoblastic leukemias (ALL) and acute myeloid leukemias (AML or ANLL),

nearly 80% (1,285 out of 1,622) of the ALL, and all 203 the AML (ANLL) cases are from France. Thus, the majority of the epidemiologic evidence for maternal coffee drinking - childhood leukemia associations appear to come from French studies.

All 4 French studies appear to use the cases from the National Registry of Childhood Hematopoietic Malignancies (NRCH) and several of the same authors' names appear on three or all four studies. All four publications appear to come from the same (ESCALE) study. Three of the four studies used leukemia data from the same time period, 1995 -1999, and these three were all published from 2004-2007. Without my doing more in-depth checking, I cannot determine if some of the cases were used in all three studies. That would violate the independence requirements of a meta-analysis.

Because of my above concerns, I decided to focus on the 4th French study, that by Bonaventure et al. (2013). The Bonaventure study has the most cases (764) and controls (1681) of any of the seven studies, and appears to me to have been well conducted by authors who have published a great deal. However, my purpose here is not to do a critical review of the quality of the entire study, but to provide an estimate of the risk of childhood leukemia from maternal coffee drinking, if that risk is a real one. This is done below.

III. Analysis of Maternal Coffee Drinking and Increased Risk of All Childhood (0 – 14) Leukemia based on the Bonaventure et. al. (2013) Study.

In their case-control study of French children who were diagnosed with acute leukemia in 2003-2004, the authors report an overall odds ratio (OR) of 1.2 ($0.01 < p < 0.05$) for "regular" maternal coffee drinking during pregnancy of at least 1 cup/week, (see Bonaventure's Table 2, reproduced below). Breaking "regular" drinkers into three increasing categories of "<1 cup/day", "1 -2 cups/day", and ">2 cups/day", yielded increasing ORs of 1.0, 1.3 ($p<0.001$), and 1.6 ($p<0.001$), respectively, plus a highly statistically significant positive test for trend ($p<0.001$).

When AL was broken into AML and ALL, the results were similar, although only the high consumption levels and the trend tests were statistically significant ($p<0.01$).

While these results, by themselves, are suggestive, they show, in my opinion, even more credibility when they are compared with the authors' same analysis for tea, cola beverages, and alcoholic beverages during pregnancy (See Table 2 below). Doing the same statistical tests as were done for coffee, there were no statistical trends and few statistically significant results with any of these other drinks. To me, this is a good test for checking for "false positives." (A small caveat is that pregnant French women seemed to prefer coffee as a beverage, in general, over these other drinks. This means that there were more coffee than other beverage drinkers in the control group; thus, the coffee group comparisons would have more statistical power.)

IV. Estimates of Increased risk of all childhood (0 – 14) Leukemia based on the Bonaventure et al. (2013) Study.

In order to estimate the childhood leukemia increased risk in the U.S. based on the ORs in the Bonaventure study, I need to, 1) choose an OR (I use OR as an estimate of relative risk, RR, for the rare disease of childhood leukemia) that represents the coffee drinking habits of pregnant women in California, and 2) estimate the background childhood leukemia rates. This is done below:

To estimate 1) I chose the OR=1.3 for the 1-2 cups/day coffee drinkers as suitable. This seems reasonable to me, that pregnant women in California will be more health conscious and drink less coffee.

To estimate 2) the background childhood leukemia incidence rates I use the U.S. National Cancer Institute's results from their SEER Cancer Statistics Review 1975-2011, for years 2007-2011:

http://seer.cancer.gov/archive/csr/1975_2010/results_merged/sect_13_leukemia.pdf

I use their tables for age-specific cancer incidence rates; Table 13.12 for four age-specific (<1, 1-4, 5-9, and 10-14) rates for ALL, and Table 13.13 for corresponding

age specific rates for AML. I added the two age-specific rates from each of these tables to get the four age group-specific rates for combined ACL plus AML. Then, I multiplied each of these rates by the number of years comprising each age-specific rate and summed these to get the lifetime probability, i.e.:

$$(1 \times 3.5) + (4 \times 8.9) + (5 \times 4.1) + (5 \times 2.7)) = 73 \text{ per } 100{,}000$$

I then checked this result doing a life-table analysis to confirm that 73 per 100,000 is the lifetime probability of childhood (<14) ALL + AML.

Using this estimate of 73/100,000 U.S. lifetime probability for ALL or AML, I then assumed that some of this risk was due to increased leukemias from coffee drinking. From my previous statement on the calculation of the excess risk of cancer to the general population from acrylamide in coffee, I used the National Coffee Association survey to estimate that 65% of Californians drink coffee. With this figure, I estimate that the increased risk of childhood leukemia from California women drinking coffee during pregnancy is **19 per 100,000**. The calculation is:

$$0.35 \times \text{Risk}_{\text{no.coffee}} + 0.65 \times (1.3) \times \text{Risk}_{\text{no coffee}} = 0.00073 \text{ lifetime risk}$$

Then, Cancer $\text{Risk}_{\text{no.coffee}} = 0.00065$ and:

Increased risk of childhood leukemia from maternal coffee drinking pregnancy is:

(Relative Risk – 1) * Unexposed Risk = 0.3 x 0.00065 = 19.5/100,000

Table 2 below is a direct copy of Table 2 from Bonaventure et al. (2013):

Table 2 Associations between childhood leukemia and self-reported maternal consumption of caffeinated and alcoholic beverages during pregnancy

	Controls $n = 1{,}681$	All AL $n = 764$	OR[a]	95 % CI	AML $n = 101$	OR[b]	95 % CI	ALL $n = 648$	OR[b]	95 % CI
Coffee during pregnancy										
Never/occasionally	669	273	1.0	Ref.	238	1.0	Ref.	30	1.0	Ref.
Regular (≥1 cup/week)	1,008	487	1.2	[1.0–1.5]*	406	1.2	[1.0–1.4]	71	1.6	[1.0–2.6]*
<1 cup/day	503	203	1.0	[0.8-1.3]	174	1.0	[0.8–1.3]	27	1.3	[0.7–2.1]
1 or 2 cups/day	259	130	1.3	[1.0–1.7]*	108	1.3	[1.0–1.7]	19	1.8	[1.0–3.3]
> 2 cups/day	246	154	1.6	[1.2–2.1]***	124	1.5	[1.1–2.0]**	25	2.4	[1.3–4.3]**
Missing	4	4		p for trend < 0.001	4		p for trend = 0.0027			p for trend = 0.0020
Tea during pregnancy										
Never/occasionally	1,009	481	1.0	Ref.	406	1.0	Ref.	64	1.0	Ref.
Regular (≥ cup/week)	666	280	0.9	[0.8–1.1]	240	0.9	[0.8–1.2]	36	0.9	[0.6–1.4]
<1 cup/day	164	85	1.1	[0.8–1.5]	69	1.1	[0.8–1.5]	15	1.5	[0.8–2.7]
1 cup/day	274	106	0.8	[0.7–1.1]	90	0.8	[0.6–1.1]	14	0.9	[0.5–1.6]
>1 cup/day	228	89	0.9	[0.7–1.2]	81	1.0	[0.7–1.3]	7	0.5	[0.2–1.1]
Missing	6	3			2			1		
Cola beverages during pregnancy										
Never/occasionally	1,087	446	1.0	Ref.	379	1.0	Ref.	61	1.0	Ref.
Regular (≥glass/week)	583	312	1.3	[1.0–1.5]*	263	1.3	[1.0–1.5]*	40	1.1	[0.7–1.7]
1 glass/week	145	68	1.1	[0.8–1.5]	59	1.2	[0.8–1.6]	7	0.8	[0.4–1.8]
>1 glass/week and at most 1/day	269	145	1.3	[1.0–1.6]*	120	1.2	[1.0–1.6]	21	1.3	[0.8–2.2]
>1 glass/day	169	99	1.3	[1.0–1.8]	84	1.3	[1.0–1.8]	12	1.1	[0.5–2.1]
Missing	11	6			6					
Alcoholic beverages during pregnancy[c]										
No alcohol drinking	1,065	468	1.0	Ref.	401	1.0	Ref.	58	1.0	Ref.
Any alcohol drinking	616	296	1.2	[1.0–1.4]	247	1.1	[0.9–1.4]	43	1.4	[0.9–2.2]
<1 glass/week	259	148	1.3	[1.1–1.7]*	123	1.3	[1.0–1.7]	23	1.8	[1.1–3.0]*
1 or 2 glasses/week	201	73	0.9	[0.6–1.2]	60	0.8	[0.6–1.1]	11	1.1	[0.6–2.2]
>2 glasses/week	125	55	1.1	[0.8–1.5]	47	1.1	[0.7–1.5]	7	1.2	[0.5–2.8]
Missing	31	20			17			2		

AL acute leukemia, *ALL* acute lymphoblastic leukemia, *AML* acute myeloblastic leukemia

*** $p < 10^{-3}$; **: $10^{-3} \leq p < 10^{-2}$; *: $10^{-2} \leq p < 0.05$

[a] Odds ratios (OR) and 95 % confidence intervals (CI) estimated by unconditional logistic models including the gender × age quota variable, birth order, breastfeeding, maternal education, parental socio-professional category, and European ancestry

[b] OR and 95 % CI estimated by polytomous models of AML and ALL including the gender × age quota variable, birth order, breastfeeding, maternal education, parental socio-professional category, and European ancestry

[c] Rudant et al. [23]