

6 October 2011

Ms. Cynthia Oshita  
Office of Environmental Health Hazard Assessment  
Proposition 65 Implementation  
P.O. Box 4010  
1001 I Street, 19th Floor  
Sacramento, California 95812-4010

Dear Ms. Oshita:

Comment re: OEHHA Notice “Request for Relevant Information on Chemicals to be Considered by the OEHHA Science Advisory Board’s Developmental and Reproductive Toxicant (DART) Identification Committee: Bromodichloromethane, Caffeine, and Methylisocyanate” by October 27, 2008 (Caffeine)

On 24 October 2008, in a letter sent on behalf of the North American Branch of the International Life Sciences Institute (ILSI North America), you were provided with comments related to caffeine and informed that the ILSI North America initiated a project to update two comprehensive reviews (published in the early 2000’s) of the scientific knowledge base related to caffeine. Enclosed is a copy of this letter with more information on the ILSI North America and its Technical Committee on Caffeine. At this time, we would like to inform you that both review articles have now been published in the peer-reviewed literature and are being provided with this letter. The authors of the two review articles have full intellectual and editorial control of their reviews.

As noted previously, in the early 2000’s, the ILSI Technical Committee on Caffeine supported the preparation of a comprehensive review of the scientific knowledge base related to caffeine. Included in this project was a lengthy article, “A Review of the Literature Relating Caffeine Consumption by Women to their Risk of Reproductive Hazards,” A. Leviton and L. Cowan, *Food and Chemical Toxicology*, Vol. 40, Number 9, (2002) 1271-1310. The article reviewed sixty-eight human studies that had been published between 1974 and 2001. Concurrent with this effort, support for a review of the animal data also was provided, “Teratogen Update: Evaluation of the Reproductive and Developmental Risks of Caffeine,” M. S. Christian and R. L. Brent, *Teratology*, Vol. 64, (2001) 51-78.

Because the issue of caffeine and reproductive health remains one that is of interest to the scientific and public health communities, the ILSI North America Technical Committee on Caffeine recently supported the preparation of updates of the two above-referenced articles for submission to the peer-reviewed literature.



The review of publications with human subjects, “A Review of the Epidemiologic Evidence Concerning the Reproductive Health Effects of Caffeine Consumption: A 2000–2009 Update,” by Jennifer D. Peck, Alan Leviton and Linda D. Cowan (*Food and Chemical Toxicology* Vol. 48, (2010) 2549-2576) is a review of human studies of caffeine and reproductive health published between January 2000 and December 2009. This manuscript serves to update the original comprehensive review published by Leviton and Cowan (2002). The adverse reproductive outcomes addressed in this review include: (1) measures of subfecundity; (2) spontaneous abortion; (3) fetal death; (4) preterm birth; (5) congenital malformations; and (6) fetal growth restriction. Methodologic challenges and considerations relevant to investigations of each reproductive endpoint were summarized, followed by a brief critical review of each study. The authors of this publication concluded that the evidence for an effect of caffeine on reproductive health and fetal development was limited by the inability to rule out plausible alternative explanations for the observed associations, namely, confounded by pregnancy symptoms and smoking, and by exposure measurement error. Because of these limitations, the weight of evidence did not support a positive relationship between caffeine consumption and adverse reproductive or perinatal outcomes. An electronic copy of this publication is enclosed.

The second review article, “Teratogen Update 2009: Evaluation of the Reproductive and Developmental Risks of Caffeine” by Robert L. Brent, Mildred S. Christian and Robert M. Diener, has been accepted for publication in the *Birth Defects Research Part B: Developmental and Reproductive Toxicology* 92 (2011) 152-187. This review article presents a risk analysis of *in utero* caffeine exposure utilizing epidemiological studies and animal studies dealing with congenital malformation, pregnancy loss and weight reduction. These effects are of interest to teratologists, because animal studies are useful in such an evaluation. The authors concluded that moderate or even high amounts of beverages and foods containing caffeine do not increase the risks of congenital malformations, miscarriage or growth retardation and that pharmacokinetic studies markedly improve the ability to perform the risk analyses. An electronic copy of this publication is enclosed and it is also available on-line: <http://onlinelibrary.wiley.com/doi/10.1002/bdrb.20288/abstract>

ILSI North America hopes our efforts will be of value to OEHHA and DART Committee members and add significantly to the scientific information base related to caffeine. I will be pleased to answer any questions you may have.

Sincerely,

Eric J. Hentges, PhD  
ILSI North America