Calorie Control Council

1100 JOHNSON FERRY ROAD, SUITE 300 • ATLANTA, GA 30342 • (404) 252-3663 • FAX (404) 252-0774
E-MAIL: CCC@KELLENCOMPANY.COM • WWW.CALORIECONTROL.ORG

October 16, 2009

Dr. Ruth M. Lunn
NIEHS
P.O. Box 12233
MD K2– 14
Research Triangle Park, NC 27709
lunn@niehs.nih.gov.

RE: National Toxicology Program (NTP): Draft Background Document for Formaldehyde

Dear Dr. Lunn:

The Calorie Control Council (the "Council) is an international association representing companies that make low-calorie and reduced fat foods and beverages. Companies that make and use aspartame are among the Council's members. The Council takes this opportunity to address remarks concerning aspartame which appear in the NTP "Draft Background Document for Formaldehyde."

The Draft Document states:

"The artificial sweetener aspartame consists of 10% methanol, which Humphries *et al.* (2008) reported can be converted to formaldehyde and other derivatives. The authors also noted that research has shown that formaldehyde adducts accumulate in the tissues after aspartame ingestion."

This comment is inappropriate for inclusion in the Draft Background Document since it is not scientifically substantiated. To the contrary, a large volume of data indicates quite the opposite. (Magnuson et al, 2007) Therefore, the Council requests that any reference to aspartame be removed from the Draft Background Document.

The safety of methanol and methanol derived from aspartame has undergone extensive evaluation. Methanol, a normal component of the human diet, has long been known to be oxidized to formaldehyde, which is rapidly degraded to formate after ingestion by

humans and monkeys. Based on studies of the metabolism of aspartame, humans cannot possibly consume enough aspartame containing products to raise blood formate concentrations. Formate does not accumulate after consumption of very large doses of aspartame, indicating that the conversion of aspartame to methanol is insufficient to induce any toxicity from methanol or its metabolites. (Butchko et al, 2002)

Aspartame doses 10-65 times the 90th percentile of daily intake have been used in human metabolic studies and provide no evidence of formaldehyde accumulation. More methanol is derived from fruits and vegetables and their juices and alcoholic beverages in the normal diet than from aspartame. According to the US Food and Drug Administration, "An adult human can metabolize up to 1500 milligrams of methanol per hour with no adverse symptoms or effects." The capacity for metabolism in humans is, therefore, far greater than the estimated dietary intake from all sources. (Butchko et al, 2002)

Furthermore, formaldehyde is a constituent of many foods and is produced in the body during the endogenous demethylation of many foods. Magnuson et al (2007) provide an extensive list of foods containing formaldehyde and note that formaldehyde is essential in one-carbon pool intermediary metabolism. The metabolite of formaldehyde, formic acid, is a substrate for purine nucleotide synthesis. More than 50,000 mg of formaldehyde is produced and metabolized in an adult human daily and the adult liver can metabolize 22 mg of formaldehyde per minute. Aspartame provides only a trivial amount of the total formaldehyde exposure and metabolism in the body. (Magnuson et al, 2007)

Importantly, the paper by Humphries *et al.* cited in the Draft Background Document has been seriously criticized. John Fernstrom, an authority on aspartame, in his letter to the editor of the *European Journal of Clinical Nutrition* concerning the Humphries *et al.* review article, states "The errors in the article are too numerous to enumerate in a letter of limited length." (Fernstrom, 2008)

In addition, the paper by Trocho *et al.* which Humphries *et al*. cite as their reference for "research has shown that formaldehyde adducts accumulate in the tissues, in both protein and nucleic acids, after ingestion" also has been criticized. T. R. Tephly states:

"The authors conclude, based on their data, that 'aspartame consumption may constitute a hazard because of its contribution to the formation of formaldehyde adducts.' In their studies, acute doses of ^{14}C-aspartame (20mg/kg) were administered to normal and cirrhotic rats, with and without 10 day pretreatment with oral aspartame (200 mg/kg). A low level of radioactivity was observed in protein, DNA and RNA isolated from various tissues, especially liver. The authors assume that the label was derived directly from formaldehyde and that adducts of formaldehyde with protein, DNA and RNA resulted. It should be noted that the authors did not employ ^{14}C-labeled methanol (at any dose) or ^{14}C-labeled formaldehyde to support or complement their claims except to show that albumin will react with formaldehyde in vitro as is well known. Thus, one must question their interpretation that methanol generated from aspartame leads to adduct formation. Furthermore, the use of rats (or for that matter any animal species other than primates or

humans) in studies of methanol disposition must take into account that methanol does not produce toxicity in this species. The doses of aspartame that the authors used do not even yield methanol concentrations in blood or tissues above control levels." (Tephly, 1999)

Thank you for considering the Calorie Control Council's comments and request that any reference to aspartame be removed from the Draft Background Document.

Sincerely,

Lyn O'Brien Nabors
President

References
(provided with comments)

Butchko, HH et al. (2002) Safety of methanol from aspartame and the diet. *Regulatory Toxicology and Pharmacology* 35(2):S36 –S41.

Fernstrom, JD. (2008) Aspartame effects on the brain (letter to the editor). *European Journal of Clinical Nutrition* doi:10.1038/ejcn.2008.5.

Magnuson, BA et al. (2007) Aspartame: A safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. *Critical Reviews in Toxicology* 37:645.

Tephly, TR. (1999) Comments on the purported generation of formaldehyde and adduct formation from the sweetener aspartame. *Life Sciences* 65:157-160.