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Formaldehyde, Aspartame, Migraines: A Possible Connection

To the Editor:

The following comments relate to the Jacob and Stechschulte case study in which the authors speculate that aspartame consumption may be associated with migraine and recurrent dermatitis (published in the May/June 2008 issue of *Dermatitis*).¹ The authors ignored the fact that aspartame metabolites bring nothing new to the human body and are in fact constituents of many common foods we consume daily. The aspartame molecule is simply a dipeptide of aspartic acid and the methyl ester of phenylalanine, (not the methyl ester of aspartic acid, as suggested by the authors). It is completely hydrolyzed in the gastrointestinal tract to the amino acids, aspartic acid, and phenylalanine, plus a small amount of methanol.² These amino acids are found in all protein-containing foods, such as dairy and meat products, and are absorbed and metabolized by the body like amino acids from any other protein-based food. Methanol is similarly present in many foods, such as fresh fruits, vegetables, and juices.³ Methanol is also a normal constituent in blood, urine, saliva, and expired air.⁴ Formaldehyde, a methanol metabolite, is produced during the demethylation of many substances, including many foods and drugs.⁵ For example, fruit juices, coffee, and alcoholic beverages produce significantly greater quantities of formaldehyde than aspartame-containing products.⁶ Thus, it would be impossible to distinguish clinically relevant patch-test reactions to formaldehyde from aspartame from such reactions in which the formaldehyde was derived from the host of other dietary sources of formaldehyde.

In their discussion, Jacob and Stechschulte raised concerns that formaldehyde may form adducts that are difficult to remove by normal metabolic pathways and that may result in their accumulation in tissues. Dietary methanol is oxidized in the liver to formaldehyde and formic acid. The metabolism of methanol to formic acid is very rapid, with formaldehyde having a half-life of 1 to 2 minutes.⁵ Hence, there is no accumulation of formaldehyde after even high doses of methanol.⁷ It is estimated that more than 50,000 mg of formaldehyde are produced and metabolized each day in a human adult and that the liver can metabolize 22 mg of formaldehyde per minute.⁸ Furthermore, formic acid, a metabolite of formaldehyde, is an essential one-carbon-pool intermediary substrate for amino acid and purine nucleotide synthesis via folate-dependent metabolism.⁷

The authors' suggestion of the development of migraine after consumption of aspartame-containing products ignored results in earlier peer-reviewed publications. Schiffman and colleagues and Leon and colleagues reported on randomized double-blind placebo-controlled studies that involved larger sample sizes (40 and 108 subjects, respectively) and evaluated the association of headache and administration of aspartame (capsules) at doses of 30 mg/kg of body weight and 75 mg/kg of body weight (the equivalent of an adult drinking 4 L and 10 L, respectively, of beverage sweetened with 100% aspartame). In both studies, the headache incidence rate in the aspartame group was not significantly different from that of the placebo group.^{9,10} As to the report of dermatitis flares after consumption of aspartame, Geha and colleagues investigated allergic-type symptoms such as urticaria and angioedema in a multicenter randomized double-blind placebo-controlled crossover clinical study of 21 subjects who received capsules containing 25 mg or 300 mg of aspartame, capsules containing 7.5 mg of diketopiperazine (DKP) and 3.75 mg of β -aspartame (conversion products of aspartame). The authors concluded that there was no statistically significant difference in the incidence of allergic-type reactions between aspartame and placebo challenges.¹¹

Although Jacob and Stechschulte commented on the limitation of their study and their drawing conclusions from their small sample, they ignored the large quantities

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of methanol ingested from foods that do not contain aspartame. They also failed to conduct a thorough review of relevant published aspartame safety studies and interpret the results of their effort in the context of previous peer-reviewed published study reports.

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Authors' Response

To the Editor:

Thank you for the comments received regarding the potential association of aspartame consumption with migraine headaches and recurrent allergic contact dermatitis (ACD). While the commentary did not address the key issues of our observations (ie, that challenge results in a response and that a patch-test challenge with formaldehyde was positive), we appreciate the opportunity to discuss this further.¹ Molecule for molecule, 11% of aspartame that is hydrolyzed becomes methanol (wood alcohol) in the blood.² The commentary authors' state-

ment suggests that methanol metabolism is very rapid; however, the Environmental Protection Agency has reported methanol to in fact be a cumulative toxin.³ It is true that methanol is generated from food, but the average intake of methanol from natural sources is reported to be about 10 mg per day while a 12-ounce aspartame beverage could generate 56 mg/L of methanol, or 22 mg per 12 ounces if fully hydrolyzed.⁴ More than 30 years ago, Oppermann and colleagues reported that there was 31% retention of radioactive methanol in rats 8 hours after ingestion, retention levels confirmed by an expert review of modern studies by Bouchard and colleagues in 2001.^{5,6}

The administration of radiolabeled aspartame to experimental animals has been shown to result in the incorporation of a significant proportion of the label into proteins (thought to be the result of the formation of formaldehyde and formate adducts) at least 6 hours after aspartame ingestion.⁷ In this study, the liver was found to retain more than 2% of the methanol carbon from a single dose of aspartame!⁷ Cumulative effects data obtained from

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