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. Molecule for molecule, 11% of aspartame that is hydrolyzed becomes methanol (wood alcohol) in the blood. The commentary authors’ statement suggests that methanol metabolism is very rapid; however, the Environmental Protection Agency has reported methanol to in fact be a cumulative toxin. 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. 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.

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. In this study, the liver was found to retain more than 2% of the methanol carbon from a single dose of aspartame. Cumulative effects data obtained from

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DOI 10.2310/6620.2009.08082X
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the chronic administration model also have suggested that regular intake of aspartame may also result in a progressive accumulation of formaldehyde adducts. Furthermore, it is important to note that the commentary authors’ assumption that the incorporation of the methanol carbon to normal amino acid structures through the “essential one-carbon” tetrahydrofolate and S-adenosylmethionine pathways from aspartame consumption is an assumption no longer maintained according to current data.

In their discussion, the commentary authors raised several false premises. For example, they concluded that aspartame does not cause allergic-type reactions, based on a study that demonstrated that aspartame and its conversion products were no more likely than placebo to cause urticaria, angioedema reactions, or both, which ignored delayed-type hypersensitivity reactions altogether. It is important to recognize that ACD is an allergic-type reaction with an entirely different mechanism (type IV T-cell–mediated reaction) from the type I reactions referenced. And notably, aspartame has been previously associated with ACD.

Furthermore, if the incidence of this aspartame-mediated migraine response is one in a thousand, then a random study group size would need to be much larger than the ones cited by Schiffman and colleagues and by Leon and colleagues. It is important to note that both Schiffman and colleagues (1987) and Leon and colleagues (1987) did not study the formaldehyde-allergic patient and that, without knowing the true incidence of aspartame sensitivity in dermatitis patients, it is impossible to make any conclusion from these studies.

We absolutely recognize the need to further study the biochemistry of these reactions and that there is speculation and concern about aspartame’s being a sufficient source of formaldehyde to evoke the response, especially when wine and many foods contain methanol or methyl esters. This being said, we believe the dose may be critical and question the effect of ingestion of aspartame as a bolus, as foods are generally more slowly metabolized. Last, the dose levels of aspartame needed to provoke an immune response in an exquisitely sensitized person may be very low, making half-life and metabolic rate less meaningful.

Thank you for this opportunity for intellectual discourse. We still maintain that a larger case study including aspartame-induced migrainous nondermatitis control patients is necessary to establish the association presented in our study, and we would like to perform an aspartame-formaldehyde challenge to show repeatable responses. Alternatively, we would like to challenge individuals known to have formaldehyde sensitivity with aspartame and demonstrate a response as an indirect proof of principle.

Acknowledgments
We acknowledge Tony E. Hugli, PhD, of the Torrey Pines Institute for Molecular Studies, for his provocative academic discourse on the metabolism of aspartame as we work toward better understanding this observed phenomenon.

Financial disclosures of authors and reviewer(s): None reported.

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References

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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 six 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 the chronic administration model also have suggested that regular intake of aspartame may also result in a progressive accumulation of formaldehyde adducts.[7]

Furthermore, it is important to note that the commentary authors' reference to the assumption that the incorporation of the methanol carbon to normal amino acid structures through the "essential one-carbon" tetrahydrofolate and S-adenosyl-methionine pathways from aspartame consumption is an assumption no longer maintained according to current data. [7]

In their discussion, the commentary authors raised several false premises. For example, they concluded that aspartame does not cause allergic-type reactions, based on a study that demonstrated that aspartame and its conversion products were no more likely than placebo to cause urticaria, angioedema reactions, or both, which ignored delayed-type hypersensitivity reactions altogether.[8] It is important to recognize that ACD is an allergic-type reaction with an entirely different mechanism (type IV T-cell mediated reaction) from the type I reactions referenced.[9] And notably, aspartame has been previously associated with ACD.[10]

Furthermore, if the incidence of this aspartame-mediated migraine response is one in a thousand, then a random study group size would need to be much larger than the ones cited by Schiffman and colleagues and Leon and colleagues. It is important to note that both Schiffman and colleagues (1987) and Leon and colleagues (1987), did not study the formaldehyde allergic patient[11],[12] and, that without knowing the true incidence of aspartame sensitivity in dermatitis patients, it is impossible to make any conclusion from these studies.

We absolutely recognize the need to further study the biochemistry of these reactions and that there is speculation and concern about aspartame's being a sufficient source of formaldehyde to evoke the response, especially when wine and many foods contain methanol and methyl esters.
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References


Formaldehyde, aspartame, and migraines: a possible connection.

Jacob SE, Stechschulte S.

Department of Dermatology and Cutaneous Surgery, University of Miami, Miami, FL, USA.

Aspartame is a widely used artificial sweetener that has been linked to pediatric and adolescent migraines. Upon ingestion, aspartame is broken, converted, and oxidized into formaldehyde in various tissues. We present the first case series of aspartame-associated migraines related to clinically relevant positive reactions to formaldehyde on patch testing.

PMID: 18627677 [PubMed - in process]


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