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Response to letter to the editor

April 29th, 2014

A. Wallace Hayes, PhD
Editor-in-Chief
Food and Chemical Toxicology
By email: awallacehayes@comcast.net

Dear Dr. Hayes:

We write in response to a recent letter to the editor by Roberts and colleagues in regard to our recent publication (Anderson et al., 2013) which evaluated the hypersensitivity potential of structurally-related diketones used in food flavorings. Findings from this manuscript also provided evidence for a possible condensation product of diacetyl (5-methyl-4-heptene-2,3,6-trione (MHT)) in select diacetyl sources. We thank the authors for their interest, calculations and insight into the diacetyl contaminant. It is encouraging that the findings from their modeling are consistent with our predicted structure based on chemical characterization and further support the potential for this contaminant to be a strong sensitizer (Anderson et al., 2013). We recognized the importance and significance of unequivocally characterizing this contaminant. Unfortunately, there were several challenges that hindered our many attempts to confirm the contaminant's identity. Specifically, MHT is not commercially available, synthesis efforts were unsuccessful, and chemical derivatization would have yielded an oxime compound that due to its mass would have gone undetected by the mass spectrometer instrument used.

While we have not definitively identified the structure of the contaminant, we suspect that it is a strong sensitizer based on the associated 10-fold change in EC3 values between two diacetyl vendors (Fluka and Aldrich). Although, we don't know absolute concentrations of the contaminant in the products, they are expected to be very small since the reported diacetyl purities ranged from 97–99%. Anderson et al. (2013) provided a report of first tier screening examining the sensitization potential of alternative butter flavorings. Similar EC3 values classified as other than strong were reported for all of the chemicals examined. The authors agree that specimen contamination is always a potential issue. However, confirmation of chemical purity was outside the scope of these hazard identification screening assays.

The EC3 value for diacetyl was reported to be 17.9% (Anderson, 2013). While this was based on the Aldrich product, in which trace amounts of the suspected contaminant were detected, this EC3 value (17.9%) was determined to be reproducible as this source had been tested multiple times in comparison to the TCI diacetyl (<25%) which had only been tested once in the local lymph node assay (LLNA). In addition, the authors would like to point out that during the validation of the LLNA, a certain degree of variability in calculated EC3 values for the same chemical was identified within and between laboratories. For example weakly sensitizing eugenol yielded EC3 values ranging between 5.8% and 13.8% among the five laboratories participating in the inter-laboratory validation. In addition more variability was observed when determining the EC3 values for weaker sensitizers (ICCVAM, 1999) as was reported for diacetyl. Also noteworthy, potency classifications from the most recent ICCVAM guidelines, report that a sensitizing chemical can be classified as strong (<10%) or other than strong (>10%) based on reported EC3 values (ICCVAM, 2011). Based on this classification system and the calculated EC3 values, diacetyl (from all sources except for Fluka) would be considered a "less than strong" sensitizer.

In addition, Roberts and co-workers explore the possibility of a potential effect of MHT or other contaminants on the epidemiology findings from inhaled diacetyl vapors. It is very speculative to extrapolate the findings from animal studies measuring the ability of dermal exposure of a chemical to produce allergic contact dermatitis to the potential causes of the human acute pulmonary toxicity observed with butter flavoring, diacetyl or other related compounds. Further, sensitization to a component of butter flavorings is not a factor in the etiology of obliterative bronchiolitis in flavoring-exposed workers. Rarely is a chemical ever truly pure and the effect of minor contaminants to overall toxicity is always a potential concern. However, there is nothing to support that the data reported in our recent publication (Anderson et al., 2013) is suggestive of the contaminant being responsible for the pulmonary toxicity of butter flavorings.

Conflict of Interest

The authors declare no competing interests and no conflicts of interest. The findings and conclusion in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health.

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