Correspondence

Diacetyl and Bronchiolitis Obliterans

To the Editor:

We read with interest the analysis by Dr. van Rooy and colleagues of the risk of developing bronchiolitis obliterans in workers involved in manufacturing flavoring ingredients (1). We comment as follows.

In their study, the fraction of suspected workers for fixed airway obstruction was 6 out of 196 workers being evaluated. This fraction was further reduced as two were not found to have disease. Of the remaining four, one worker refused to have high-resolution computed tomography; three were subsequently diagnosed with bronchiolitis obliterans syndrome, unverified by lung biopsy. The worker refusing computed tomography had a heavy smoking history.

Exposure to diacetyl for process operators only existed at the end of the production process, and none of the workers were exposed to the heated compound—a much different scenario than mixers in microwave popcorn facilities. In the only subject who actually underwent lung biopsy, the histology showed "no signs of constrictive bronchiolitis."

In a previously published abstract (2), van Rooy and coworkers reported "no clear relationship between lung function and cumulative exposure." The authors stated: "Estimated historic exposure levels are subject to considerable measurement error and it is likely that exposure misclassification obscured exposure–response relationships." If these were problems in 2006, their 2007 analysis should also be at risk for the same issues.

The authors believe that animal studies confirm airway injury with diacetyl vapor. What is not mentioned is that this damage was consistently noted by Hubbs and coworkers (3) to be tracheal and upper bronchial in location, *not* terminal bronchiolar and alveolar injury as seen in constrictive bronchiolitis.

van Rooy and coworkers do not discuss respiratory protection measures routinely employed by process operators. The "control measures" instituted in 2001 are not described, nor are any worker respiratory complaints that might be indicative of high exposures summarized. These basic facts are important for proper comparison with popcorn worker studies, and for understanding industrial hygiene and worker safety.

We applaud the efforts of van Rooy and coworkers to examine the incidence of lung disease in workers exposed to diacetyl and other chemical agents. Prevention of occupational lung disease is predicated on a clear understanding of risk factors, disease mechanism, and confounding variables, and we share their desire to protect workers from dangerous exposures. Unfortunately, it seems that their survey has done little to demonstrate an association between diacetyl exposure and the development of bronchiolitis obliterans.

Conflict of Interest Statement: D.A.G. has been a consultant for Kerry Foods and Chemtura Corporation. D.W. has been a consultant for Chemtura.

David A. Galbraith
Palo Alto Medical Foundation
Palo Alto, California

David Weill
Stanford University School of Medicine
Stanford, California

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From the Authors:

Drs. Galbraith and Weill question whether the subjects described in our article (1) have bronchiolitis obliterans syndrome (BOS) and whether their small numbers are worthy of concern. In response, we make the following points.

To find 4 out of 103 operators with severe impairment from airway obstruction is an excessively high number, arguing for an occupational cause. The BOS diagnosis is best made by high-resolution computed tomography showing air trapping on expiratory films. Lung biopsy has not proved to be sensitive in cases of flavoring-related BOS (2, 3), and absence of a confirmatory biopsy is no reason to dispute or diminish the findings of this study.

Operators were exposed during several tasks in the process. The production process was *open* from 1960 until 2001. In 2001, the control measures introduced were to enclose the batch process, which lowered exposures. We have no information on use of respiratory protection measures employed by operators. All cases became symptomatic before control measures were taken in 2001. As our 2005 study participants no longer worked at the diacetyl plant, which closed in 2003, we did not collect information on recalled irritative symptoms that might have been expected with high historical exposures.

Our previously published abstract and current article are consistent with respect to exposure–response analyses. Historic exposure data are limited, subject to misclassification, and likely insufficient to support quantitative exposure–response relations for cumulative exposure, if they existed. Findings suggestive of an exposure–response relationship include the clustering of cases among operators, who also had significantly lower FEV_1 values than other workers in the group.

Hubbs and colleagues (4–6) confirm airway injury in animals following exposure to butter flavoring or diacetyl vapor. Akpinar-Elci and colleagues (3) demonstrated upper airway and bronchiolar injury in humans. Morgan and coworkers (7) demonstrated fibrosis at the bronchoalveolar junction in mice exposed to diacetyl. Thus, both animal and human studies demonstrate upper airway and bronchiolar injury following exposure to butter flavoring and/or diacetyl under some exposure conditions.

Despite the limitations of a small cohort and scant exposure data, our study contributes to narrowing the potential causative agents of occupational BOS seen in microwave popcorn workers and flavoring manufacturing workers to the chemicals found in diacetyl production. Our study is consistent with the likely role of diacetyl in causing this lung disease. The precautionary principle dictates action to protect workers from these potentially very hazardous exposures.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.