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LETTER TO THE EDITOR

Letter to the Editor

RE: Galbraith D and Weill D (2009), Popcorn lung and bronchiolitis obliterans: a critical appraisal 82:407–416

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Dear Editors,

We are concerned that readers may be mislead by David Galbraith and David Weill's criticisms of several recent studies that have shown risk to workers from exposures to butter flavoring chemicals (Galbraith and Weill 2009). Some of their criticisms are largely semantic. As previously noted, "The terminology of bronchiolitis obliterans has been a source of confusion which has not yet been completely resolved" (Cordier 2007). This semantic confusion regarding bronchiolitis obliterans terminology does not affect the science of recent research on workers. More disturbing are the misconceptions, inaccuracies, and omissions in their review. We appreciate the opportunity to clarify the peer-reviewed literature on diacetyl and flavorings-related lung disease.

In epidemiologic study of an emerging health issue, invasive evaluation with biopsy is unnecessary to establish excess of disease and work-related risk factors. In two microwave popcorn plants, 27% of worker-participants had abnormal pulmonary function. Open lung biopsy supported a diagnosis of constrictive bronchiolitis in two of the three biopsied sentinel cases (Akpinar-Elci et al. 2004) and three of six biopsied cases in another microwave popcorn plant (Kanwal et al. 2006). However, constrictive bronchiolitis can be difficult to identify on biopsy due to its patchy distribution (Markopoulou et al. 2002). As a result, we did not advocate open lung biopsy in flavoring-exposed workers with fixed airways obstruction when no other condition was suspected. However, a spectrum of disease exists among flavoring-exposed workers (Kreiss 2007a), and workers with restrictive disease may benefit from diagnostic biopsy until more is understood about the range of flavoring-related lung disease, response to therapy, and natural history. In considering the advisability of biopsy, the clinician must recognize that a pathologic diagnosis of constrictive bronchiolitis is difficult in the small samples obtained at biopsy, particularly when the disease is advanced (Visscher and Myers 2006). The pathologic diagnosis does not change medical therapy in patients with fixed airways obstruction, because popcorn plant workers with moderate to severe cases of lung disease did not respond to high dose prednisone, and two severely ill workers treated with cytotoxic drugs also did not respond. When multiple cases of a rare clinical syndrome are identified in a flavoring-exposed worker group, and no medical treatment is available, invasive diagnostic procedures are difficult to justify in the care of individual patients. We demonstrated that exposure cessation slowly led to diminution of cough and stabilization of severely abnormal pulmonary function in sentinel cases (Akpinar-Elci et al. 2004) and also among current workers after butter flavoring exposures were controlled in the index plant (Kreiss 2007b). Beyond work restriction for exposure cessation, all that the medical community has to offer these irreversibly affected workers is supportive care. It would be unfortunate if legal defense required patients to undergo a potentially risky invasive procedure that might not identify the disease even when it is present.

We do not agree with Galbraith and Weill's statement that "…chemical properties of diacetyl…do not appear to

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be consistent with a disease process known to target the deep lung." Worker studies have indicated damage to both upper and lower airways, including mucous membrane irritation, tracheo- and bronchiolomalacia, cylindrical bronchiectasis, and bronchial wall thickening, as well as constrictive bronchiolitis. Chemical characteristics of diacetyl that suggest a risk to intrapulmonary airways include the chemical reactivity of diacetyl and related α-diketones (Wondrak et al. 2002). This reactivity is supported by the ability of diacetyl to cause necrosis of airway epithelium in rats and mice. The risk to intrapulmonary airways is additionally supported by subchronic exposures to diacetyl causing epithelial denudation, atrophy and regeneration, and lymphocytic inflammation in intrapulmonary bronchi of mice at occupationally relevant exposure levels (Hubbs et al. 2008; Morgan et al. 2008a, b). Recent computational fluid dynamic physiologically based pharmacokinetic modeling of diacetyl uptake indicates greater diacetyl penetration to the intrapulmonary airways of humans than in rodents (Morris and Hubbs 2009). These studies represent additional evidence indicating a respiratory hazard from inhaled diacetyl vapors.

One of the misconceptions in the Galbraith and Weill review is their characterization of packaging workers as having "little or no exposure", as an argument that no dose–response exists. Among former workers, packagers had a much lower estimated prevalence compared to mixers [Centers for Disease Control and Prevention (CDC) 2002], consistent with their much lower average exposures (Kreiss et al. 2002). In our cross-sectional study of current workers, no mixers were initially affected, but a very young mixer did develop severe fixed airways obstruction during our longitudinal follow up [National Institute for Occupational Safety and Health (NIOSH) 2006]. This discrepancy between former worker and current worker prevalences reflects the healthy worker effect, in which ill workers leave the workforce, the small number of mixers in any plant (generally three or fewer mixers per work shift), and the substantial risk to non-mixers in microwave popcorn production. Galbraith and Weill raise concern about exposures to respirable dust, molds, and pesticides, although no evidence exists for worrisome levels of these agents.

Inaccuracies include our alleged omission of statistical tests when we compared the Gilster-Mary Lee plant population and national data; we gave statistical comparisons graphically with error bars (Kreiss et al. 2002), leaving no doubt about significant excesses of symptoms, self-reported physician diagnoses, and measured airways obstruction. While some plants had too few workers for us to have power to detect statistically significant excesses, we found cases of obstructive impairment in five of six plants, most of which were moderate to severe. The population rate of severe airways obstruction with FEV_1 below 40% of predicted is about one in a thousand (Kreiss 2007b). Taken as a body of work, the absence of statistically significant differences in any one plant does not prevent the overall conclusion that fixed obstruction was an industry-wide risk, as has now been shown by cases documented in numerous flavoring manufacturing plants (CDC 2007). Most of the workers did not have any significant history of farm work exposures, and the comparison of NIOSH data to national reference data from the Third National Health and Nutrition Examination Survey (NHANES III) is particularly apt, because NIOSH provided the same pool of volume spirometers, training, and quality assurance to the NHANES project as for our own work. No other robust national or regional population prevalence data are available for external comparisons, and the excess risk—particularly excess severe obstruction prevalence—far exceeds any regional or rural-urban differences. No incidence data exist, and we did not report incidence in our cross-sectional studies, as was suggested by Galbraith and Weill.

Omissions include Galbraith and Weill's observation that the prevalences of obstructive abnormality are similar between ever-mixers and never-mixers, while neglecting to point out that mixers who have >12 months tenure in their jobs, compared to those with less tenure, have significantly lower percent predicted FEV_1 and greater prevalence of exertional dyspnea, and a marginally significant excess of airways obstruction (19.2 vs. 4.4%) (Kanwal et al. 2006). In arguing that many persons in the index plant had non-occupational exposures which might have been associated with lung health risk, they neglected to mention that the subset of workers without flavoring exposure had statistically higher prevalence of such exposures compared to production workers, who had the burden of excess disease.

Finally, we would like to clarify that diacetyl vapor is a hazard that meets multiple criteria for causation of the severe respiratory impairment found in flavoring-exposed workers (Kreiss 2007b). In our early published work (Kreiss et al. 2002), we used diacetyl as a marker of flavoring exposure because it was the predominant chemical in plant air in the microwave popcorn industry. This statement, accurate in 2001, has been misused by many. Since that time, we have demonstrated the criteria for causal associations that have long been honored in epidemiologic study: strength of association; consistency across many industries and investigators; temporal requirement in incident cases; exposure–response relation; and biologic plausibility. In addition, diacetyl manufacturing workers have developed clinical bronchiolitis obliterans with exposures much less complex than those found in microwave popcorn and flavoring manufacturing workers (van Rooy et al. 2007). For these reasons, the NIOSH has committed resources for diacetyl risk assessment toward development of a criteria document for a recommended exposure limit. However, the

existing scientific evidence does not preclude a contribution of other flavoring ingredients to work-related lung disease through their own toxicity or through their effects on diacetyl absorption and metabolism. We agree with Galbraith and Weill that the scientific investigation of mechanism and other flavoring ingredients needs to continue.

In addition to this review, Drs. Galbraith and Weill have authored letters critical of two of the most recently published scientific studies on diacetyl toxicity (Finley et al. 2008; Galbraith and Weill 2008). In each case, the authors of those studies have defended their work by correcting misconceptions, inaccuracies, and omissions (Morgan et al. 2008b; van Rooy et al. 2008). While we understand the role that Drs. Galbraith and Weill have played in keeping the scientific community focused on flavoring-related lung disease, the findings from multiple workplace and animal studies constitute strong evidence that exposure to butter flavorings and diacetyl can lead to severe occupational lung disease. We hope that this letter helps to separate the known semantic difficulties with the use of the term bronchiolitis obliterans from the scientific issues. Uncertainties raised by such critical reviews should not delay preventive action to diminish the occupational lung disease associated with flavorings exposures.

Conflict of interest statement The authors declare that they have no conflict of interest. As U.S. government workers, we have no benefits from any commercial entity directly or indirectly for any of our work. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the NIOSH.

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