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# Re: Pierce et al. Diacetyl and 2,3-Pentanedione Exposures Associated with Cigarette Smoking: Implications for Risk Assessment of Food and Flavoring Workers *Crit Rev Toxicol*, 2014; 44(5): 420-435

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## LETTER TO THE EDITOR

**Re: Pierce et al. Diacetyl and 2,3-pentanedione exposures associated with cigarette smoking: implications for risk assessment of food and flavoring workers Crit Rev Toxicol, 2014; 44(5):420–435****Microwave popcorn production workers and smoking**Muge Akpınar-Elci<sup>1</sup> and Omur Cinar Elci<sup>2</sup><sup>1</sup>Center for Global Health, College of Health Sciences, Old Dominion University, Norfolk, VA, USA and <sup>2</sup>Department of Public Health and Preventive Medicine, School of Medicine, St. George's University, WI, Grenada**To the Editor:**

We were greatly dismayed by Pierce et al.'s report on the associations between exposure to Diacetyl and 2,3-pentanedione and cigarette smoking (Pierce et al. 2014). It stated that "Diacetyl and 2,3-pentanedione exposures from cigarette smoking far exceed occupational exposures for most food/flavoring workers who smoke." Based on this finding, the authors suggested that "previous claims of a significant exposure–response relationship between diacetyl inhalation and respiratory disease in food/flavoring workers were confounded because none of the investigations considered or quantified the non-occupational diacetyl exposure from cigarette smoke, yet all the cohorts evaluated had considerable smoking histories."

Regretfully, the authors misrepresented cases of Bronchiolitis obliterans among the microwave popcorn production workers, who were exposed to artificial butter flavoring. Pierce et al.'s claim that "all of the cohorts evaluated had considerable smoking histories" is false. Our study documented the sentinel cases and clearly stated that of the nine cases only one of the workers was a current smoker (Akpınar-Elci et al. 2004). Three (33.3%) of the remaining eight workers had never smoked. The remaining five (55.6%) sentinel cases were former smokers. Regardless of any clinical, toxicological, or exposure analysis, basic principles of epidemiology highlight the importance of identifying such unusual disease clusters among workers in the same plant. A cluster of such a rare disease as Bronchiolitis obliterans indicates a possible causal factor related to the work environment and/or occupational exposures.

Pierce et al. also included our two epidemiological studies in their review. Throughout our occupational health and inflammatory markers investigation among the microwave

**History**

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popcorn workers, we controlled for possible confounding effects of smoking, age, and gender. In one of these two studies, we investigated whether exhaled nitric oxide (FE<sub>NO</sub>) levels were associated with exposure, respiratory symptoms, or airways obstruction (Akpınar-Elci et al. 2006). A questionnaire, spirometry, and FE<sub>NO</sub> measurements were completed by 135 workers—52.6% of whom were nonsmokers. Workers, who were current smokers, had significantly lower FE<sub>NO</sub> levels when compared with nonsmokers ( $p < 0.01$ ). FE<sub>NO</sub> levels were also low in the high-exposure group compared with those of the low-exposure group ( $p < 0.05$ ). When we excluded smokers, FE<sub>NO</sub> levels were still lower in the high-exposure group than those in either the healthy control group or the low exposure group. A low FE<sub>NO</sub> level is not a normal finding and has been associated with lung diseases other than asthma such as primary pulmonary hypertension, COPD, cystic fibrosis, and ciliary dyskinesia. (Chatkin et al. 1999, Clini et al. 2000, Kharitonov and Barnes 2001) Although a FE<sub>NO</sub> increase or decrease depends on the outcome of exposure, previous studies have shown that changes in FE<sub>NO</sub> depend on the type of exposure. Kim et al. reported an inverse exposure–response between the FE<sub>NO</sub> and metal exposure in boilermakers similar to our results: Occupational exposure was associated with a significant decrease in FE<sub>NO</sub> (Kim et al. 2003a, b).

Our other study evaluated the association between airway inflammation markers from induced sputum and popcorn flavoring agent exposure among 81 workers (of whom 53.1% were nonsmokers). (Akpınar-Elci et al. 2005) Because current smoking is known to affect cell count, we adjusted our analysis of associations between exposures, symptoms, lung function, and airways inflammation for smoking status. We calculated the smoking-adjusted odds ratios (ORs) to assess relationships

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among various symptoms or worker characteristics and high sputum cell counts. In this study, absolute neutrophil counts were higher in nonsmoking popcorn production workers compared to a nonsmoking healthy external control group. Even after controlling for smoking, the relationship between high exposure to flavoring agents and neutrophilic inflammation remained significant.

Therefore, it is important to note that:

1. Eight of nine sentinel cases and a significant portion of workers who participated in our studies were nonsmokers.
2. All of our analyses have been carefully controlled for confounds with age, gender, and smoking.
3. Besides all these observations, nonsmoker workers demonstrated cyto-pathological changes, which are signs and symptoms of a suspected occupational exposure to butter flavoring agents.

We would have expected Pierce et al. to have reviewed our observations more carefully and to have noted our findings that strongly indicate a relationship between occupational butter flavoring exposure and respiratory diseases among popcorn production workers. When we conducted our research, we adhered to basic ethical principles that dictate objectivity and fairness in evaluating the scientific evidence. These principles have been summarized in the Hippocratic Oath as "*primum non nocere*": "First, do no harm". We believe that failing to practice this oath raises questions regarding the validity of scientific conclusions. We are aware that the conclusions that we published might have a significant impact on human health, which we all aim to protect.

## Declaration of interest

Neither author ever offered testimony during any regulatory proceeding concerning flavoring agents nor was an expert witness in any related litigation. Each author completed research on flavoring during his/her employment at The National Institute for Occupational Safety and Health (NIOSH). The authors have sole responsibility for this letter. They do not have any conflicts of interest to declare.

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