



Respiratory follow-up pre- and post-engineering controls or cessation of added diacetyl at four microwave popcorn facilities

To the Editor:

We previously reported significant cross-sectional decrements in forced expiratory volume in 1 s (FEV_1) from 2005 to 2006 among mixing room employees (mixers) with exposure to the butter flavouring diacetyl at four US microwave popcorn facilities [1]. Other studies with similar findings have been summarised by the US National Institute for Occupational Health and Safety (NIOSH) [2]. Diacetyl (2,3-butanedione) is a soluble diketone that vaporises when heated. Though use in the popcorn industry has declined, diacetyl has been documented in cigarette smoke, electronic cigarettes and coffee [2]. The aim of this follow-up study was to examine lung function in three cohorts. Cohort 1 began their employment before 2003, and aimed to identify any significant longitudinal decline among those with higher exposures and less extensive exposure controls. Cohort 2 began their employment between 2003 and 2007, and examined the impact of changes after implementation of additional exposure controls. Cohort 3 began their employment during or after 2008, when added diacetyl use was discontinued. These cohorts included all current full-time employees at the four facilities tested previously. Informed consent, and pulmonary and work histories were collected.

Pulmonary function tests (PFTs) were conducted on-site by technicians with NIOSH-certified training [1] in accordance with published guidelines [3]. All 4409 PFTs received expert review (R.T. McKay) for inclusion. Predicted values included the previously used 6% lower adjustment for Asians [4, 5]. PFTs were administered three times in 2005, yearly from 2006 to 2009, and in 2011. There were 25 nonparticipants; 98% participated at least once. Several Asian ethnicities were represented in Plant 4, which closed in 2007. Excluded from statistical analyses were office employees with minimal potential for exposure ($n=21$), those with unusable PFTs or incomplete occupational histories ($n=9$), and those having cardiovascular disease ($n=3$).

Diacetyl use in the facilities began in 1994. To reduce exposure, engineering and work practice changes were implemented in 2003–2005 including isolating the mixing rooms, increasing mixing room air ventilation, treating powders with 0.25% food grade oil to minimise dust, installing exhaust hoods for quality assurance operators, and in 2003, requiring mixers to wear powered air purifying respirators. Exposure monitoring began at all plants in 2005 [6]. Our previous job–exposure matrix [1, 6, 7] was utilised with these updates: additional ventilation controls in Plant 1 in June 2006 reduced mean exposures for nonmixers (0.07 to 0.02 ppm) and mixers (0.94 to 0.07 ppm); and subsequent sampling in Plant 2 demonstrated lower mean exposures for nonmixers (0.12 to 0.09 ppm) and mixers (0.84 to 0.61 ppm). While these measurements are considerably lower than in other studies [2], they exceeded the subsequent 2016 NIOSH Recommended Exposure Limit of 5 ppb [2]. Added diacetyl use was phased out late 2007 and 2,3-pentanedione was used for 1–2 months. In early 2008, the flavouring agents were reformulated and contained no added diacetyl, acetoin or 2,3-pentanedione. Sampling in 2008 after this change almost



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In a 7-year study at 4 microwave popcorn facilities, mixing room employees exposed to diacetyl prior to the introduction of respirators showed significant loss of lung function but did not continue to decline longitudinally faster than other job categories <http://bit.ly/2xwWRiw>

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exclusively gave results below the limit of detection for diacetyl. Cohort 1 (pre-2003) included 302 non-Asian males (NAMs), 47 Asian males, 181 non-Asian females (NAFs) and 64 Asian females. The Asian females were excluded from analyses as 62 out of 64 were in the “other” job category, and had minimal and homogenous exposure. The mean number of PFTs for cohort 1 was 4.9 and 85% had three or more PFTs. At the last PFT, their mean cumulative diacetyl was 0.9 ppm-years (range 0.1–25.3 ppm-years), mean employment duration was 11.7 years (range 2.2–23.8 years) and mean tobacco exposure for ever-smokers was 20.6 pack-years (range 0.1–100 pack-years). The Asian males averaged longer employment and higher exposure estimates than NAMs and NAFs.

Cohort 2 (2003–2007) included 300 NAMs and 155 NAFs, each with mean of 2.7 PFTs. At the last PFT, their mean cumulative diacetyl exposure was 0.1 ppm-years (range 0.1–0.5 ppm-years), mean employment duration was 2.7 years (range 0.1–8.5 years) and mean tobacco exposure for ever-smokers was 15.0 pack-years (range 0.1–87.7 pack-years).

Cohort 3 (≥ 2008) included 114 NAMs and 42 NAFs, with a mean of 1.6 and 1.8 PFTs, respectively. At the last PFT, their mean employment duration was 1.8 years (range 0.1–4.2 years) and mean tobacco exposure for ever-smokers was 15.8 pack-years (range 0.1–74 pack-years).

Linear mixed regression models used all available PFTs to evaluate associations between exposure metrics and % predicted forced vital capacity (FVC) and FEV₁ stratified by sex and race (Asian or non-Asian). Three exposure variables for cohort 1 included: 1) job category (pre-2003 mixer, pre-2003 intermittent mixer (maintenance and supervisors), pre-2003 quality assurance operator and other); 2) logarithmically transformed cumulative exposure at first PFT; and 3) duration of employment since 1994. Each model included an interaction term of time since first test (TSFT). TSFT adjusts for changes from the first to each subsequent test. Cohort 2 was analysed by current exposure at time of PFT \times TSFT and employment duration. Few mixers began their employment after 2003, preventing a separate job category analysis. No Asians were included in cohort 2 or 3 as only 15 began their employment after 2003. Cohort 3 was analysed by employment duration since there was no current added diacetyl. All regression models were adjusted by body mass index (BMI) at first PFT, change in BMI since first PFT, current smoking status and pack-years of smoking.

Table 1 shows the primary analysis for cohort 1. Pre-2003 job categories of mixer, intermittent mixer and quality assurance operator as main effects and by interaction with TSFT were compared to other jobs. For NAMs, the main effects of pack-years of smoking, BMI at first PFT, BMI change and TSFT were consistently associated with significant losses in both % predicted FEV₁ and FVC. For the mixer category main effect there was a significant loss in % predicted FEV₁ for NAMs (n=27) and Asian males (n=7) of -7.92 ($p<0.01$) and -13.7 ($p<0.01$), respectively. Asian male mixers had a significant loss of % predicted FVC of -9.94 ($p<0.02$). No significant changes in the main effect were observed for NAF mixers (n=8) or any group within intermittent mixer or quality assurance job categories. A small but significant annual longitudinal decline was observed for NAF quality assurance operators (n=20) for % predicted FVC of -0.75 ($p=0.04$) and was similar for FEV₁ (-0.71 , $p=0.06$). No similar annual longitudinal decline was noted for any group within the mixers or intermittent mixers. No group showed a significant longitudinal decline when evaluating logarithmically transformed cumulative exposure at first PFT \times TSFT or employment duration \times TSFT.

For cohort 2, current exposure \times TSFT was not associated with any significant longitudinal decline in % predicted FVC or FEV₁ for either NAFs or NAMs. Small but significant annual losses were observed for % predicted FVC and FEV₁ when employment duration was examined: for NAFs, -0.31 ($p=0.04$) and -0.48 ($p<0.01$), and for NAMs -0.47 ($p<0.01$) and -0.65 ($p<0.01$), respectively. In cohort 3, employment duration analysis showed no significant loss for either NAFs or NAMs.

In a *post hoc* analysis, we identified employees with at least five tests covering >4 years (n=291). An unadjusted regression line was plotted through each employee's FEV₁ data and the slope was evaluated for accelerated decline of >90 mL \cdot year⁻¹ as has been used by others [8, 9]. 26 (8.9%) of the 291 met these criteria: mixers, two (9.1%) out of 22; intermittent mixers, six (8.1%) out of 74; quality assurance operators, two (18.2%) out of 11; and others, 16 (8.7%) out of 184. Of these 26, six had normal lung function at the last PFT. Among the nonsmokers (n=112), the mean decline in FEV₁ was 30.0 mL \cdot year⁻¹ and for ever-smokers (n=179), the decline was 45.1 mL \cdot year⁻¹. To allow comparison of abnormal spirometry with other microwave popcorn facilities [2], results from the last PFT for cohorts 1 and 2 were: spirometric abnormalities, 164 (16.7%) out of 982; subdivided as restrictive, n=79; obstructive, n=65; and mixed, n=20 (abnormal pattern definitions match those used by NIOSH) [8]. Three workers with invalid FVC at the last test were not included. The percentage of restrictive changes in workers with abnormal spirometry (79 out of 164, 48.2%) was similar to those documented in other diacetyl-exposed workers [2]. The overall rate of restrictive changes (79 out of 982, 8.0%) was increased compared to the US background rate of 5.4% [10]; the rate was similar between nonsmokers (31 out of 364, 8.5%) and ever-smokers (48 out of 618, 7.8%). We have previously reported on lung obstruction among these employees [1].

TABLE 1 Relationship between job category and lung function for those beginning their employment pre-2003 (cohort 1) by sex and racial group

Variable	Non-Asian males (n=302)		Asian males (n=47)		Non-Asian females (n=181)	
	Estimated change in % predicted FEV ₁ (p-value)	Estimated change in % predicted FVC (p-value)	Estimated change in % predicted FEV ₁ (p-value)	Estimated change in % predicted FVC (p-value)	Estimated change in % predicted FEV ₁ (p-value)	Estimated change in % predicted FVC (p-value)
Pack-years of smoking	-0.30 (<0.01)	-0.13 (<0.01)	-0.13 (0.27)	-0.03 (0.76)	-0.31 (<0.01)	-0.16 (0.05)
Current smoker[#]	-0.37 (0.56)	-0.08 (0.88)	-0.91 (0.70)	2.9 (0.21)	-0.90 (0.32)	0.15 (0.86)
BMI at first PFT	-0.38 (<0.01)	-0.62 (<0.01)	-0.66 (0.12)	-1.13 (<0.01)	-0.14 (0.35)	-0.38 (<0.01)
BMI change since first PFT	-0.45 (<0.01)	-0.43 (<0.01)	-0.39 (0.36)	-0.38 (0.35)	-0.2 (0.01)	-0.27 (<0.01)
Time since first PFT	-0.57 (<0.01)	-0.55 (<0.01)	-0.39 (0.51)	0.75 (0.19)	-0.30 (0.02)	-0.23 (0.04)
Mixer	-7.92 (<0.01)	-1.78 (0.46)	-13.7 (<0.01)	-9.94 (0.02)	4.13 (0.44)	-0.70 (0.89)
Intermittent mixer	2.74 (0.10)	2.63 (0.07)	6.19 (0.15)	6.70 (0.12)	2.47 (0.65)	2.03 (0.69)
QA	2.05 (0.79)	4.06 (0.55)	NA	NA	-1.38 (0.70)	-2.12 (0.52)
Interaction mixer×time since first PFT[¶]	0.02 (0.96)	-0.16 (0.64)	0.68 (0.62)	0.72 (0.59)	0.00 (0.99)	0.40 (0.43)
Interaction intermittent mixer×time since first PFT[¶]	0.41 (0.06)	0.27 (0.17)	0.88 (0.34)	-0.12 (0.90)	-0.77 (0.12)	-0.61 (0.18)
Interaction QA×time since first PFT[¶]	1.3 (0.29)	1.3 (0.26)	NA	NA	-0.71 (0.06)	-0.75 (0.04)

Non-Asian males: mixers (n=27), intermittent mixers (n=111), quality assurance operators (QA) (n=3), other (n=161); Asian males: mixers (n=7), intermittent mixers (n=6), QA (n=0), other (n=34); non-Asian females: mixers (n=8), intermittent mixers (n=8), QA (n=20), other (n=145). FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; PFT: pulmonary function test; NA: not applicable. [#]: compared with never- and ex-smokers. [¶]: compared to “others” defined as employees without employment as pre-2003 mixer, pre-2003 intermittent mixer (maintenance and supervisors) or pre-2003 QA operator.

The primary analysis showed that in cohort 1, only NAM and Asian male mixers demonstrated a significant loss in % predicted FEV₁ as they did in our previous cross-sectional analyses [1]. An additional finding was the significant loss in % predicted FVC in Asian male mixers. Only quality assurance workers demonstrated significant longitudinal declines in % predicted FEV₁ and FVC. Two out of 11 quality assurance workers with at least five tests over >4 years had abnormal spirometry at time of the last test (one obstructive and one restrictive pattern). From our previous analysis [1], among the quality assurance workers in cohort 1 (n=23), there was one restrictive and one mixed pattern based on best of three tests in 2005. In contrast to a Missouri popcorn plant, no increased obstructive pattern was identified in the quality assurance operators [11]. In cohort 1, there was no association between logarithmic cumulative exposure or duration of employment and longitudinal decline. In cohort 2, employment duration but not current exposure was associated with annual decline in % predicted FEV₁ and FVC.

In conclusion, the pre-2003 mixers, the work group at highest risk of an adverse impact from historical diacetyl exposure, demonstrated a significant but relatively stable loss in lung function over time. This study confirms an increased restrictive lung function pattern in microwave popcorn facility workers in comparison to the general population. The cause of significant parallel declines in % predicted FVC and FEV₁ in the quality assurance workers in cohort 1, and especially the NAFs and NAMs in cohort 2, is not clear in view of lower cohort 2 cumulative exposures. One possible explanation is that chronic occupational exposure to diacetyl can result in low-grade bronchiolitis reflected by small annual decrements in both FVC and FEV₁ parameters, and subsequent restrictive pattern. Historically, when full-shift exposures were higher and perhaps associated with short-term excursions, the health outcome was a more significant bronchiolitis resulting in airway obstruction and, in susceptible individuals, constrictive bronchiolitis. Loss of these workers from the workforce would result in observing a healthy worker effect that, with continuing employment, might be associated with a long-term impact from chronic low-grade bronchiolitis leading to a restrictive pattern.

Strengths of this study include length of follow-up, high participation rate, high-quality spirometry and measured full-shift exposures. A limitation is the lack of short-term peak exposure measurements and that pre-2005 exposures were assumed the same as those measured in 2005. Given the 2003–2005 exposure controls, this assumption may underestimate pre-2005 exposures, resulting in a potential exposure misclassification. However, samples from a 2003 NIOSH Health Hazard Evaluation [12] in Plant 1 were similar to those obtained in 2005 [6]. Exposures in Plant 1 may not be representative of other facilities. Furthermore, the follow-up time for cohort 3 may be insufficient to evaluate any potential hazard from the flavouring formulation used during that time. The 6% adjustment used for Asians may be too small for some Asian ethnicities. In addition, the relatively small number of mixers and quality assurance workers limits overall statistical power, and the results can be impacted by outlying data points.

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