Adjustment for temporal confounders in a reanalysis of a case–control study of beryllium and lung cancer

M K Schubauer-Berigan,[1] J A Deddens,[1] K Steenland,[2] W T Sanderson,[3] M R Petersen[1]

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[1] National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Cincinnati, Ohio, USA; [2] Emory University School of Public Health, Atlanta, Georgia, USA; [3] University of Iowa School of Public Health, Iowa City, Lowa, USA

Correspondence to: Dr Mary K Schubauer-Berigan, NIOSH, DSHEFS, MS-R15, 4676 Columbia Pkwy, Cincinnati, Ohio 45226, USA; zcg3@cdc.gov

Accepted 7 September 2007
Published Online First 21 September 2007

ABSTRACT

Objectives: To evaluate potential confounding of the association between beryllium and lung cancer in a reanalysis of data from a published case–control study of workers at a beryllium processing facility.

Methods: The association of cumulative and average beryllium exposure with lung cancer among 142 cases and five age-match controls per case was reanalysed using conditional logistic regression. Adjustment was made independently for potential confounders of hire age and birth year. Alternative adjustments to avoid taking the logarithm of zero were explored.

Results: Adjustment for either birth cohort or hire age (two highly correlated factors) attenuated lung cancer risk associated with cumulative exposure; however, lung cancer risk was significantly associated with average exposure using a 10-year lag following adjustment. Stratification of analyses by birth cohort found greater lung cancer risk from cumulative and average exposure for workers born before 1900 than for workers born later. The magnitude of the association between lung cancer and average exposure was not reduced by modifying the method used to take the log of exposure.

Conclusion: In this reanalysis, average, but not cumulative, beryllium exposure was related to lung cancer risk after adjustment for birth cohort. Confounding by birth cohort is likely related to differences in smoking patterns for workers born before 1900 and the tendency for workers hired during the World War II era to have been older at hire.

Beryllium, a metal with unique properties rendering it useful as a stable, lightweight alloy component, has been the subject of intensive epidemiological investigation since its immunological properties and role in causing a granulomatous lung disease (chronic beryllium disease) became known decades ago. Beryllium has been designated a known human carcinogen by the International Agency for Research on Cancer,[1] based largely upon epidemiological studies of two cohorts conducted at the National Institute for Occupational Safety and Health (NIOSH).[2 3]

A lung cancer case–control study, nested within one of the NIOSH cohorts (in Reading, PA), was recently published.[4] This study of 142 cases, each matched to five controls on attained age and race, concluded that, with a 20-year lag, cumulative, average and maximum beryllium exposures were associated with lung cancer. No direct information on smoking was available in the case–control study, and the study did not adjust for birth year. A critique[5] of this study has been largely refuted by the study authors and others.[6 7] However, one remaining criticism was the observation that cases were hired at younger ages (average of 33) than controls (average of 37). This was posited by Deubner and colleagues[5] as due to bias in the selection of cases and controls through incidence density (or risk set) sampling. However, risk set sampling has been shown to provide unbiased estimates of cohort parameters in numerous studies. In this analysis we ascertain whether uncontrolled confounding results in the observed difference in age at hire of cases and controls. More importantly, we explore the effect of adjustment for temporal factors (independently associated with both beryllium exposure and likely smoking patterns) on lung cancer risk in the case–control study of Sanderson and colleagues.[4]

The objective for the reanalysis was to properly adjust the case–control study for the effects of birth cohort, to account for known differences in smoking rates by birth year. A minor objective was to evaluate the choice of exposure value added in continuous analyses using the log of dose. Life table analyses and the vast majority of cohort[2] and incidence-density-sampled case–control[8–11] studies of lung cancer adjust, or evaluate adjustment, for calendar year (or, approximately equivalently, birth cohort) in addition to age, in either the design or analysis phase. This is especially important for lung cancer because age-specific rates increased greatly across birth cohorts between the late 1800s and about 1930, peaking in the late 1920s for males, due primarily to birth cohort changes in cigarette smoking rates.[12 13] An example of the expected birth cohort effect (derived from the variation in age-adjusted US lung cancer rates due to differences in smoking rates by birth year) is shown in the first two columns of table 1 (data from Brown and Kessler[12]). Most exposures also exhibit secular variability; thus, birth cohort or (approximately equivalently when combined with age) calendar year is a very important potential confounder. We also separately evaluated age at hire, which is not typically considered a confounder, to determine the nature of its association with birth cohort and lung cancer risk, in order to seek an explanation for the observation, noted again in a recent analysis,[14] that controls in the Sanderson study were hired at older ages than cases. Lastly, we considered alternative choices about the minimal exposure value to be added when using the log of exposure in continuous exposure-risk analyses (to avoid taking the log of zero for those who were unexposed). This choice was also criticised in the recent analysis by Levy and colleagues.[14]

Table 1 Expected and observed birth cohort effect in the Sanderson *et al*[4] case–control study of lung cancer following beryllium exposure

Birth cohort*	Birth cohort effect C_i in US males*	Birth cohort midpoint	Fraction of Sanderson birth cohort having category midpoint year			
			Born ⩽1899	Born 1900–1910	Born 1911–1920	Born ⩾1921
1869–1877	0.13	1873	0.010	0	0	0
1874–1882	0.37	1878	0.109	0	0	0
1879–1887	0.64	1883	0.168	0	0	0
1884–1892	0.96	1888	0.243	0	0	0
1889–1897	1.22	1893	0.272	0	0	0
1894–1902	1.42	1898	0.198	0	0	0
1899–1907	1.56	1903	0	0.468	0	0
1904–1912	1.64	1908	0	0.532	0	0
1909–1917	1.72	1913	0	0	0.471	0
1914–1922	1.79	1918	0	0	0.529	0
1919–1927	1.85	1923	0	0	0	0.644
1924–1932	1.92	1928	0	0	0	0.248
1929–1937	1.87	1933	0	0	0	0.092
1934–1942	1.75	1938	0	0	0	0.016
1939–1947	1.52	1943	0	0	0	0
1944–1952	1.21	1948	0	0	0	0
Average expected birth cohort effect on lung cancer rates in Sanderson case–control study			1.00	1.74	2.03	2.26
Observed birth cohort rate ratios in Sanderson case–control study (95% CI)			1.00	2.59 (1.41 to 4.75)	2.55 (1.37 to 4.74)	2.61 (1.35 to 5.04)

The first three columns contain the expected relative lung cancer rates for male birth cohorts (termed "birth cohort effect") spanning a 100-year period, based on US data. Weights are the fraction in the case–control group for the birth year range, and they are applied to the midpoint to assess the expected effect of birth cohort.
*From table 2 of Brown and Kessler[12] parameter estimate (C_i) for birth cohort i. Exp(C_i) represents the age-adjusted relative rate of lung cancer in that birth cohort group.

METHODS

The dataset used in the previous NIOSH nested case–control study[4] was reanalysed using conditional logistic regression (conditioning on strata defined by case age). Average and cumulative exposures were analysed using the values reported in the original case–control study. To estimate the expected magnitude of the birth cohort effect on lung cancer in the case–control study, we divided the study group into birth cohort quartiles and determined the fraction of each quartile represented by the midpoint of a birth year category for which birth cohort differences in lung cancer risk, largely from smoking rate differences, have been calculated for US men (table 1).[12] The product of the exponentiated birth cohort parameter (from table 2 of Brown and Kessler[12]) and the case–control fraction for each birth year midpoint was summed for each birth cohort quartile. These expected average birth cohort effects were standardised to the lowest quartile and compared across each birth cohort quartile to the actual observed univariable birth cohort risk ratio calculated for the case–control study.

The effect of birth cohort adjustment on the beryllium–lung cancer association was evaluated by adjusting in a multivariable model for indicator variables for the birth cohort quartiles. Similar adjustment for hire age was conducted separately. Some analyses were conducted within two separate strata representing the earliest birth year quartile (those born before 1900) and the combined upper three quartiles. A formal test of effect modification was conducted between beryllium exposure (cumulative and average) and birth cohort by conducting a likelihood ratio test of nested models with and without interaction terms against a χ^2 distribution with degrees of freedom equal to the number of interaction terms added.

For analyses based on trends in exposure–response with the log of dose (ie, table IV of the Sanderson study[4]), the original choice of minimal value to be added to all exposures (generally, 0.01) was compared against analyses in which the lowest detectable exposure level divided by 2 was added to each worker's exposure. All analyses were conducted using SAS v 9.1.

For all analyses, the objective was to replicate original analyses by Sanderson and colleagues; however, we have also included confidence interval (CI) estimates in all analyses.

RESULTS

Table 1 shows the univariable lung cancer rate ratios observed for the later birth cohorts, as compared to the workers born before 1900. The patterns of observed risk are similar to those estimated from literature values, although the magnitude of the rate ratios is slightly greater than expected. Comparisons of the average date of birth and hire age of workers across (unlagged) cumulative exposure strata show that cases were born about 5 years later than controls in nearly all exposure strata and were hired at a younger age across nearly all exposure strata (data not shown).

Tables 2 and 3 replicate, using the adjustments described in the Methods, the cumulative and average exposure sections of tables III and IV of the Sanderson study.[4] In table 2, within each exposure type (ie, cumulative or average) and lag length (0-, 10- and 20-year), the quartiles of exposure are shown, and the unadjusted OR estimates are essentially the same as the risk estimates in table III of the Sanderson study.

The unadjusted analyses using cumulative exposure (table 2A) show little evidence of beryllium-associated risk until a 20-year lag is used. Adjusting for either birth cohort or age at hire greatly attenuates the lung cancer risk estimates associated with cumulative exposure; however, some evidence of elevation in the non-baseline categories remains with a 20-year lag. Within strata defined by birth years before and after 1900, neither birth cohort shows a positive association between unlagged cumulative beryllium exposure and lung cancer risk (table 2A). With a 10- or 20-year lag, workers born in 1900 or later show little evidence of increased lung cancer risk associated with beryllium exposure, while workers born before 1900 show weak elevation in risk with increased exposure.

For average exposure, both unlagged and lagged analyses show elevations in lung cancer risk among the higher exposure

 Occup Environ Med 2008;65:379–383. doi:10.1136/oem.2007.033654

Table 2 Odds ratios (95% CI) replicating table III of Sanderson *et al*[4] for cumulative and average exposures

A. Odds ratios (95% CI) replicating table III of Sanderson *et al*[4] for cumulative exposure, adjusting for birth year (BY) and age at hire (AH), and stratifying results on birth year before 1900 and during or after 1900

Quartiles of cumulative exposure (μg/m³ days)							Dose × birth cohort interaction χ^2, df
0 Lag	All birth years	Quartile ranges	<1425	1426–5600	5601–28 123	>28 124	
		OR (unadjusted)	1.00	0.73 (0.44 to 1.18)	0.85 (0.53 to 1.36)	0.57 (0.34 to 0.96)	
		OR (BY-adjusted)*	1.00	0.77 (0.47 to 1.27)	0.89 (0.55 to 1.44)	0.61 (0.36 to 1.02)	
		OR (AH-adjusted)†	1.00	0.75 (0.45 to 1.23)	0.85 (0.53 to 1.37)	0.56 (0.33 to 0.94)	
	Birth year <1900	OR (unadjusted)	1.00	0.58 (0.08 to 4.02)	0.66 (0.15 to 3.01)	0.09 (0.01 to 1.11)	6.62, 3, p = 0.085
	Birth year ⩾1900	OR (unadjusted)	1.00	0.65 (0.36 to 1.14)	0.82 (0.48 to 1.40)	0.66 (0.37 to 1.16)	
10-Year lag	All birth years	Quartile ranges	<808	809–3970	3971–20 996	>20 997	
		OR (unadjusted)	1.00	1.38 (0.83 to 2.29)	1.38 (0.83 to 2.29)	0.92 (0.53 to 1.60)	
		OR (BY-adjusted)*	1.00	1.27 (0.76 to 2.11)	1.23 (0.73 to 2.05)	0.83 (0.48 to 1.46)	
		OR (AH-adjusted)†	1.00	1.24 (0.74 to 2.08)	1.18 (0.71 to 1.98)	0.78 (0.45 to 1.37)	
	Birth year <1900	OR (unadjusted)	1.00	1.94 (0.39 to 9.78)	2.59 (0.49 to 13.6)	0.53 (0.07 to 4.22)	5.35, 3, p = 0.148
	Birth year ⩾1900	OR (unadjusted)	1.00	1.02 (0.58 to 1.80)	0.97 (0.55 to 1.70)	0.74 (0.41 to 1.37)	
20-Year lag	All birth years	Quartile ranges	<20	21–2195	2196–12 376	>12 377	
		OR (unadjusted)	1.00	2.18 (1.25 to 3.82)	1.89 (1.06 to 3.36)	1.89 (1.06 to 3.36)	
		OR (BY-adjusted)*	1.00	1.46 (0.72 to 2.97)	1.29 (0.64 to 2.61)	1.30 (0.64 to 2.65)	
		OR (AH-adjusted)†	1.00	1.37 (0.66 to 2.84)	1.21 (0.59 to 2.52)	1.18 (0.56 to 2.50)	
	Birth year <1900	OR (unadjusted)	1.00	2.88 (0.45 to 18.5)	1.23 (0.22 to 6.76)	0.61 (0.09 to 4.39)	3.25, 3, p = 0.355
	Birth year ⩾1900	OR (unadjusted)	1.00	1.15 (0.54 to 2.48)	0.96 (0.44 to 2.09)	1.07 (0.50 to 2.32)	

B. Odds ratios (95% CI) replicating table III of Sanderson *et al*[4] for average exposure, adjusting for birth year (BY) and age at hire (AH), and stratifying results on birth year before 1900 and during or after 1900

Quartiles of average exposure (μg/m³)							Dose × birth cohort interaction χ^2, df
0 lag	All birth years	Quartile ranges	<11.2	11.3–24.9	25.0–34.0	>34.1	
		OR (unadjusted)	1.00	1.60 (0.94 to 2.72)	1.77 (1.03 to 3.04)	1.27 (0.72 to 2.23)	
		OR (BY-adjusted)*	1.00	1.68 (0.99 to 2.87)	2.02 (1.16 to 3.51)	1.33 (0.76 to 2.34)	
		OR (AH-adjusted)†	1.00	1.55 (0.91 to 2.65)	1.80 (1.04 to 3.11)	1.21 (0.69 to 2.12)	
	Birth year <1900	OR (unadjusted)	1.00	0.27 (0.02 to 3.91)	1.59 (0.16 to 16.0)	0.67 (0.05 to 9.31)	6.42, 3, p = 0.093
	Birth year ⩾1900	OR (unadjusted)	1.00	1.81 (1.03 to 3.15)	1.66 (0.91 to 3.02)	1.10 (0.60 to 2.01)	
10-Year lag	All birth years	Quartile ranges	<9.5	9.6–23.6	23.7–32.8	>32.9	
		OR (unadjusted)	1.00	2.41 (1.36 to 4.28)	2.70 (1.53 to 4.79)	1.81 (1.00 to 3.29)	
		OR (BY-adjusted)*	1.00	2.04 (1.14 to 3.66)	2.47 (1.38 to 4.42)	1.59 (0.87 to 2.91)	
		OR (AH-adjusted)†	1.00	2.05 (1.14 to 3.68)	2.38 (1.33 to 4.26)	1.54 (0.84 to 2.83)	
	Birth year <1900	OR (unadjusted)	1.00	0.68 (0.04 to 12.9)	7.25 (0.79 to 66.9)	4.10 (0.37 to 45.1)	11.90, 3, p = 0.007
	Birth year ⩾1900	OR (unadjusted)	1.00	1.84 (0.99 to 3.40)	1.77 (0.94 to 3.34)	1.07 (0.56 to 2.06)	
20-Year lag	All birth years	Quartile ranges	<1.0	1.1–19.3	19.4–25.5	>25.6	
		OR (unadjusted)	1.00	1.91 (1.06 to 3.44)	3.08 (1.74 to 5.45)	1.70 (0.94 to 3.07)	
		OR (BY-adjusted)*	1.00	1.29 (0.61 to 2.71)	2.14 (1.07 to 4.28)	1.19 (0.58 to 2.44)	
		OR (AH-adjusted)†	1.00	1.24 (0.58 to 2.65)	2.05 (0.99 to 4.24)	1.11 (0.52 to 2.37)	
	Birth year <1900	OR (unadjusted)	1.00	0.72 (0.07 to 7.55)	1.50 (0.30 to 7.60)	1.25 (0.23 to 6.64)	1.28, 3, p = 0.734
	Birth year ⩾1900	OR (unadjusted)	1.00	1.18 (0.54 to 2.60)	1.83 (0.84 to 3.96)	0.93 (0.42 to 2.06)	

*BY (birth year) categories: ⩽1899, 1900–1910, 1911–1920, ⩾1921; †AH (age at hire) categories: ⩽24.99, 25.0–34.99, 35.0–44.99, ⩾45.0.

categories, whether unadjusted, birth cohort-adjusted or hire age-adjusted (table 2B). This increased beryllium-associated risk appears more pronounced among the earlier birth cohort for the 10-year lag, although confidence intervals are very wide for the birth-cohort-specific results. Workers born later show an observed elevated risk in the two intermediate exposure groups, but no elevation in risk within the highest exposure category. With a 20-year lag, both birth cohorts show lung cancer risk attenuation in the highest exposure category, although risk remains elevated in the second highest exposure category.

Significant effect modification by birth cohort is observed only for average exposure with a 10-year lag (table 2B).

For continuous exposure-risk analyses (table 3), similar patterns are observed. Unadjusted analyses of the log of cumulative exposure (with 0.01 added to the dose of each worker to facilitate use of the logarithm for those with zero dose) show positive trends when applying a 10- or 20-year lag. Adjustment for birth year greatly attenuates the observed trend for cumulative exposure. However, the lung cancer risk associated with average exposure (lagged 10 years) changes little with adjustment for birth year, and remained significantly positive. Analyses conducted adding half the minimum exposure (to avoid taking the logarithm of zero) tend to reduce the cumulative beryllium exposure risk coefficient but to increase the average beryllium exposure risk coefficient.

Patterns observed for exposure tenure (duration) are very similar to those reported for cumulative exposure, and patterns observed for maximum exposure are very similar to those reported for average exposure (not shown). Reanalyses of the other tables contained within the Sanderson study[4] are available by contacting the authors of this analysis.

Table 3 Replication of table IV of Sanderson *et al*,[4] adjusting for birth year (BY*)

		Parameter estimate (95% CI)	Wald statistic	p Value
Logarithm of continuous cumulative exposure (μg/m³ days)				
0 lag	Unadjusted	−0.064 (−0.144 to 0.017)	2.38	0.123
	BY-adjusted†	−0.055 (−0.137 to 0.026)	1.79	0.181
10-Year lag	Unadjusted	0.060 (0.009 to 0.111)	5.35	0.021
	BY-adjusted†	0.038 (−0.019 to 0.094)	1.71	0.192
	BY-adjusted‡	0.018 (−0.051 to 0.086)	0.25	0.616
20-Year lag	Unadjusted	0.041 (0.007 to 0.075)	5.61	0.018
	BY-adjusted†	0.012 (−0.031 to 0.055)	0.30	0.585
	BY-adjusted‡	0.00034 (−0.069 to 0.070)	0.001	0.992
Logarithm of continuous average exposure (μg/m³)				
0 lag	Unadjusted	0.110 (−0.037 to 0.256)	2.15	0.143
	BY-adjusted†	0.119 (−0.025 to 0.264)	2.60	0.107
10-Year lag	Unadjusted	0.184 (0.083 to 0.286)	12.62	0.0004
	BY-adjusted†	0.159 (0.051 to 0.268)	8.25	0.0041
	BY-adjusted‡	0.164 (0.049 to 0.278)	7.79	0.0052
20-Year lag	Unadjusted	0.088 (0.029 to 0.148)	8.35	0.0039
	BY-adjusted†	0.048 (−0.026 to 0.123)	1.59	0.207
	BY-adjusted‡	0.069 (−0.048 to 0.186)	1.32	0.251

*BY (birth year) categories: ⩽1899, 1900–1910, 1911–1920, ⩾1921; †as in the original study (Sanderson *et al*[4]), 0.01 was added to each worker's cumulative and average exposures to permit use of logarithms for workers with zero dose (due to lagging); ‡(min exposure)/2 was added to each worker's cumulative and average exposures to permit use of logarithms for workers with zero dose (due to lagging).

DISCUSSION

These reanalyses show that, with adjustment for birth year, lung cancer risk shows little association with cumulative beryllium exposure. However, average and maximum beryllium exposures remain significantly related to lung cancer risk after birth cohort adjustment. As observed in the original study, lung cancer risk does not generally increase monotonically with exposure level. In contrast to the original study findings, the lag producing the most consistently elevated association with average exposure is 10 rather than 20 years. The choice of the minimal exposure value to be added in continuous analyses has the opposite effect on the associations with lung cancer for the cumulative and average exposure metrics: adding half the minimum estimable exposure value instead of 0.01 decreases the trend statistic for cumulative exposure but increases it for average exposure.

Birth year and hire age are highly correlated within the Reading cohort (Pearson's $r = -0.906$, $p<0.001$); hence they have virtually identical effects on the attenuation of beryllium-associated lung cancer risk. This correlation appears primarily to be due to the characteristics of male wartime-era workers (hired 1941–1945), who were all born before 1900 and hired during or after their late 40s. Examination of the distribution of age-at-hire by year-of-hire reveals this to be anomalous—the plant tended to hire younger men in every employment era except 1941–1945. Most (65%) of these wartime-era workers, hired at an older age, have their entire exposure history excluded in the 20-year lag analysis, because they tended to die of other causes before the lag period was reached. They also belong to a birth cohort with a baseline risk of lung cancer expected to be 60–90% lower than the others in the study (table 1). Thus, most of the workers in the lowest exposure group of the 20-year lag in the Sanderson analysis have no exposure because they were older when hired and did not survive the 20-year lag period. For this reason, stratifying results by birth cohort provides important supplemental information about beryllium-associated lung cancer risk.

The results of this reanalysis indicate that the differences in hire ages among cases and controls first noted by Deubner and colleagues[5] and recently remarked upon by Levy and colleagues[14] are primarily due to the fact that birth years are earlier among controls than among cases, resulting from the much lower baseline risk of lung cancer for men born before 1900. It would not be appropriate to simultaneously adjust for both birth year and age at hire in a reanalysis, as these factors are nearly collinear in this cohort and age at hire is not an independent risk factor for lung cancer.

It may be argued that beryllium exposure and birth cohort are so highly correlated that their effects cannot be separated even by adjusting for the latter in analyses of the association between exposure and lung cancer risk. The overall correlation between year of birth and the log of cumulative 20-year lagged exposure is moderate (Pearson's $r = 0.51$, $p<0.001$) but is greatly reduced (0.18, $p<0.001$) for the group of workers born in 1900 or later. The magnitude of these correlations is similar to that between year of birth and the log of average 20-year lagged exposure for the entire cohort ($r = 0.50$) and workers born in 1900 or later ($r = 0.16$). While it is true that earliest birth cohort is highly determinant of the tendency for beryllium exposure to be entirely lagged out, for the reasons described above (ie, most of these workers—hired at an older age during the World War II era—did not survive to achieve a 20-year lag), other birth cohorts in the Sanderson study did have a fairly wide range of exposures, although just 10% of the cases and controls born in 1900 or later had less than 1.5 μg/m³ average exposure, under a 20-year lag assumption.

Separate analysis of beryllium-associated lung cancer risk by birth cohort was done for two reasons: first, this interaction is of general interest. Second, evaluating risk separately by birth cohort may avoid potential bias by under-adjustment for birth cohort through its modelling as a covariate. We report that most of the subjects whose exposures lagged to zero were born before 1900. As this group (whose baseline risk from smoking is expected to be much lower than the later birth cohorts which comprise the higher exposure groups) forms a large proportion of those in the lowest exposure group, the identifiability of an unbiased exposure–response with simple model adjustment may be of concern. The results stratified by birth cohort show

Main messages

- Average (but not cumulative) beryllium exposure was related to lung cancer risk after adjusting for birth year, an important confounder in this case–control study.
- It is inappropriate to simultaneously adjust for age-at-hire and birth year, as these two factors are highly correlated in this study.
- Since the logarithm cannot be taken of zero exposure, a small value must be added to each exposure. The association of average beryllium exposure with lung cancer risk was affected little by the choice of value added.

Policy implications

- Beryllium has been designated a known human carcinogen by the International Agency for Research on Cancer.
- The quantitative association of different beryllium metrics with lung cancer risk may be useful for risk assessment.

modest evidence of effect modification by year of birth, which is particularly strong for average beryllium exposure with a 10-year lag. Workers born before 1900 tended to have higher beryllium-associated lung cancer risk with either cumulative or average exposure than did workers born later. This observation may reflect chance variation (particularly for the cumulative exposure metric), a non-multiplicative interaction of smoking with beryllium (as workers born early belonged to a birth cohort that smoked less than those born later) or a non-linear exposure–response curve, or it may be due to underestimation of beryllium exposures during the early years of operation, when these workers were employed.

In summary, this reanalysis of the previous NIOSH case–control study[4] suggests that the relationship observed previously between cumulative beryllium exposure and lung cancer is greatly attenuated by adjustment for birth cohort. However, the log of average and maximum exposure remains significantly associated with lung cancer mortality. Contrary to a recent critique of the original study by Levy *et al*,[14] the choice of a small value to add to each exposure to avoid taking the logarithm of zero did not reduce the magnitude of this association. To address the demographic limitations inherent in the Reading cohort discussed above, an updated cohort mortality study, which includes an additional 13 years of follow-up and two additional beryllium processing facilities (both of which started in the late 1950s) with available job-exposure matrices, is currently being conducted by NIOSH[15] and should be available soon. The updated study will include more lung cancers and thus will improve study power. Because the updated study covers a broader range of years of operation and plant exposure levels, a wider birth cohort distribution will be associated with a range of different exposures. This should reduce the tight coupling between exposure, older age at hire (which leads to a tendency for person-time and events from the earliest birth cohort to accrue in the lowest exposure category) and baseline disease risk (eg, from birth cohort) that appear to be confounding the ability to evaluate the association between cumulative beryllium exposure and lung cancer. Future studies should also improve upon smoking estimation methods and further elucidate the potential for modification of beryllium risk ratios by smoking status and by exposure metric. It is expected that such studies will provide a more definitive assessment of the carcinogenicity of beryllium.

Competing interests: None.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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