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Beryllium exposure and pulmonary function: a cross sectional study of beryllium workers

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ABSTRACT A cross sectional study of 297 white male workers employed in a large beryllium plant was conducted to test the hypothesis that long term exposure to beryllium is associated with decrements in pulmonary function. Spirometric measurement of pulmonary function, chest radiographs, and arterial blood gas measurements were collected. After controlling for age, height, and smoking in multivariate regression models, decrements in FVC and FEV_1 were found to be associated with cumulative exposure to beryllium in the period up until 20 years before the health survey. These decrements were observed in workers who had no radiographic abnormalities. The alveolar-arterial oxygen difference was associated with cumulative exposure in the 10 years immediately before survey, after controlling for age and smoking. These findings suggest that beryllium may have both short and long term pulmonary effects that are distinct from the classic forms of acute and chronic beryllium disease.

Beryllium disease of the lung is a potentially disabling granulomatous disorder caused by inhaling beryllium compounds.[1] Much of the research on the health effects of beryllium has focused on the chronic form of the disease, which is generally progressive, often disabling, and is characterised by pronounced radiographic changes and functional impairments in the lungs. Less well understood are the subclinical effects of beryllium and the relation between exposure to beryllium and the degree of lung dysfunction. Such studies require medical monitoring of a large group of workers exposed to estimable levels of the metal for long periods but this has seldom been done.[2-4] In one group of workers an early, reversible condition was described and characterised by mild hypoxaemia, increased alveolar-arterial oxygen gradient, and mild interstitial infiltrates.[2,3] A similar effect has been observed experimentally in dogs.[5]

We describe the changes in lung function and the radiographic changes in workers at a large beryllium extraction and manufacturing plant who have been under study by one of us (NS) since 1977. Elsewhere we have provided estimates of exposure to beryllium in the plant.[6] We describe results of a cross sectional examination of this group using the health effects data obtained in 1977.

The availability of medical monitoring data and historical industrial hygiene surveys at this large beryllium plant enabled us to test the hypothesis that long term exposure to beryllium was associated with decrements in pulmonary function and interstitial changes seen on chest radiographs and to assess the modifying effects of such factors as the timing and intensity of the exposure.

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Methods

EXPOSURE ASSESSMENT

A preceding paper detailed the estimation of beryllium exposure histories for each worker in the cohort and the development of exposure parameters.[6]

MEASUREMENT OF HEALTH EFFECTS

Spirometry—Lung spirometry was performed on each subject while seated using a heated Fleisch No 3 pneumotachograph (Hewlett Packard). Measurements were obtained for forced vital capacity (FVC) forced expiratory volume in one second

(FEV_1), and maximum mid-expiratory flow (MMEF). For FVC and FEV_1, the maximum value of three acceptable blows (without regard to the variance of the measurements) was used, even if the selected FVC and FEV_1 values came from separate blows.[7] The MMEF was obtained from the blow with the largest sum of FVC and FEV_1. Standing height was measured in inches without shoes.

Chest radiographs—Posteroanterior chest radiographs were taken on each worker and read by a certified B-reader using the current ILO system for reading and coding pneumoconioses.[8]

Blood gases—Arterial blood gases were determined for each worker while at rest. With the subject seated and breathing room air, blood was collected from the radial artery into heparinised syringes and analysed immediately at 37°C for PaO_2, $PaCO_2$, and pH (Instrumentation Laboratories, model 213, Boston, MA). The alveolar-arterial oxygen gradient ($AaDO_2$) was calculated using the ideal alveolar air equation.[9]

Questionnaire—The British Medical Research Council questionnaire was administered to collect information on respiratory symptoms and smoking; additional data were collected from job histories. Pack-years of smoking were calculated as the product of the number of years of smoking and the average number of packs a day of cigarettes consumed.

STATISTICAL METHODS

In a preliminary analysis the FVC and FEV_1 values for white men were compared with data from a large standard population[10]: per cent predicted values were calculated using predicted values based on age and height. The average total cumulative exposure was compared for those workers in the lowest decile of function with those in the upper 50% of the distribution, after adjusting for age, height, and smoking.

Conditional associations between outcome variables and exposure parameters were assessed using multivariate models. Least squares regression was used for continuous dependent variables; logistic regression was used for dichotomous outcomes. Both linear and logistic models are shown in a linear form; it should be noted that when a dichotomous outcome variable is referred to, the dependent variable is not y but the logit of the probability of the dichotomous outcome—that is, ln[p/1−p].

Variables assumed a priori to be effect modifiers (age and height for FVC, FEV_1, MMEF; age for $AaDO_2$, and radiographic abnormalities) were included in all models, regardless of the magnitudes of their effects or the results of statistical tests. Quadratic forms for the age and height variables changed neither the overall fit of the models nor the magnitudes of exposure effect estimates, hence the simple linear forms are reported. The possibility of a different effect of smoking among ex-smokers was accounted for by creating two pack-year variables, one for current smokers and one for ex-smokers. Never smokers and smokers of pipes and cigars were assigned zero for both pack-year terms. Smoking exposure interactions were investigated with product terms: smoker (yes/no) × exposure, pack-years × exposure.

Regression coefficients (b values) were used to characterise the magnitude of effects and the respective standard errors were used to assess the precision of the estimates. Significance levels of b values were determined from F tests of the null hypothesis that an individual b was equal to zero. When a set of exposure variables was assessed—for example, exposures occurring in three different periods—an effect estimate was termed "conditional" when the other exposure parameters of the set were included in the model and "unconditional" when they were not. A series of sensitivity analyses were performed to investigate the robustness of the main findings. These consisted of fitting exposure response models in which the exposure parameters were expressed in different mathematical forms and in which exposure terms were fitted both unconditionally and conditionally on other exposure parameters.

Results

The total production workforce in 1977 consisted of 350 workers, of whom 309 were studied. Measurements were obtained from 297 white men who represented 85% of the workforce. This group had an average age of 43 and had worked on average 17 years in the plant (table 1): 44% had worked more than 20

Table 1 *Summary statistics of study population of 297 white men*

	Mean	*Median*	*SD**
Age (years)	43·2	44·0	11·0
Years employed	17·1	17·0	10·3
Height (inches)	68·8	69·0	2·4
Smoking status:			
Current	48%		
Ex-smoker	24%		
Never smoker	22%		
Pipe/cigar	6%		
Pack-years of cigarettes†	32·0	26·0	25·3
Pulmonary function:			
FVC (l)	4·69	4·77	0·85
FEV_1 (l)	3·44	3·48	0·76
MMEF (l)	3·10	3·09	1·26
$AaDO_2$ (mm Hg)	11·6	11·2	10·0
Profusion of small and irregular opacities:			
−/0, 0/0	91%		
0/1	1%		
1/0, 1/1	7%		
1/2 and greater	1%		

*Standard deviation.
†For current and ex-smokers.

years and 17% for less than five years. About half the cohort were current smokers.

The substantial majority of chest radiographs were normal. A total of 28 subjects (9%) had profusions of small or irregular opacities with a score of 0/1 or greater. For analysis, these data were collapsed into the presence or absence of profusions of 0/1 or greater. Large opacities and pleural changes were rare and these data were not analysed.

For both current smokers and never-smokers, FVC was slightly higher than predicted by the equations of Dockery *et al*[10] which were used to adjust for differences in age, height, and amount of smoking (table 2). Mean FEV_1 was lower than predicted, particularly in never smokers.

As a first step in examining exposure response relation, members of the cohort were identified who represented the "worst" decile for a particular outcome measure, after adjusting for age, height, and smoking. Those in the lowest decile for FVC and FEV_1 had higher exposure levels and had worked longer than had the comparison groups, although *t* tests of the differences in the geometric means were not significant at p = 0·05 (table 3). A similar result occurred when those workers with high values of $AaDo_2$ were compared with subjects who had a normal $AaDO_2$. By contrast, similar exposure estimates were found when adjusted MMEF levels were used (table 3).

Several multivariate models were examined that included terms for exposure and for the effect modifiers and smoking. The simplest models included either total cumulative exposure, years worked, or both terms as continuous variables (tables 4 and 5). Age, height, and smoking terms behaved as expected. The exposure coefficients were of the correct sign to indicate an exposure effect but the magnitudes of association were generally small and statistically unstable. Only in models for $AaDO_2$ were these exposure parameters important predictors of outcome. Models that used categorical codings for cumulative exposure or years worked gave similar results.

Table 2 *Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1): crude and predicted values for never-smokers and current smokers**

		Litres		*% predicted*	
	No	*Mean*	*SD*	*Mean*	*SD*
Never-smokers:					
FVC	63	4·82	0·79	102	13
FEV_1	63	3·62	0·70	95	15
Current smokers:					
FVC	141	4·71	0·88	105	14
FEV_1	141	3·40	0·85	98	17

*Predicted values obtained from equations of Dockery *et al*.[10]

Exposure response models were constructed which allowed for differences in the strength of the association between health effects and cumulative exposures that occurred during different periods. Three exposure parameters, CE_{1-10}, CE_{11-20}, and $CE_{\geq 21}$ were used and are described in the previous paper[6]; these represent the sum of exposure to beryllium received in the three periods 1 to 10, 11 to 20, and more than 20 years before the health survey, respectively. This exposure response model was given by:

$$y = b_0 + b_1 \text{ age} + b_2 \text{ height} + b_3 \text{ current pack-years} + b_4 \text{ ex-pack-years} + b_5 CE_{1\text{-}10} + b_6 CE_{11\text{-}20} + b_7 CE_{\geq 21} \quad (1)$$

Both FVC and FEV_1 were associated strongly and negatively with exposures in the distant past (more

Table 3 *Comparison of cumulative exposure and duration of exposure for the lowest decile and upper 50% of the population on adjusted measures of pulmonary function*

		Cumulative exposure ($\mu g/m^3$ – years)				*Duration of employment (years)*			
	No	*Geometric Mean*	*SD*	*p*	*Median*	*Arithmetic Mean*	*SD*	*p*	*Median*
FVC:									
Lowest 10%	29	56	11·0		140	19	9·8		23
Highest 50%	149	30	9·7	0·18	65	16	11·0	0·12	16
FEV_1:									
Lowest 10%	29	46	11·0		66	19	10·0		23
Highest 50%	149	32	9·8	0·45	46	16	11·0	0·27	13
MMEF:									
Lowest 10%	27	37	9·7		47	17	11·0		12
Highest 50%	131	33	10·0	0·82	45	16	10·0	0·87	14
$AaDO_2$:									
Highest 10%	29	63	9·3		140	18	9·3		21
Lowest 50%	149	35	10·0	0·21	63	19	10·0	0·64	19
Full cohort	297	39	9·8		65	17	10·0		18

Table 4 *Models for three measures of pulmonary function using the exposure variables total cumulative exposure and number of years worked. Regression parameter ± standard error (p value*)*

	FVC	*FEV_1*	*MMEF*
Constant	−4706	−2230	755
Age (years)	−27 ± 5·4 (<0·001)	−31 ± 4·6 (<0·001)	−47 ± 9·5 (<0·001)
Height (inches)	156 ± 15 (<0·001)	105 ± 13 (<0·001)	69 ± 26 (<0·001)
Pack-years (current)	−3·4 ± 1·5 (0·03)	−7·6 ± 1·3 (<0·001)	−14 ± 2·7 (<0·001)
Pack-years (ex-)	1·9 ± 2·4 (0·61)	−1·4 ± 2·1 (0·51)	−6·9 ± 4·3 (0·11)
Cumulative exposure:			
($\mu g/m^3$ − years)	10 ± 27 (0·71)	−14 ± 23 (0·53)	−64 ± 48 (0·18)
(Alone in model†)	−15 ± 21 (0·47)	−20 ± 18 (0·28)	−38 ± 37 (0·31)
Years worked	−11 ± 7·2 (0·13)	−2·3 ± 6·1 (0·71)	11 ± 13·0 (0·38)
(Alone in model)	−9·3 ± 5·7 (0·10)	−4·7 ± 4·8 (0·34)	0·1 ± 10·0 (0·95)
Adjusted R^2	0·49	0·54	0·34

*From one df F test of H_0: b = 0.
†In a model with all the terms shown, except the years worked term.

than 20 years before the health survey) and were associated weakly with more recent exposures (tables 6 and 7). The MMEF was not associated with past or recent exposures. A positive association was observed between $AaDO_2$ and recent exposure but past exposures showed no association. Radiographic abnormalities were associated weakly with recent exposures (tables 6 and 7). No evidence was found for an interaction between smoking and any of the parameters of beryllium exposure.

These analyses were repeated with each of the exposure effects estimated unconditionally—that is, from models that included effect modifiers and smoking but no other exposure parameter. The unconditional results agreed closely with those in tables 6 and 7.

The periods for partitioning cumulative exposure were selected arbitrarily. The importance of the particular cut off points chosen for the three periods was investigated by testing exposure parameters for alternative sets of periods. The association of $AaDO_2$ with exposures of the most recent past persisted when this period was redefined as the most recent five years (rather than ten years) and an association was found when just the two years was considered, although this latter effect was relatively unstable. When the remote period was redefined to begin 10 or 15 years before the survey (rather than 20 years), the strength of the associations between cumulative exposure in this period and FVC or FEV_1 was diminished.

Both $AaDO_2$ and radiographic abnormalities were associated with exposures during the past 10 years. To investigate whether these changes are seen equally among those employed for more than and less than 10 years, or whether the effect of recent exposure is greater among those with longer employment, an interaction term for recent and long term exposure was added to the model as follows:

$$y = b_0 + b_1 \text{ age} + b_2 \text{ current pack-years} + b_3 \text{ ex-pack-years} + b_4 CE_{1-10} + b_5 \text{ years}_{\geqslant 11} + b_6 (CE_{1-10} * \text{years}_{\geqslant 11}) \quad (2)$$

Table 5 *Models for alveolar-arterial oxygen gradient ($AaDO_2$) and the profusion of small and irregular radiographic opacities, using the exposure variables total cumulative exposure and number of years worked. Regression parameter ± standard error (p value*)*

	$AaDO_2$	*Profusions†*
Constant	−8·9	−3·9
Age (years)	0·43 ± 0·07 (<0·001)	0·02 ± 0·03 (0·52)
Pack-years (current)	0·09 ± 0·02 (<0·001)	0·01 ± 0·01 (0·06)
Pack-years (ex-)	0·02 ± 0·03 (0·48)	0·009 ± 0·01 (0·43)
Cumulative exposure	1·0 ± 0·37 (0·01)	0·09 ± 0·16 (0·56)
(Alone in model‡)	0·53 ± 0·29 (0·07)	0·10 ± 0·13 (0·43)
Years worked	−0·21 ± 0·10 (0·04)	0·005 ± 0·04 (0·90)
(Alone in model)	−0·04 ± 0·08 (0·58)	0·02 ± 0·03 (0·57)
Adjusted R^2	0·31	na§

*From one df F test of H_0: b = 0.
†From logistic model with dependent variable: any profusion of 0/1 or greater yes/no (see text).
‡In a model with all the terms shown except the years worked term.
§Not applicable to logistic models.

Table 6 *Models for three measures of pulmonary function with variables representing exposure at different times before health survey. Regression parameter* ± standard error (p value†)*

	FVC	*FEV_1*	*MMEF*
Exposure 0–10 years before	46 ± 29 (0·12)	13 ± 25 (0·60)	−12 ± 51 (0·82)
Exposure 11–20 years before	13 ± 20 (0·53)	7·3 ± 17 (0·67)	−13 ± 35 (0·70)
Exposure ⩾21 years before	−47 ± 17 (0·005)	−33 ± 15 (0·03)	−15 ± 30 (0·63)
Adjusted R^2	0·50	0·55	0·34

*Estimated from linear models of the form: $y = b_0 + b_1$ age + b_2 height + b_3 current pack-years + b_4 ex-pack-years + b_5 $\text{exposure}_{0\ 10}$ + b_6 $\text{exposure}_{11\ 20}$ + b_7 $\text{exposure}_{\geqslant 21}$ where b_5, b_6, b_7 are shown above.
†From one df F test of H_0: b = 0.

Table 7 *Models for alveolar-arterial oxygen gradient ($AaDO_2$) and the profusion of small and irregular radiographic opacities, using variables representing exposure at different times before health survey. Regression parameter* ± standard error (p value†)*

	$AaDO_2$	Profusions‡
Exposure 0–10 years before	1·1 ± 0·40 (0·01)	0·32 ± 0·18 (0·08)
Exposure 11–20 years before	−0·12 ± 0·28 (0·66)	0·006 ± 0·12 (0·96)
Exposure ⩾21 years before	−0·06 ± 0·24 (0·80)	0·006 ± 0·10 (0·95)
Adjusted R^2	0·31	na§

*Estimated from linear models of the form: $y = b_0 + b_1$ age $+ b_2$ current pack-years $+ b_3$ ex-pack-years $+ b_4$ $exposure_{1\ 10} + b_5$ $exposure_{11\ 20} + b_6$ $exposure_{\geqslant 21}$, where b_4, b_5, b_6 are shown above.
†From one df F test of H_0: $b = 0$.
‡From logistic model with dependent variable: any profusion of 0/1 or greater yes/no (see text).
§Not applicable to logistic models.

where $years_{\geqslant 11}$ is a dummy variable coded 0 for years worked < 10, and 1 otherwise. For radiographic abnormalities, there was no additional effect of longer term employment, either on the intercept or slope of the exposure response relation (table 8). For $AaDO_2$, the model was more complex. Workers with more than 10 years tenure had a lower intercept than those with less tenure. The parameter estimate for the interaction term indicates a marginal difference in the slopes of the exposure response relation for those with short and long tenure (p = 0·08). These findings suggest that workers with more than 10 years in the plant had generally lower levels of $AaDO_2$, after correcting for age and smoking differences.

To test for the possibility that exposures received at different intensities might have different magnitudes of effect, cumulative exposure was partitioned into two exposure parameters: $intensity_{<25}$ and $intensity_{\geqslant 25}$.[6] These two parameters represent the sum of all annual exposures that were above and below 25 $\mu g/m^3$ respectively. Exposures partitioned by intensity in this way showed no clear association with any of the lung function measurements and this partitioning approach was not investigated further.

Because cumulative exposure data were transformed logarithmically in all models, the effect of alternative transformations of the cumulative exposure parameters partitioned by period was investigated. Similar patterns of associations among periods were observed using untransformed cumulative exposures, but the coefficients for the exposure parameters were less stable and the overall goodness of fit for the models (measured by adjusted R^2) was poorer. When the exposure data were transformed by taking the square root or fourth root, the results were again qualitatively similar with tests for goodness of fit that were intermediate between the untransformed and logarithmic versions.

Finally, the data were restricted to the subset of the population with normal chest radiographs, so that an association between exposure to beryllium and decrements in pulmonary function could be assessed in a population with no evidence that might suggest clinical beryllium disease. Again, the associations of FVC and FEV_1 with exposures in the distant past were observed, and the point estimates, about −50 and −30 ml per $\ln(\mu g/m^3$ −year) of beryllium respectively, were similar to those for the full data set.

Discussion

SOURCES OF BIAS

An accurate retrospective estimate of exposure is difficult and some misclassification of true exposures doubtless occurred.[6] The extent of this misclassification cannot be assessed, although such misclassification was random with respect to health state and therefore conservative.

Selection effects were perhaps a more serious source of potential bias. Exposure to beryllium in some operations was measured at levels above 100 $\mu g/m^3$, a concentration which is reported to cause acute beryllium disease in man.[6] In 1943 labour turnover in the plant approached 100% a year.[11] The present workers, and particularly the subgroup with many years of service, are therefore likely to be a "survivor" population. Assuming that workers who left work due to the acute effects of beryllium would have been at greater risk of developing more chronic effects had

Table 8 *Models for alveolar-arterial oxygen gradient ($AaDO_2$) and the profusion of small and irregular radiographic opacities, allowing for interaction between exposure and duration of employment. Regression parameter* ± standard error (p value†)*

	$AaDO_2$	Profusions
Constant	−9·3 ± 2·3 (<0·001)	−4·1 ± 1·2 (<0·001)
Age (years)	0·44 ± 0·06 (<0·001)	0·02 ± 0·03 (0·48)
Pack-years (current)	0·09 ± 0·02 (<0·001)	0·01 ± 0·01 (0·08)
Pack-years (ex)	0·02 ± 0·03 (0·57)	0·01 ± 0·01 (0·52)
$CE_{1\ 10}$	0·53 ± 0·51 (0·30)	0·19 ± 0·29 (0·51)
$Years_{\geqslant 11}$	−5·8 ± 2·2 (0·01)	−0·36 ± 1·1 (0·74)
Interaction of $CE_{1\ 10}$ *$years_{\geqslant 11}$	1·3 ± 0·72 (0·08)	0·20 ± 0·36 (0·58)

*Estimated from linear models of the form: $y = b_0 + b_1$ age $+ b_2$ current pack-years $+ b_3$ ex-pack-years $+ b_4$ $CE_{1\ 10} + b_5$ $years_{\geqslant 11} + b_6$ ($CE_{1\ 10}$ *$years_{\geqslant 11}$). See text for descriptions of parameters.
†From one df F test of H_0: $b = 0$.

they remained exposed, then the bias would be conservative. The observation that workers with more than 10 years of tenure at the plant had lower—that is, "better"—values of $AaDO_2$ on average than those with less tenure may be evidence for this survivor effect.

LIMITATIONS OF MODELLING METHODS

A search was made for alternative explanations of the observed exposure response associations. The associations of exposure in the distant past with decrements in FVC and FEV_1 and of exposure in the recent past with increases in $AaDO_2$ were found to be fairly robust to changes in the form of the models used to estimate them. When modelling exposure response relation, the choice of scale for the exposure parameters has implications for the shape of the exposure response curves. Logarithmic transformation of exposure parameters implies a linear relation between exposure and response on a logarithmic scale. In this study the log models fit the data better than did other transformations of the exposure parameters but the differences were not great and the data lacked the statistical power to distinguish between the various models.

The linear models reported here may be thought of as predicting changes in the mean values of outcome variables as functions of the exposure parameters. It is difficult to say whether the observed exposure response associations are the result of exposure related effects confined to a small group of "susceptible" individuals or an association of constant magnitude for all. Such a distinction is best investigated by longitudinal studies of exposed individuals.

INTERPRETATION OF RESULTS

If cross sectional associations reported here can be interpreted causally and can be applied to the longitudinal experience of similarly exposed individuals they confirm that beryllium has both short and long term effects on lung function, as indicated by exposure related increases in $AaDO_2$ and decrements in FVC and FEV_1, respectively.

The models in tables 6 and 7 predict a loss of FVC and FEV_1 proportional to exposures more than 20 years before the survey. A hypothetical worker assigned the median values on all covariates (age, height, pack-years, and exposures in more recent periods) would be expected to have the following decrements in function when compared with the same worker with no exposure 21 or more years before survey: a cumulative exposure of 100 $\mu g/m^3$ −years would predict a decrement of 220 ml in FVC and 150 ml in FEV_1; a cumulative exposure of 1000 $\mu g/m^3$ −years would predict a decrement of 330 ml in FVC and 220 ml in FEV_1. Twenty one per cent of the cohort received estimated cumulative exposures to beryllium of greater than 100 $\mu g/m^3$ −years, and about 2% received cumulative exposures over 1000 $\mu g/m^3$ −years in the relevant period.

An association between exposure to beryllium and FVC or FEV_1 has not been reported in epidemiological studies of beryllium workers. The present finding is important for several reasons. Firstly, decrements in FVC and FEV_1 were observed in workers who had no radiographic abnormalities, thus raising the possibility that radiographically diagnosed beryllium disease is not the only long term effect of exposure to beryllium.

A second important feature of the decrements in FVC and FEV_1 is that these losses in function were proportional to cumulative exposure. The existence of an immunological component to chronic beryllium disease has led to suggestions that the effects may not be dose related.[12] Whether this is true for chronic beryllium disease (as traditionally defined) is not clear but our findings suggest that there may be subclinical decrements in function that progress with continuing exposure. The magnitudes of the observed associations between beryllium and decrements in FVC and FEV_1 were not great but our estimates are probably conservative and an underestimation of the true association could have resulted from several forms of bias (as described above). The strength of the present findings lies more in the observed patterns of association over time, and the persistence of these patterns through a number of alternative statistical models, than in the magnitudes of the predicted relations between exposure and response.

Previous studies of groups of beryllium workers failed to find an effect of beryllium exposure on either FVC or FEV_1.[2-4] The studies by Sprince *et al* and Kanarek *et al* examined workers in another United States beryllium extraction plant that had been operating for only 15 years at the time of the first survey,[2 3] Since exposure to beryllium in the preceding 15 years was not associated with decrements in pulmonary function in the present study, our findings are consistent with the earlier studies. Cotes *et al* followed up a small cohort in a British beryllium plant and found essentially no exposure related effects on lung function,[4] but exposures were considerably lower than those estimated for workers in the present study. Thus an insufficient period of exposure or low intensities of exposure to beryllium may explain the negative findings in these other studies.

The association of exposure to beryllium with decrements in FEV_1 observed in our study suggests that beryllium may have an effect on airways. Both obstructive and restrictive defects in pulmonary function were reported by Andrews *et al* in a large series of patients with chronic beryllium disease.[13] They also

found subjects who had normal lung volumes and flows but reduced diffusing capacity, suggesting an impairment at the level of the alveolocapillary membrane. Available evidence from lung function studies thus indicates that beryllium can affect airways and lung parenchyma, so that predominantly "obstructive" or "restrictive" ventilatory patterns are expected; a mixed "obstructive-restrictive" pattern is also possible.

The $AaDO_2$ was associated with exposures in the recent past. A worker with a cumulative exposure of 10 $\mu g/m^3$ – years in the 10 years before survey would be expected to have an $AaDO_2$ 5 mm Hg higher than the same worker without such exposure; at exposure levels of 100 $\mu g/m^3$ – years in the past 10 years, the increase in $AaDO_2$ would be 7 mm Hg. Kanarek *et al* and Sprince *et al* have reported an association between beryllium exposure and $AaDO_2$ in another exposed population,[2 3] and Stokinger found hypoxaemia in dogs with beryllium exposures below which any other lung function effects were observed.[5] Sprince *et al* reported that $AaDO_2$ improved after a substantial reduction in beryllium air levels.[3] They hypothesised that there was an early, reversible component to beryllium disease manifested by an increased $AaDO_2$ and mild interstitial infiltrates visible on chest radiograph.[3] The observation that recent exposures to beryllium were associated with increased $AaDO_2$, whereas longer term exposures were not, is consistent with a reversible defect at the level of the alveolocapillary membrane. Possibly the absence of an association between longer term (more than 10 years) exposure and $AaDO_2$ is a result of selection bias. The observation that workers with more than 10 years of tenure have more normal values of $AaDO_2$ on average than do workers more recently hired (table 8) suggests that a healthy worker effect may be operating.

Beryllium exposure was weakly associated with the profusion of small and irregular opacities on chest radiograph. The association appeared only with recent exposure (in the 10 years before survey). Most of the abnormalities were mild. Kanarek *et al* and Sprince *et al* also reported radiographic changes of mild interstitial infiltrates that appeared to resolve after reduction of beryllium exposures.[2 3] Possibly the radiographic changes seen in the present study and by Kanarek and Sprince represent inflammatory changes that are potentially reversible.

Despite methodological weaknesses inherent in cross sectional studies, the present findings among workers exposed to beryllium indicate both short and long term effects on lung parenchyma and the airways. These changes are distinct from "classical" chronic beryllium disease. Longitudinal studies of exposed workers are needed to define further the subclinical effects of beryllium and to investigate whether a mild abnormality in $AaDO_2$ predicts further lung function changes.

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