Final Performance Report

1. Title page information

Dose-Response Assessment Issues in Occupational Mortality Studies

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HR: hazard ratio

CI: confidence interval

g, mg: grams, milligrams

m^3: cubic meter

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This project addressed a methodologic issue in occupational studies. The healthy worker survivor effect is one of several selective processes that comprise the healthy worker effect and that may produce biases in studies examining work exposures in relation to diseases and mortality. Methods to adjust for the healthy worker survivor effect are complex and have not been used extensively in occupational epidemiology. Simpler means to control this bias would be useful. This project examined absenteeism as a surrogate for ill-health and its usefulness in the context of the differential survival problem. Results indicated that information on absenteeism without knowledge of the reasons for gaps in employment does not appear to be useful by itself. The findings point to the need for investigations of workplace exposures to collect data on absenteeism with the reasons for absence. Such data may prove useful in assessing the health status of workers at different stages of their work careers. which in turn would contribute to measuring the magnitude of differences in survivorship among workers whose health status differs.

7. Usefulness of Findings.

This project addressed a methodologic issue in occupational studies. The healthy worker survivor effect may produce biases in studies examining work exposures in relation to diseases and mortality. Without adjustment for this bias, conclusions regarding the health effects of these exposures may be suspect: the harm from such exposures could be under-estimated or possibly over-estimated. Methods to adjust for the healthy worker survivor effect are complex and have therefore have, for the most part. been ignored in occupational epidemiology. Simpler means to control this bias would be useful. This project examined absenteeism as a surrogate for ill-health and its usefulness in occupational mortality studies. We found that information on absenteeism without knowledge of the reasons for the absence does not appear to be useful by itself. These results point to the need for investigations of workplace exposures to collect data on absenteeism with the reasons for absences. Such data may prove useful in assessing the health status of workers at different stages of their work careers, and ultimately, in improving the validity of occupational studies.

8. Abstract

The healthy worker survivor effect is one of several selective processes that comprise the healthy worker effect. Employees who are less healthy tend to leave employment sooner, so that the healthier ones survive longer, in the same jobs. The result is biased measures of the effects of exposure. Adjustment for this bias in studies of occupational exposures and disease incidence or mortality is not straightforward. This project examined absenteeism as a surrogate for ill-health and its usefulness in the context of the differential survival problem. Data were from a cohort of workers exposed to arsenic in a smelter.

Results showed that cumulative exposure (up to one year previously) was associated with an increased risk of an extended (30-day or longer) absence, whereas current exposure was associated with a reduced risk of such a gap in employment. After adjustment for exposure, length of follow-up and age and year at hire, a history of having had at least one such extended absence predicted a slightly lower probability of early termination (pre-retirement) from employment at the smelter. Absence history predicted a reduced risk of respiratory cancer mortality in the first 13 years after start of employment, but not subsequently. Other causes of death were not associated with a worker's absence history. Because extended gaps in employment history may reflect employment and personal events other than ill-health, the utility of absenteeism as a surrogate for health status is limited. It is recommended that occupational studies obtain information on reasons for extended absences in order to make full use of employment histories in studies of health effects from work exposures.

9. Body of report

Introduction

The healthy worker survivor effect is one of several selective processes that comprise the healthy worker effect. Employees who are less healthy tend to leave employment sooner, so that the healthier ones survive longer, in the same jobs. In studies of occupational exposures and mortality this differential survival leads to biases in measures of the effect of exposure, since those who survive longer will accrue greater cumulative exposures but will tend to have lower mortality. Robins (1987) noted further that termination of employment may be related not only to underlying health status but also to prior occupational exposures; in addition, it is an independent risk factor for death. Robins has also demonstrated that under the scenario of time-dependent confounding, standard statistical methods to adjust for ordinary confounding are insufficient. Instead, methods that control for total work history and exposure patterns are required.

Underlying health status cannot be observed, but persons whose health differs might be expected to have different rates of absenteeism. We undertook this investigation in order to (1) determine whether the conditions for time-dependent confounding were met in an occupational cohort study of arsenic-exposed workers; and (2) assess the utility of measures of absenteeism as a surrogate for health status.

Prior work on absenteeism has addressed its relation to length of employment, age, and occupation. Pocock (1973) studied the relationship between absence due to sickness and length of employment in male workers at one site of a large continuous process industry in England. He observed that sickness absence rates in the first six months of employment were less than half the rates during the next four and a half years in a cohort of new employees. Cross-sectionally, he also found that men with long service (e.g., over 10 years) were less frequently absent than those with less service, although total number of days of absence due to sickness was not associated with length of service. Cooper and Payne (1965) studied the relationship between age and absence in long-service workers from three firms in Merseyside, England that manufactured soap powders, chemicals, animal

foodstuffs, and edible fats. They concluded that frequency of absence did not decrease with age. Indeed, two of the firms showed consistent increases in absence with age. This finding was supported by Taylor (1967), whose secular study showed that sickness spells at an oil refinery in England did not decrease with age. He also found that the distribution of sickness absence resembled a negative binomial distribution, not a Poisson distribution, and the pattern of distribution was not related to occupation or to length of service.

None of the papers on absenteeism examined its relation to occupational exposures: for instance, whether exposure level predicts absenteeism, and whether absenteeism is related to subsequent changes in exposure level. Nor did they address the relation between absenteeism and either early termination or mortality. The current investigation evaluated all four of these questions.

Methods and Materials

Data for this investigation came from an occupational cohort study of arsenic and lung cancer. The cohort consists of all white male workers hired for 1 year or more between 1940 and 1964 at a copper smelter in Tacoma, Washington. For the analysis, we truncated the cohort to employees who started their jobs after 1940 for two reasons: First, the quality of exposure data from before 1940 appeared to be less reliable. Figure 1 shows average concentration of current ambient arsenic (mg/m^3) in these two different time periods. The lower level of ambient arsenic in the early period may have reflected inadequacies in the measurement techniques. Second, mortality data before 1940 was not available, therefore among those hired before 1940 only survivors were in this dataset. These survivors were excluded for the analyses reported here. Hence follow-up began 1 year after hire for all workers studied, as this was the minimum follow-up time used by the original investigators (Enterline and Marsh, 1982; Enterline et al. 1987). The study cohort used for the current investigation included 1,599 workers with 359 deaths. Respiratory cancer accounted for 44 deaths.

Our interest was in off-work time as a surrogate for health status. Although the data did not include reasons for off-work time, e.g., layoff, personal leaves etc., illness is one of the main causes of off-work time. An index was therefore constructed based on episodes of 30 consecutive days or more of off-work time (termed gaps or off-work episodes). To assess differences between those who experienced gaps and those who did not, the time-weighted exposure (TWE) of each worker was calculated by dividing cumulative exposure by total days of work. Total days of work was corrected by subtracting any days of absence from the total length of employment. Primary analyses focused on the associations between measures of exposure and the first occurrence of a gap, between the history of at least one gap and the likelihood of permanently leaving work prior to retirement, and between the history of at least one gap and risk of death from several specific causes.

For each of these analyses a Cox proportional hazards model was used to analyze time to the event using PHREG procedure in SAS (ver. 6.09). The hazard of the first 30-day absence of each employee of the cohort $h_i(t)$ is expressed as

$$h_i(t) = h_0(t)exp(Z_i'\beta)*exp\{(Z_i(t)'\gamma\}$$

where t represents time since hire, $h_0(t)$ is an arbitrary baseline hazard function; Z_i is the vector of measured time constant explanatory variables for the i-th study subject; β is the vector of unknown regression parameters associated with the time constant explanatory variables; $Z_i(t)$ is the vector of time-dependent explanatory variables and γ is the vector of unknown regression coefficients associated with the time-dependent explanatory variables. We treat both current (mg/m^3) and cumulative (mg/m^3-year) arsenic exposure levels as time-dependent variables. Age at hire and calendar year of hire, time constant variables, were entered into all models. Workers whose employment terminated without any absences of 30 days or more were censored at the date of termination. Similar models were used for the hazard of early termination, where those who terminated at age 63 or later were considered as censored at the time of retirement, and for the hazard of death from respiratory cancer (or death from circulatory disease), where deaths from other causes were considered as censored. We also modeled the hazard of overall mortality and mortality from cardiovascular disease. The employment status of a member of the cohort (on or off-work) at the time of death or censoring was included as a time-dependent covariate in models predicting mortality. We evaluated for any violation of the proportional hazard assumption by examining interactions between each covariate and time since hire, and by using analyses stratified on time since hire. In the stratified models, substantial variation of estimated coefficients across strata is evidence of a violation of the assumption.

Results

1. Prediction of absenteeism

There were 1083 out of the 1599 men who were absent at least one day during their employment at the smelter. About 60% (655) of these 1083 employees had an off-work episode of more than 30 days. We refer to these 30-day or greater episodes as gaps. Thus, 41% of the cohort experienced at least one gap during their employment at the smelter. There was little difference in overall time-weighted exposure. cumulative exposure levels, or total length of employment between those who had at least one gap in employment and those who did not (Table 1).

Results from Cox proportional hazards models are shown in Table 2 and 3. The interactions between follow-up time and three main exposure variables (cumulative exposure, current exposure and calendar year of hire) indicate that the effect of exposure in predicting a first gap is not constant across years of follow-up. In the model with time interaction terms, the hazard ratio for a one g/m^3-year increase in cumulative exposure after one year of employment was 1.39 but declines to 1.08 after 20 years of employment. Thus, cumulative exposure to arsenic is a prediction of having a first gap in the early years of employment, but the hazard ratio decreases as their employment period increases (Table 2). The association with current exposure measured in 100 mg/m^3 was inverse: the greater the current exposure the smaller the hazard of gap. This effect was negligible in the first year of employment, but as the length of employment increased, the inverse effect of current exposure on the first gap was magnified: after 20 years, the HR=0.68. The hazard for a gap declines with higher age at hire, but increases with later calendar year at hire. The effect of year at hire increased substantially with longer employment.

To allow for a non-monotonic interaction with time since hire, the analysis is stratified by time since hire (Table 3). Increasing cumulative exposure is predictive of an elevated risk of experiencing a "gap" except during the first year of follow-up and after 20 years of follow-up. The result of stratified survival analysis by the different times since hire (<2, 2-4,5-9, 10-19, and 20+ years) indicates that the impact of time since hire on the other effects is not always monotonic. Cumulative exposure shows the strongest association with gaps in years 2-4, and this effect declines with longer time since hire. Current exposure, in contrast. shows the strongest inverse association with absences between 10 and 19

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years, but not after 20 years. The other two variables also showed erratic associations over time. In summary, increasing cumulative exposure to arsenic generally predicts a higher risk of having a 30-day or greater gap in employment, whereas higher current exposure predicts a reduced risk. A person hired at a younger age experiences a greater hazard for a gap occurrence until ten years after employment begins.

2. Effect of first gap on subsequent work history and exposure

Among employees who had an absence of 30 days or longer, 61% (399/655) experienced the first gap within a year of employment. Among those who experienced at least one gap in their employment, 43% (284) experienced a second gap. Of these, almost half had their first gap within 6 months of hire. If an employee experienced his first absence within a year of employment, he had a 20% higher risk of experiencing another gap during his later employment than a worker whose first absence occurred after 1 year of employment.

We found that except in the first 6 months of employment, if an employee had a gap, his exposure level after returning to the workplace decreased only trivially (less than a 5% reduction). Since exposures decline slowly over time anyway, there is no evidence to suggest that workers who return from a gap are placed in jobs with lower exposures than those who did not leave work temporarily.

Thus, the probability of a first 30-day absence decreases with time since hire, a first absence in the first year of employment increases the risk of a subsequent gap, and exposures upon return after a gap closely resemble levels prior to it.

3. Prediction of early termination.

Termination of employment before retirement age was examined in relation to absenteeism. Those who left work after age 62 were considered censored. Based on the Cox proportional hazards model (Table 4), history of at least one 30-day or longer off-work episode predicts about a 10% lower hazard of early termination from work after controlling for other predictors of early termination (crude HR = 0.91; 95% CI = [0.81, 1.02]). The other four variables are strongly associated with length of employment: higher current exposure, later year at hire, younger age at hire and lower cumulative exposure predict a higher risk for early termination. Removing the term for employment gaps from the

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model had little impact on the coefficients for cumulative or current exposure, hence it is not a confounder of the association between cumulative ambient arsenic exposure level and length of employment. From the model with an interaction between time and gap, the negative effect of gap declines with longer length of employment. From the stratified analysis, it can be seen that the risks of early termination are similar over first 20 years of employment. The risk from current exposure showed the most drastic change after 20 years of employment. Among workers who work more than 20 years, each 100 mg/m^3 of current ambient arsenic concentration is associated with a 20% reduction in risk of early termination (HR=0.80). A relation between exposure and job termination is one precondition for the bias induced by the healthy worker survival phenomenon.

We also examined whether any recent gap would be a predictor of early termination. A gap was considered recent if it occurred in the current year or the previous 3 years. Similar to the results using history of any gap, a recent gap was associated with about a 10% reduction in the hazard for early termination.

4. Prediction of mortality with an absence.

The crude odds ratio for death from all causes for workers who experienced a gap versus those who did not was 0.58 (95% CI = [0.45, 0.75]), and the OR for death from respiratory-related cancer is 0.31 (95% CI = [0.14, 0.68]). Using a Cox proportional hazards model, the hazard ratio for respiratory cancer death associated with any history of a 30-day absence was 0.41 (95% CI = [0.18, 0.89]) (Table 5). If we included a time interaction term between follow-up and gap (assuming a linear change in the effect of a gap over time), the result shows that ever having had a gap is associated with a higher risk of death from respiratory cancer in the first 13 years of employment. After 13 years of employment, the effect of gap on respiratory cancer death was inverse. The average length of follow-up was 13.7 years. Results from the model using a recent gap as a predictor (a time-dependent and potentially recurrent indicator variable) shows it to be a strong but statistically unstable risk factor for respiratory cancer death (HR = 2.20; 95% CI = [0.27, 18.0]).

In summary, during the first decade after start of employment, a 30-day absence is associated with an elevated risk of respiratory cancer death among arsenic exposed workers, particularly if it occurred recently. As is well known, higher cumulative exposure to arsenic is a significant risk factor for death from lung cancer. Current employment status of an employee did not seem to have any effect

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on death from respiratory cancer. However, the status was associated with a death from all causes. The result indicated that being off-work increased the risk of dying from all causes (HR = 1.67).

In Cox proportional hazards models, absence was not an important predictor of mortality from all causes or from circulatory diseases, although being off-work at the time of death strongly predicts death from all causes and from circulatory diseases. Neither cumulative nor current arsenic exposure is related to increased mortality from these causes.

Discussion

This investigation examined absenteeism in a cohort of workers exposed to arsenic to determine its relation to exposure, to early termination of employment, and to mortality form all causes and from specific causes. After controlling for the level of current exposure, age at hire and year at hire, the risk of having a 30-day or longer absence (termed a gap) is generally higher with increased level of cumulative exposure. In contrast, current exposure level shows an inverse relationship with absence.

Our proposed hypotheses were that absenteeism would be related to the length of employment and to the subsequent level of exposure to arsenic after experiencing an absence, and that exposure-induced mortality from lung cancer might differ from persons who experienced no such absences. The data did not support decreases in either time-weighted exposure or current exposure levels after experiencing an absence. Experience of a gap was negatively related to early termination of employment but this association was small and not statistically significant.

From the mortality analyses, we may conclude that a recent absence of more than 30 days is associated with a higher risk of death from respiratory cancer among employees exposed to arsenic. Since cumulative exposure predicts an increased hazard of absence as well as a increased risk of respiratory cancer death, one might expect a positive relation between a gap and exposure-related respiratory cancer death. Indeed the relation was strong in the first few years of employment but declined with time.

In this occupational cohort, we observed that although a gap was related to past exposure, it was unrelated to subsequent arsenic exposure. A gap also predicted longer survival at the workplace, but was not associated with all-cause mortality nor circulatory disease mortality. A recent gap of more than 30 days was found to be a strong but unstable risk factor for death from respiratory cancer. At this stage, it is not clear why a history of an extended absence during employment is associated with longer survival at the workplace, after controlling for exposure, time since hire, and other work-related

factors. Absenteeism was not a confounder of the association between respiratory cancer mortality and either cumulative or current arsenic exposure.

Employment status at the time of death or censoring is a strong risk factor for all cause mortality and for deaths from circulatory diseases. The persons who were off-work had about 2 times higher risk of all cause death or death from circulatory diseases than those currently on-work. Nevertheless, use of any absence of more than 30 days as a surrogate measure for sickness absence introduces misclassification, since the absence may not be related sickness at all. Absenteeism can be caused by physical or mental illness, layoff, intrusion of other responsibilities, or leave-taking for purposes of pleasure. Thus, the use of extended absences as a surrogate for health status could introduce measurement error. Since we lacked information on the reason for absence, these errors could not be avoided. There is no specific reason to believe the error is differential with respect to the level of cumulative or current arsenic exposure, age at hire or calendar year of hire. The magnitude of bias will depend on the characteristics of employees who experience 30 days or more off-work days for reasons other than sickness. Further analyses should be conducted with data in which information on the reason for absence from the workplace is included. Incorporation of such data into work histories could provide critical insights into the development of differentials in health status among different exposure groups, the critical link in understanding the healthy worker survivor effect.

Acknowledgements:

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SAS (ver 6.09)

Fig-1. Distribution of average DOSE by calender year
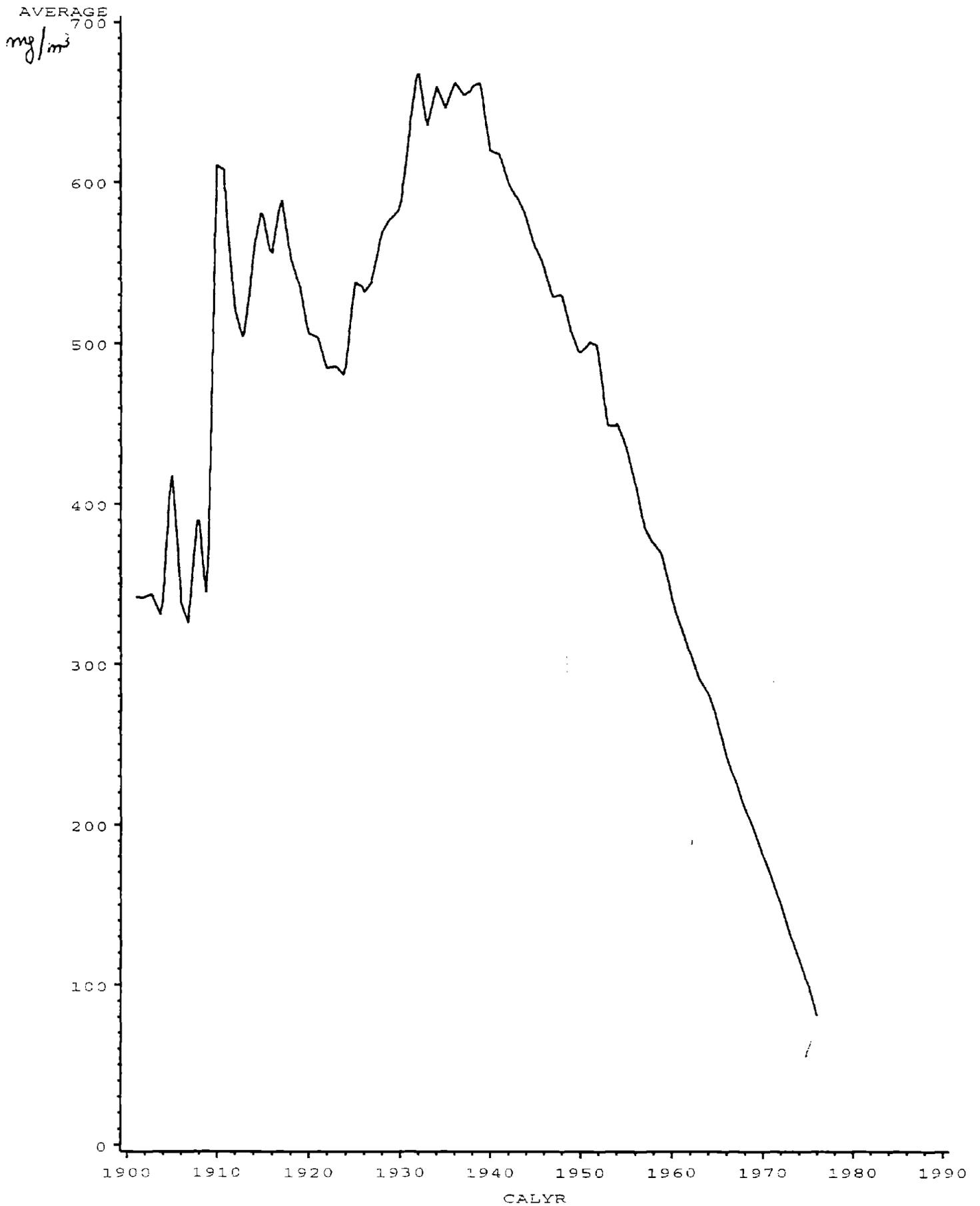— Arsenic.Personyr.dataset

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Table 1. Number and percent of workers in arsenic-exposed cohort who experienced at least one gap in employment of 30 days or longer, stratified by (a) time-weighted exposure, (b) length of employment, and (c) cumulative exposure.

	Number of men (%) GAP (>30 days)	
	No	Yes
Time-weighted exposure (mg/m^3)		
<400	610 (.65)	427 (.65)
400+	334 (.35)	228 (.35)
Length of employment (year)		
5>	544 (.57)	340 (.52)
5-20	208 (.23)	178 (.27)
20+	192 (.20)	137 (.21)
Cumulative exposure ($mg/m^3*100/days$)		
<8000	570 (.60)	393 (.60)
8000+	374 (.40)	262 (.40)
Total	944	655

Table 2. Predictors of time to the first gap (>30 days) in employment in proportional hazards models stratified by length of employment.

Variables	Estimated Coefficient (standard error)	Risk Ratio (p-value)[**] Length of employment (year)			
		1	5	10	20
Cumulative exposure (100 mg/m^3-year)	0.034 (.008)	1.39	1.32	1.23	1.08
Cumulative exposure*time[*]	-0.0013 (6.06E-4)				
Current exposure (100 mg/m^3)	-0.003 (.009)	0.98	0.91	0.82	0.68
Current exposure*time	-0.019 (.007)				
Age at hire (per year)	-0.029 (.006)	0.76	0.79	0.83	0.91
Age at hire*time	0.001 (.002)				
Year at hire (per year since 1940)	0.007 (.008)	1.15	1.52	2.16	4.35
Year at hire*time	0.007 (.004)				

*: "Time" was measured in year.
**: The unit difference of risk ratio for cumulative exposure = 1 g/m^3-year,
current exposure = 100 mg/m^3,
age at hire = 10 years,
and year at hire = 10 years.

Table 3. Parameter estimates (β_{ij}, i for covariates and j for length of employment) from stratified survival analysis of 1-st GAP occurrence by the length of employment, using the Cox proportional hazard model.

Variables	Length of employment (year)				
	<2	2-4	5-9	10-19	20+
Cumulative exposure (100 $mg/m^3 \cdot year$)	-0.041	0.032	0.021	0.008	-0.004
Current exposure (100 mg/m^3)	0.004	-0.065	-0.075	-0.419	0.060
Age at hire	-0.020	-0.043	-0.030	0.046	-0.178
year at hire	0.010	0.021	0.071	-0.290	-0.090

Table 4. Predictors of time to early termination from employment in proportional hazards models.

Variables	Parameter estimate (standard error)	Risk Ratio (p-value)[**] Length of employment (year).[*]			
		1	5	10	20
GAP	-0.071 (.060)	0.93	0.93	0.93	0.93
Cumulative exposure (100 mg/m^3-year)	-0.003 (.001)	0.97	0.97	0.97	0.97
Current exposure (100 mg/m^3)	0.035 (.006)	1.04	1.04	1.04	1.04
Age at hire (per year)	-0.036 (.005)	0.72	0.81	0.94	1.27
Age at hire*time	0.003 (5.94E-4)				
Year at hire (per year since 1940)	-0.009 (.008)	0.96	1.17	1.51	2.48
Year at hire*time	0.005 (.001)				

* : "Time" was measured in year.
** : The unit difference of risk ratio for cumulative exposure = 1 g/m^3-year,
current exposure = 100 mg/m^3,
age at hire = 10 years,
and year at hire = 10 years.

Table 5. Predictors of time to death from respiratory cancer in proportional hazards models with time interactions.

Variables	Parameter estimate (standard error)	Risk Ratio (p-value)[**] Length of follow-up (year)			
		1	5	10	20
GAP	1.270 (1.36)	3.20	2.10	1.23	0.43
GAP*time	-0.106 (.066)				
Cumulative exposure (100 mg/m^3-year)	-0.009 (.011)	0.92	0.94	0.97	1.03
Cumulative exposure*time[*]	0.0006 (.0004)				
Current exposure (100 mg/m^3)	0.239 (.282)	1.25	1.15	1.05	0.87
Current exposure*time	-0.019 (.016)				
Age at hire (per year)	0.148 (.054)	4.22	3.60	2.94	1.97
Age at hire*time	-0.004 (.0024)				
Year at hire (per year since 1940)	0.044 (.132)	1.56	1.60	1.65	1.75
Year at hire*time	0.0006 (.007)				

*: "Time" was measured in year.
**: The unit difference of risk ratio for cumulative exposure = 1 g/m^3-year,
                                         current exposure = 100 mg/m^3,
                                         age at hire = 10 years,
                                 and year at hire = 10 years.

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Possible Future Publications

Employee absenteeism as a surrogate for morbidity status and its relation to the healthy worker survivor effect.   Hertz-Picciotto I, Lee J-T, Arrighi HM