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Effect of Follow-Up Time on Risk Estimates: A Longitudinal Examination of the Relative Risks of Leukemia and Multiple Myeloma in a Rubber Hydrochloride Cohort

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Background *Choice of follow-up time for an occupational cohort can influence risk estimates. We examined the effects of follow-up time on relative risk estimates for leukemia and multiple myeloma in a cohort of 1,845 rubber hydrochloride workers.*
Materials and Methods *We generated standardized mortality ratios (SMRs) for yearly follow-ups, beginning each study in 1940 and increasing study end dates from 1950 through 1996. We used Cox proportional hazards modeling to explore the effects of follow-up time on the exposure–response relationship.*
Results *The SMR for leukemia rose to 13.55 in 1961 and fell nearly monotonically to 2.47 by 1996. Cox modeling suggested interaction between cumulative exposure and time since exposure. A longer time to peak risk was seen for multiple myeloma.*
Conclusions *Because summary risk estimates change with follow-up time, exposure limits set using these estimates may not adequately protect workers. Consideration of appropriate follow-up time and use of more complex temporal models are critical to the risk assessment process.* Am. J. Ind. Med. 42:481–489, 2002. *Published 2002 Wiley-Liss, Inc.*†

KEY WORDS: risk estimates; temporal changes; benzene; leukemia; follow-up time; rubber workers; risk analysis

INTRODUCTION

Occupational epidemiology is an observational and not an experimental activity. The decision of when to conduct an occupational mortality study is usually a matter of opportunity rather than a strategic selection. Subsequent to an initial study, investigators often reason that a follow-up study after a number of years will result in increased study power by accounting for the natural history of disease, allowing accumulation of more person-years at risk and a larger number of deaths. A longer follow-up period is generally expected to result in a more precise estimate of the relative risk for exposed members of the population. How extending follow-up time affects the generalizability of risk estimates has been given less attention.

Researchers have noted temporal changes in relative risk estimates for specific health outcomes following

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occupational exposures. For example, studies have noted decreases in the risk of lung cancer mortality with time since exposure to radon [Hornung and Meinhardt, 1987; Hornung et al., 1998; Langholz et al., 1999] and in leukemia with time since exposure to benzene [Hoel, 1985; Finkelstein, 2000]. If cohort risk changes over time, the appropriate time to evaluate a cohort and methodologies for evaluating the relationship between exposure, time since exposure, and risk must be considered carefully. Depending on the relationship between these factors, the practice of extending follow-up may result in summary estimates of risk which are not generalizable to the same or other cohorts followed for different lengths of time. If these estimates are used to set exposure limits, the limits may be inadequately or overly protective, depending on length of follow-up.

Twenty-five years have passed since Infante et al. [1977] published the first findings on risk of leukemia in workers exposed to benzene at two rubber hydrochloride plants in Ohio. Infante et al. described an excess of leukemia in a group of 748 white male workers exposed to benzene in the production of rubber hydrochloride between 1940 and 1949 and followed for vital status from 1950 until 1975. With vital status follow-up 75% complete, seven leukemia deaths were seen in this group, compared with 1.38 expected, for an overall standardized mortality ratio (SMR) of 5.06 (based on unrounded expected numbers) for this outcome. Subsequent to the initial report, the vital status of the rubber hydrochloride cohort has been followed forward. Rinsky et al. [1981] completed vital status ascertainment for this group to 98% and reported the same seven deaths from leukemia versus 1.25 expected, for an SMR of 5.60. When the cohort was expanded to include workers exposed to benzene for at least a day between January 1, 1940 and December 31, 1965, and followed through December 31, 1981 [Rinsky et al., 1987], there were nine deaths from leukemia versus 2.7 expected, for an SMR of 3.37 (95% CI = 1.54–6.41). Using data collected by Rinsky et al. for a NIOSH follow-up of these workers through 1987, Paxton [1996] published a report showing 14 leukemia deaths among male workers versus an expected number of 3.89, for an SMR of 3.60 (95% CI 1.97–6.04). Vital status of the cohort has subsequently been followed through 1996 [Rinsky et al., 2002, this issue], with 15 deaths and an SMR for leukemia of 2.56 (95% CI = 1.43–4.22) observed among white males. Multiple myeloma also showed an elevated SMR at the 1981 follow-up, with four deaths observed versus one expected (SMR = 4.09; 95% CI = 1.10–10.47). The SMR for multiple myeloma declined to 2.11(0.69–4.96) in the 1996 follow-up. Thus in this cohort, risk estimates for both outcomes have declined through successive follow-up periods.

The findings of Infante et al. [1977] and of other epidemiologic studies of benzene led NIOSH to recommend in 1976 that the Occupational Safety and Health Administration (OSHA) reduce the ceiling for occupational exposure from 10 to 1 ppm. As a result, OSHA issued a temporary emergency standard limiting exposure to 1 ppm as an 8-hr time-weighted average (TWA), with a ceiling limit of 5 ppm [Rinsky et al., 1981], followed by a permanent standard in 1978. However, the permanent standard was rejected by the Fifth Circuit Federal Court, and that court's ruling was upheld by the United States Supreme Court on the basis of insufficient empiric evidence of a significant reduction of leukemia risk if exposures to benzene concentrations were reduced to less than 10 ppm. The 10 ppm 8-hr TWA, with a ceiling limit of 25 ppm, remained the standard until 1987, when OSHA reimposed a 1 ppm 8-hr TWA standard, in light of new epidemiologic and toxicologic data [Rinsky et al., 1987; Nicholson and Landrigan, 1989].

While there has been much examination of how exposure estimates for the cohort impact risk estimates [Crump and Allen, 1984; Paustenbach et al., 1992; Utterback and Rinsky, 1995], little attention has been given to the temporal changes in risk estimates for the cohort and the impact of this temporal variability on risk assessment and standard setting. In setting exposure standards, excess risk is used to project an excess number of deaths over a working lifetime. One of the perceived benefits of extending follow-up time is the increased precision of the resulting risk estimates. However, the impact of increasing follow-up on risk estimates has not always been fully considered. The disease induction period is traditionally dealt with by lagging exposures so that the most recent exposures, which are thought to have occurred after the disease is induced, but not yet manifest, are discounted. Lamm et al. [1989] noted that while *time since first exposed* is traditionally included in models to account for latency, time between last exposure and date of diagnosis or death may be more pertinent, particularly if risk of disease decreases with time since exposure, indicating that the substance acts as a promotor or progressor, rather than an initiator.

In addition to including a term for latency or *time since exposure* in models, other more complex approaches such as weighted exposure windows have been invoked to address these and related temporal issues. Crump [1996] developed a function in which exposure weights increase between zero years post exposure and the mode of the latency distribution and then decrease toward zero, so that exposures at the mode are weighted most heavily. Langholz et al. [1999] has proposed alternative approaches to evaluating latency using bilinear and exponential decay models.

In the current study, we investigated temporal changes in risk estimates for the rubber hydrochloride cohort through a series of analyses with increasing follow-up time. We also explored the relationship between *cumulative exposure* and *time since exposure* using different models. We examined both leukemia and multiple myeloma mortality to allow comparison of temporal changes in risk for two outcomes with different expected latencies.

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METHODS

The rubber hydrochloride cohort comprises workers employed at three facilities at two locations in Ohio in which production began as early as 1936 and ended by 1976. In the most recent follow-up in 1996 [Rinsky et al., 2002], the study population included 1,845 male and female workers, including 1,291 exposed to at least 1 ppm-day of benzene. The history of the study population is described in a companion article and exposure assessment methods have been published previously [Infante et al., 1977; Rinsky et al., 1981; Rinsky, 1989; Utterback and Rinsky, 1995].

SMR Analyses

We investigated temporal changes in risk estimates for leukemia and multiple myeloma by performing a series of SMR analyses on the subcohort of exposed workers. The SMR procedures are described in Rinsky et al. [2002] in this issue.

The study begin-date was retained at January 1, 1940, for each of the analyses. We included workers who were employed in an exposed area for at least 1 day after January 1, 1940, and were still alive as of January 1, 1950. We began observation of person-years at risk and of leukemia deaths on January 1, 1950. For multiple myeloma, we began to observe person-years at risk and deaths on January 1, 1960, because appropriate vital statistics for multiple myeloma were not available before that date. Thus for the leukemia analyses, the first person-day at risk was January 1, 1950, or the first day of employment in an exposed department, whichever was later. The first person-day at risk for multiple myeloma was January 1, 1960, or the first day of employment in an exposed department, whichever was later. The first annual study end-date examined was December 31, 1950, for leukemia and December 31, 1960, for multiple myeloma. For each outcome, the study end-date was moved forward by a year at a time until the end of follow-up was reached (December 31, 1996).

Modeling

To allow for a more complex examination of factors related to follow-up time, we also performed Cox proportional hazards modeling using SAS PROC PHREG (SAS Institute, Inc., Cary, NC) on the full cohort of all exposed and unexposed workers. All workers employed for at least 1 day in the rubber hydrochloride departments after January 1, 1940, and still alive as of January 1, 1950, were eligible for inclusion in the risk sets. We also ran models on the exposed cohort alone. Criteria for inclusion in the risk set are described in the companion paper. For each member of the risk set, observation was terminated when that employee reached the age of the case at time of death, so that accumulation of exposure and all other time-dependent variables was truncated at that point.

We estimated the relative risk of each outcome (leukemia and multiple myeloma) per person-year of benzene exposure using the log-linear model $RR = \exp(\beta \times \text{cumulative exposure})$, which was employed in most of the previous analyses of the cohort and which fit as well as the linear model, as shown in the companion paper. As with the SMR series, the first annual study end-date examined was December 31, 1950, for leukemia and December 31, 1960, for multiple myeloma. For each outcome, the study end-date was again moved forward by a year at a time until the end of follow-up was reached (December 31, 1996). We did not impose lags in the analyses to avoid confusing the temporal effect of interest, length of follow-up.

To examine whether including temporal variables in the model is sufficient to account for temporal changes in risk estimates, the series of models described above was run three more times with models that included the main effect of cumulative exposure plus one of the following temporal covariates: (1) time since first exposed/employed, (2) time since median exposure, and (3) time since last exposed/employed. Both continuous and dichotomous temporal variates were examined. We compared risk estimates from 1961 and 1996 to determine whether adding a temporal variable reduces the difference in risk estimates and the variability in risk estimates for cumulative exposure over this time period.

To further investigate the shape of the relationship between *cumulative exposure* and *time since exposure*, we performed analyses stratifying on time since last exposed. We also divided cumulative exposure into windows of follow-up time to contrast the influence of different exposure windows on risk estimates. All multivariate analyses were restricted to the leukemia outcome due to the small number of cases of multiple myeloma.

RESULTS

SMR Analyses

Leukemia (disease of short latency)

SMRs for the sequential studies ranged from a high of 32.51 in the first year, 1950, to a low of 2.47 in the last year of follow-up, 1996. Statistical significance was reached in 1954, and Figure 1 presents results from that point forward, as the estimates for 1950–1953 have extremely wide confidence intervals. The confidence intervals narrowed considerably with additional follow-up. All yearly results are presented in Appendix A.

Once statistical significance is attained, the point estimate quickly rises to a peak of 13.55 in 1961 and then

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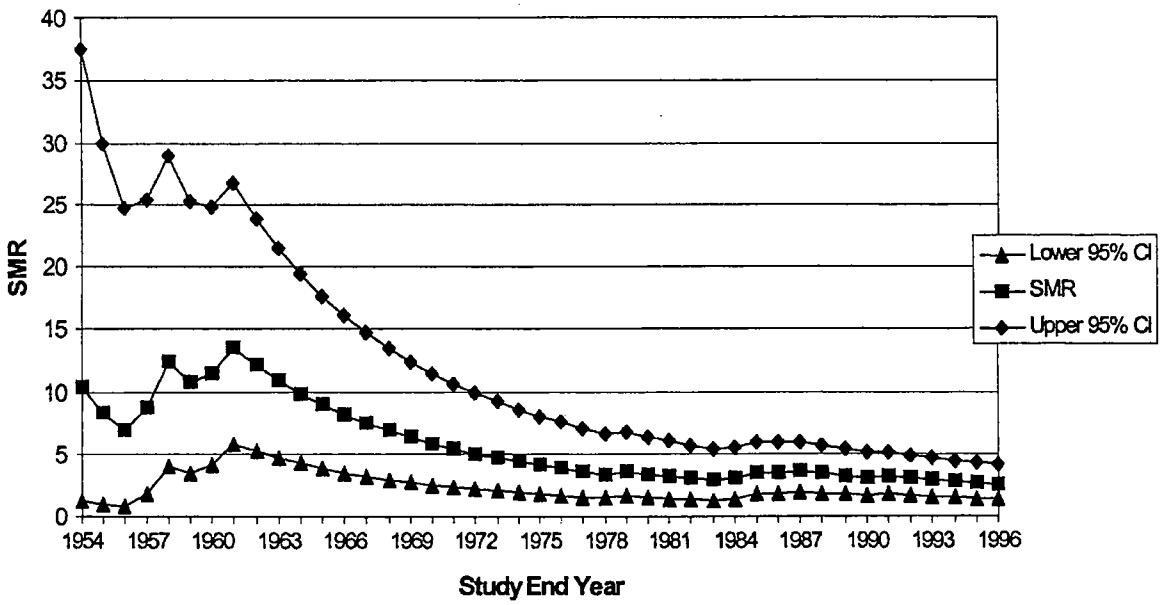


FIGURE 1. Leukemia SMRs by study end date beginning with achievement of statistical significance in 1954.

begins a fairly sharp decline, which is strictly monotonic until 1977. The decline continues through the most recent follow-up in 1996, with small excursions as each new case is encountered.

As Table I shows, the confidence intervals for the periods 1961–1963 and 1993–1996 are mutually exclusive, with the lower bound for 1961–1963 greater than the upper bound for 1993–1996.

Multiple myeloma (disease of long latency)

For multiple myeloma, the point estimates also exhibit an initial rise and then begin to decline (Fig. 2). The point estimates are statistically significant (95% confidence intervals exclude 1.0) for the time period 1981–1983, after the 4th death occurred, and again in 1989, when the 5th death occurred. For the remaining time periods, the risk estimates were elevated but not statistically significant. While there was a total of eight cases, three were in persons who were judged to have jobs that did not bring them into contact with benzene and were, therefore, not included in calculations of the SMR.

Visual examination of Figure 2 reveals a general downward trend in the point estimates, interrupted by excursions from 1979 to 1981 as new deaths are added to the small number of cases (see Appendix B for yearly results).

Modeling

For leukemia, Cox proportional hazards modeling results confirm the temporal changes observed in the SMR.

TABLE I. Highest and Lowest Year Estimates for Risk of Leukemia

Highest SMRs				Lowest SMRs			
Year	Cumulative cases	SMR	95% CI	Year	Cumulative cases	SMR	95% CI
1960	6	11.42	4.17–24.87	1993	15	2.83	1.58–4.67
1961	8	13.55	5.83–26.70	1994	15	2.7	1.51–4.45
1962	8	12.13	5.22–23.90	1995	15	2.58	1.44–4.25
1963	8	10.91	4.70–21.50	1996	15	2.47	1.38–4.07

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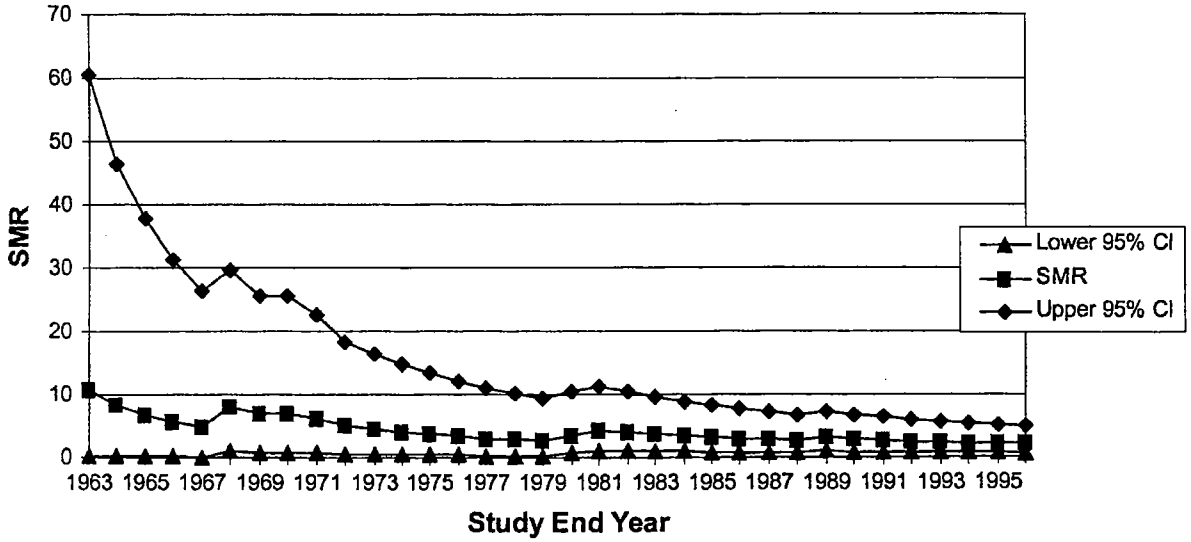


FIGURE 2. Multiple myeloma SMRs by study end date, beginning with first observed case in 1963.

When we modeled risk for the entire cohort, both exposed and unexposed, we observed a similar initial elevation with the peak statistically significant estimate for the 1961 follow-up, followed by a decline through the 1996 follow-up. We tested the proportional hazards assumption on the 1996 data set and that while in the strict sense it does hold for this cohort, with no significant interaction observed between case age at death and *cumulative exposure*, the parameter estimate was negative, suggesting a decrease in risk with attained age (parameter estimate = −0.0002, standard error = 0.00011, *P*-value = 0.12).

Because temporal changes in risk have sometimes been addressed simply by adding temporal variables to a cumulative exposure model at a single point in time, we next investigated whether this approach actually yields risk estimates that are more nearly constant over time. We found that when *time since exposure* was added to the model, whether modeled as time since first, median, or last exposure, and whether in continuous or dichotomous form, the wave form of the risk estimates persisted over time, with risk for leukemia peaking in the early 1960s and reaching its lowest point in 1996. Addition of the temporal variables did not significantly reduce the difference over time or the variability of the estimates. For example, the per unit relative risk estimate for part-per-million-year (ppm-year) of exposure peaked at 1.01 (95% CI 1.006–1.014) in 1961 and fell to 1.005 (95% CI 1.003–1.008) in 1996 for the simple Cox model of cumulative exposure among exposed workers. When *time since last exposure* dichotomized at 5 years was added to the model, the per unit relative risk estimate peaked at 1.009 (95% CI 1.004–1.013) in 1961 and fell to 1.004 (95% CI 1.001–1.007) in 1996. Adding an interaction term between *cumulative exposure* and *time since last exposure* reduced this difference, but the confidence intervals for the two periods continued to overlap. For example, when an interaction term between *cumulative exposure* and *time since last exposure* dichotomized at 5 years was included in the model, the per-unit peak relative risk fell from 1.009 (95% CI 1.004–1.013) in 1961 to 1.007(95% CI 1.002–1.011) in 1996. We looked at a series of models with interaction terms including *time since last exposure* dichotomized at 5, 10, 15, and 20 years, respectively, and found that the 5-year dichotomization minimized both the difference over time and the variability of the estimates during this period. However, in this small cohort, the confidence intervals for the 1961 and 1996 estimates overlapped in all models. Thus the size of the cohort hindered evaluation of the efficacy of adding interaction terms for reducing the change over time, as well as assessment of the extent of any residual change in relative risk estimates over time.

We used the 1996 data to further examine the relationship between *cumulative exposure* and *time since exposure* (Table II). We found that when entered as a continuous variable, *time since exposure* is not statistically significant in a bivariate model with *cumulative exposure*. However, in a model which includes the interaction between *cumulative exposure* and *time since exposure*, the interaction term was significant. On the other hand, when *time since exposure* was dichotomized at 5, 10, or 20 years, *time since exposure* was significant in the bivariate model. In the model, which

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TABLE II. Relative Risk of Leukemia (1996)—Cumulative Exposure and Time Since Last Exposed

Model	Parameter estimate	Standard error	*P*-value
Cumulative exposure (ppm-years)	0.00520	0.00116	0.0001
Cumulative exposure (ppm-years)	0.00352	0.00150	0.0188
Time since last exposure (years)	−0.04214	0.02683	0.1162
Cumulative exposure (ppm-years)	0.00719	0.00186	0.0001
Time since last exposure (years)	−0.01988	0.02745	0.4690
Cumulative exposure × time since last exposure	−0.00041	0.00019	0.0252
Cumulative exposure (ppm-years)	0.00383	0.00137	0.0053
Time since last exposure (dichotomized at 5 years)	−2.11796	0.72001	0.0033
Cumulative exposure	0.00667	0.0021	0.0011
Time since last exposure (dichotomized at 5 years)	−1.03691	0.9752	0.2876
Cumulative exposure × time since last exposure (dichotomized at 5 years)	−0.00573	0.0034	0.0946

included the interaction term, that term was not significant but was in the same direction as found using *time since exposure* as a continuous variable. These observed differences in statistical significance are likely due to the small number of cases in the study.

To further investigate the shape of this relationship, we stratified on time since last exposed, with each member of each risk set falling into one of four *time since exposure* categories. The results (Table III) suggest that risk is maximal in the first 5 years since last exposure, and decreases with increasing time since last exposure.

We obtained similar results when we divided cumulative exposure into windows of follow-up time. Each worker's cumulative exposure was split out into exposure received 0–4.9, 5–9.9, 10–14.9, and 15 years or more prior to the cutoff (age at death of the case), and terms for all the exposure windows were included simultaneously in the model. We found that exposures received in the interval 5–9.9 years prior to cutoff appear to be most pertinent, although sparse data again hinder precise definition of the relative risks (Table IV).

Results for multiple myeloma also suggest a decline with *time since last exposure*. However, with only five exposed cases available, the relationship is not well defined.

DISCUSSION

In this rubber hydrochloride cohort, the risk observed for leukemia mortality at first follow-up (shortly after the facility closed) showed a large and statistically significant elevation, despite the small number of cases. In occupational studies today, risks are usually much lower. Researchers are

TABLE III. Relative Risk of Leukemia (1996)—Stratified on Time Since Last Exposed to Benzene

Category	Parameter estimate	Standard error	*P*-value	Relative risk
Cumulative exposure	0.00377	0.0015	0.0120	1.004[a]
0 years since last exposed	Reference	—	—	1.000
0.01–4.9 years since last exposed	0.23939	0.90917	0.7923	1.270
5–19.9 years since last exposed	−1.80472	1.01307	0.0748	0.165
> 20 years since last exposed	−2.05808	1.09567	0.0603	0.128

[a]Change in relative risk per unit change in exposure (per ppm-year of benzene).

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TABLE IV. Relative Risk of Leukemia (1996)—Exposure Windows

Category	Parameter estimate	Standard error	*P*-value	Relative risk
Exposure 0–4.9 years prior to cutoff	Reference	—	—	1.000[a]
Exposure 5–9.9 years prior to cutoff	0.01925	0.00712	0.0069	1.019[a]
Exposure 10–14.9 years prior to cutoff	0.01344	0.00733	0.0665	1.014[a]
Exposure ≥ 15 years prior to cutoff	−0.00159	0.00336	0.6354	0.998[a]

[a]Change in relative risk per unit change in exposure (per ppm-year of benzene).

motivated to extend follow-up time in order to account for the natural history of disease, increasing observed cases and hence the power to observe a statistically significant effect. However, as our findings demonstrate, extending follow-up time can affect relative risk estimates, even when a cohort meets proportional hazards assumptions.

The summary relative risk estimate of 13.55 for leukemia in 1961 is nearly threefold the estimate of 5.06 described in the first published report in 1977, which led to the call for reduced exposure limits. For this cohort, summary relative risk estimates for both leukemia and multiple myeloma change over time, rising to a peak and then falling off over a number of years. The decline in summary estimates of relative risk of leukemia, from a peak of 13.55 to a low of 2.47, will soon approach 10-fold if no new cases occur as the cohort continues to age. The positive exposure response curve remains, however, even after prolonged follow-up.

Stratified analyses suggest that for this cohort, relative risk peaks in the first few years after cessation of exposure and that exposures 5–10 years prior to the cutoff have the maximal impact on risk, although relative risk in other periods is elevated as well. The results suggest that ensuring maximum protection for benzene workers requires assessing risk at its peak of 5–10 years since last exposure. Finkelstein [2000], studying this same cohort, found that exposures in the most recent 10 years were most pertinent and suggested that occupational standards should, therefore, be based on control of risk during that interval. These results suggest that it is insufficient to adjust for temporal changes by simply adding to the model a term for time since exposure, because the shape of the relative risk estimates over time is wave-like, rising quickly, and then falling off. Treating temporal variables as confounders, simply adding them to the model with cumulative exposure, or stratifying in an SMR analysis, is not adequate in this case, because the temporal variables are acting as effect modifiers, rather than as confounders. Given the presence of this interaction, summary estimates are misleading and time-specific risk estimates must be provided.

The observation of similar temporal changes in risk estimates in other cohorts suggests that these issues are not limited to this benzene-exposed cohort. Finkelstein [2000] noted that studies of ionizing radiation have found that excess relative risk peaks a number of years post-exposure and then begins to decline, for some cancers under certain exposure scenarios. For example, in the case of the acutely exposed atomic bomb survivors, the relative risk of leukemia peaked within 10 years of exposure and then declined. Excess risk for lung cancer in cohorts of occupationally exposed uranium miners also exhibited an increase followed by a decrease. Studying asbestos exposure and lung cancer, Stayner et al. [1997] found that the best fitting model included an interaction between asbestos exposure and *time since first exposure*, with a peak slope among workers with 30–39 years since first exposure. However, among the atomic bomb survivors, stomach cancer exhibited no such trend, highlighting the need to address this question for different health outcomes, in acute versus chronic exposure scenarios, and with different agents. Moreover, the small number of cases in this cohort, particularly for multiple myeloma, reduces the ability to rule out chance as the source of these findings, highlighting the need to replicate these findings in other, larger cohorts.

A number of factors may contribute to the observed decline in relative risk with increasing *time since last exposure* in this cohort. The role of these factors must be considered within the context of the cohort's history. The rubber hydrochloride production facilities used benzene for four decades (mid 1930s to 1976), and by the 1996 follow-up, 20 years had passed since any worker was last exposed in these plants. Latency is one potential explanation for the decline in relative risk for hematopoietic malignancies with time since exposure. In particular, latency for leukemia is believed to be relatively short, although it may vary by subtype. As time passes since anyone in the cohort was last exposed at these facilities, new exposure-related cases become less likely. An alternative explanation is that workers who were highly susceptible to leukemia succumbed to the disease early, leaving a less susceptible population at risk for the majority of the follow-up period. The decrease

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in observed relative risk began while new workers were still being hired, allowing the continuing introduction of susceptible individuals and of individuals in the relevant latent period. However, more than 90% of the cohort was hired prior to 1960, so the expectation for new cases to appear among the few new workers was small. Another possibility is that changes in exposure or exposure-rate may be involved, although no clear patterns are evident among the cases.

In occupational cohorts, these temporal variables are often correlated with exposure, as well as with each other. Correlations between the temporal variables are particularly strong in this cohort. The short operating history of the facilities leads to strong correlations between birth cohort and age first employed ($R = -0.91$), and between birth cohort and age first exposed ($R = -0.91$). Age at first exposure is strongly correlated with age at first employment for the exposed members of the cohort ($R = 0.99$). Time since last exposure is likely to be highly correlated with the other temporal variables due to the history of the facilities. Each of these temporal variables, (*time since exposure*, *birth cohort*, and to a lesser extent, *age first exposed*) adds significant explanatory value when added to a *cumulative exposure* model for the updated cohort. Intercorrelations between these temporal variables, as well as the size of the cohort, hinder assessment of whether some residual temporal variability remains even after adding to the model a temporal variable such as *time since exposure* and an interaction term between the temporal variable and *cumulative exposure*.

This examination of temporal changes in relative risk in the rubber hydrochloride cohort highlights the importance of examining the relationship between follow-up time and risk estimates as part of the risk assessment process. These results show that when risk is examined can impact the adequacy of protective measures based on the relative risk estimates, and also highlight the importance of ceasing exposure as quickly as possible once an excess is observed in an exposed population, as well as limiting overall exposure, because the observed relative risk may not be the maximum risk experienced by the cohort. Hoel [1985] illustrated the repercussions of extrapolating temporally dependent risk estimates to a working lifetime under different exposure scenarios and different risk models (multiplicative versus additive). Hoel found that using long-term follow-up after a short-term exposure leads to an underestimate of lifetime relative risk using either additive or multiplicative models, while short-term follow-up for an exposure of a short-term exposure led to an overestimate of risk using an additive model but an underestimate of lifetime risk using a multiplicative model. Serious consideration of when to examine risk, and how to contend with temporal changes in risk estimates, is critical if these estimates are to serve as the basis for occupational standards which adequately protect workers.

APPENDIX A: Longitudinal SMR Results—Leukemia in a Rubber Hydrochloride Cohort

Study end year	Cumulative cases	SMR	95% CI
1950	1	32.51	0.82–180.60
1951	1	15.06	0.38–83.69
1952	1	9.49	0.24–52.72
1953	1	6.79	0.17–37.73
1954	2	10.41	1.26–37.57
1955	2	8.30	1.00–29.96
1956	2	6.85	0.83–24.72
1957	3	8.67	1.79–25.35
1958	5	12.41	4.01–28.98
1959	5	10.79	3.49–25.22
1960	6	11.42	4.17–24.87
1961	8	13.55	5.83–26.70
1962	8	12.13	5.22–23.90
1963	8	10.91	4.70–21.50
1964	8	9.86	4.25–19.43
1965	8	8.96	3.86–17.65
1966	8	8.17	3.52–16.09
1967	8	7.46	3.21–14.70
1968	8	6.83	2.94–13.47
1969	8	6.28	2.70–12.38
1970	8	5.81	2.50–11.46
1971	8	5.39	2.32–10.63
1972	8	5.01	2.16–9.87
1973	8	4.66	2.01–9.18
1974	8	4.35	1.87–8.57
1975	8	4.07	1.75–8.02
1976	8	3.82	1.64–7.52
1977	8	3.58	1.54–7.06
1978	8	3.37	1.45–6.63
1979	9	3.56	1.63–6.76
1980	9	3.35	1.53–6.37
1981	9	3.16	1.44–6.01
1982	9	2.99	1.36–5.68
1983	9	2.83	1.29–5.37
1984	10	2.97	1.42–5.47
1985	12	3.38	1.75–5.91
1986	13	3.48	1.85–5.95
1987	14	3.56	1.95–5.98
1988	14	3.39	1.85–5.68
1989	14	3.22	1.76–5.40
1990	14	3.06	1.67–5.13
1991	15	3.12	1.74–5.14
1992	15	2.97	1.66–4.89
1993	15	2.83	1.58–4.67
1994	15	2.70	1.51–4.45
1995	15	2.58	1.44–4.25
1996	15	2.47	1.38–4.07

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APPENDIX B: Longitudinal SMR Results—Multiple Myeloma in a Rubber Hydrochloride Cohort

Study end year	Cumulative cases	SMR	95% CI
1960	0	*	*
1961	0	*	*
1962	0	*	*
1963	1	10.90	0.28–60.58
1964	1	8.36	0.21–46.46
1965	1	6.79	0.17–37.71
1966	1	5.65	0.14–31.37
1967	1	4.78	0.12–26.54
1968	2	8.20	0.99–29.61
1969	2	7.13	0.86–25.73
1970	2	7.13	0.86–25.73
1971	2	6.33	0.77–22.83
1972	2	5.07	0.61–18.31
1973	2	4.57	0.55–16.51
1974	2	4.15	0.50–14.97
1975	2	3.75	0.45–13.52
1976	2	3.40	0.41–12.28
1977	2	3.10	0.38–11.20
1978	2	2.84	0.34–10.25
1979	2	2.61	0.32–9.41
1980	3	3.59	0.74–10.50
1981	4	4.42	1.20–11.30
1982	4	4.09	1.11–10.45
1983	4	3.79	1.03–9.70
1984	4	3.53	0.96–9.03
1985	4	3.27	0.89–8.37
1986	4	3.04	0.83–7.79
1987	4	2.84	0.77–7.27
1988	4	2.66	0.72–6.79
1989	5	3.11	1.01–7.26
1990	5	2.90	0.94–6.78
1991	5	2.72	0.88–6.35
1992	5	2.55	0.83–5.97
1993	5	2.40	0.78–5.62
1994	5	2.27	0.73–5.30
1995	5	2.15	0.69–5.02
1996	5	2.04	0.66–4.76

*Observed = 0 for the time period.

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