Environmental Health Perspectives
Vol. 82, pp. 199-206, 1989

Use of Longitudinal Analysis of Peripheral Blood Counts to Validate Historical Reconstructions of Benzene Exposure

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We studied over 17,000 peripheral blood counts, accumulated during hematologic surveillance from 1940 through 1975, from a cohort of 459 benzene-exposed workers. Linear regressions demonstrated significant decreases in white and red cell counts, as well as hemoglobin, for workers exposed during the 1940s, without persistent trends over the ensuing 25 years. Strongly positive correlations were observed between these blood count fluctuations and fluctuations in retrospective estimates of benzene exposures for these workers in the earlier period of surveillance (mean estimated exposure 1940 to 1948, 75 ppm); but not for later years, (mean estimated exposure 1948 to 1975, 15 to 20 ppm). These data suggest substantial limitations of hematologic examination of populations to detect abnormalities in populations currently exposed to benzene. The analysis also demonstrates a novel approach to the biological validation of exposure estimates based upon limited industrial hygiene and historical record data. The application of biologic monitoring data may be useful for assisting decisions in reconstruction of a previous exposure.

Introduction

Determination and quantification of the adverse health effects of environmental and occupational exposure to xenobiotics has become a major concern of government, industry, and the public. Because of cost and time constraints, as well as our inability to forecast future health problems, many epidemiological studies of such exposure-effect relationships are retrospective rather than prospective. To perform such retrospective studies, it is necessary to analyze records on populations exposed to chemicals 30 to 50 years ago.

In contrast to the relatively advanced and standardized epidemiologic techniques available for evaluation of disease occurrence, methods for retrospectively assessing exposures are not well standardized, and are often custom designed for a particular project. One commonly used method involved defining a cohort of people as "exposed" by virtue of their employment by a single company or within a single industry. An improvement on this exposure assignment is to include duration of employment in the analysis. A further level of refinement is to subclassify employees according to their actual job within the factory, presuming that some jobs had more exposure to particular agents of interest than did others. The investigator tries to identify areas small enough to have had relatively uniform exposure, but large enough to contain sufficient numbers of workers for the analysis (*1*). Next, knowledge about levels of exposure to a particular agent for a specific job over a given period of time can be used to attempt definition of dose-response relationships, often a prelude to a risk assessment. Calculation of cohort mortality or assignment of a person to a job at a particular time based on a personnel record are accomplished by relatively straightforward techniques. In contrast, retrospective assignment of actual exposure concentrations of an inhaled or dermally absorbed compound to specific areas or jobs at specific times is more difficult and lacks standardized methods. Records available for assigning exposures are inconsistent and vary more from company to company than do usual personnel files.

As more detailed indicators of past exposures are sought in order to quantify dose-response relationships for human disease, investigators have utilized previously recorded industrial hygiene data. The utility of these data varies with respect to technical quality, spatio-temporal pattern of collection relative to where, when, and how long an individual worked at a particular job, changes made in the process of data collection, and changes in the

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associated protective machinery and personal equipment that would affect exposures over time. Frequently, only small numbers of actual measurements taken at a few time points are available, and these must be generalized or extrapolated to cover an entire workforce over an extended period of time. Because of the large amount of extrapolation and generalization required to characterize a workforce, disagreement has arisen between investigators on characterization of exposures. In this regard, an objective biological guide that would at least indicate the direction of trends or changes in exposure is desirable, since it may provide some biological input into determinations of which jobs actually entailed greater or lesser exposures, or what exposure ranges were associated with particular jobs or areas.

We recently had the opportunity to compare two different sets of retrospective exposure estimates for a cohort of benzene-exposed rubber workers (*2,3*). These estimates were based on identical, sparse industrial hygiene data and relatively complete individual job history information. These two evaluations used significantly different assumptions for assigning exposures when time- and job-specific exposure data were lacking, as was often the case. The cohort is known to have a statistically significant excess of leukemia [standard mortality ratio (SMR = 330)] and possibly other hemolymphopoietic malignancies (for multiple myeloma, SMR = 400) (*4*). It is widely acknowledged to be the best cohort available on which to base a human risk assessment for benzene (*5*), and thus the benzene exposures associated with the increased mortality are of great importance.

It is well documented in the literature that benzene exposure is associated with pancytopenias as well as lesser reductions in peripheral blood counts, in an apparent dose-dependent manner (*6*). Although the precise nature of the dose-response curve is not known, it may be inferred that when an exposed cohort as a whole has lower average blood counts, higher benzene exposures are a likely explanation. It is important to note that this does not refer to frank cases of marrow aplasia associated with a 50% mortality and a documented increased risk of leukemia, but rather to dose-dependent and reversible cytopenias. Based on this well-documented ability to depress peripheral blood counts, we hypothesized that inferences could be made about benzene exposure if appropriate longitudinal hematologic surveillance data were available on a cohort. Our findings suggest that hematologic surveillance data does in fact distinguish between widely divergent competing exposure estimates and may even be used to validate a post-hoc exposure scheme based on nonsystematically collected industrial hygiene data.

Methods

For our studies, which have been described in greater detail previously (*7*), we used hematologic surveillance records of 459 rubber hydrochloride workers from the Pliofilm production departments of an Ohio rubber products manufacturer. This group is derived from a cohort of approximately 1200 rubber workers from 2 separate locations (St. Mary's, OH, and Akron, OH) whose mortality has previously been described (*2,4,8,9*). The American Petroleum Institute, through a Freedom of Information request, provided us with complete work records and hematologic surveillance data on 459 workers, all from the St. Mary's, OH, location. As far as we know, no other hematologic surveillance records are currently available for this cohort, although it is likely that surveillance was performed on some of the workers at the Akron location as well as on other individuals at the St. Mary's plant.

For each individual, we obtained a cover sheet which showed demographic data and a chronologic work history of his rubber hydrochloride jobs with beginning and ending dates, as well as records of his raw blood counts.

The exposure estimates for the plant in St Mary's are based on multiple retrospective sources including periodic air monitoring in the 1940s, 1950s, and 1960s by the company, the state of Ohio and the University of North Carolina, as well as one day of sampling in 1976 by National Institute of Occupational Health and Safety (NIOSH). Specific annual exposures were delineated for each of 35 different job titles in the location under study. The ambitious effort of amassing and interpreting the basic industrial hygiene data was originally performed by NIOSH and possibly represents the most comprehensive retrospective industrial hygiene effort to date (*2,9*). In the Rinsky et al. studies, time-weighted average (TWA) exposure concentrations were estimated for each of 13 distinct areas in the plant, referred to as "exposure classes," associated with specific manufacturing areas in which industrial hygiene data had been collected (*2*). These investigators created a job-exposure matrix, tabulating an estimated concentration of benzene for each exposure class (as well as some hybrid classes) for each year that the cohort worked, from 1939 to 1976. When available, actual results of past industrial hygiene measurements were included in the matrix, accounting for 86 of the 493 cells, or 17%. The remaining cells of the matrix were filled by interpolating between measured values, or the backward or forward projection of those measured values which were either the first or last in a given exposure class. Since the earliest industrial hygiene measurement was in 1947, all exposure values in cells prior to 1947 are based on backward projection of measurements taken after this year. The large majority of pre-1947 exposure estimates are based directly on measurements obtained in the early 1960s, since only five of the classes had a measurement taken as early as the 1950s (*2*).

Exposure estimates presented by Crump and Allen (*3*) were based on Rinsky et al. data except for one substantial difference. For the estimation of early exposures, in the absence of actual measurements, Crump and Allen took into account the facts that the recommended occupational benzene exposure standard was revised downwards in certain years (1941, 1947, 1948, 1957, 1963, and 1969) and that substantial improvement in the exhaust system at the presses of the plant occurred in 1946 (*9*). In general, these differences made the Crump estimates

substantially higher than the Rinsky estimates during the first decade of benzene exposure. In our studies, we linked individual jobs (exposure code and time period) in the Pliofilm process with estimated benzene exposure according to the Rinsky et al. estimates of exposure and according to the Crump and Allen estimates of exposure. Thus, at any time, all jobs in the Pliofilm unit have an assigned benzene exposure concentration from each of the estimates. From here on, the NIOSH exposure estimates of Rinsky et al. are referred to as exposure approach A, and the Crump and Allen estimates are referred to as exposure approach B.

Our data set consisted of handwritten medical department records of about 18,000 blood counts performed on 459 employees from the St. Mary's plant. The date of sampling (from 1940–1975) and handwritten results were legible for 17,279 of the counts. As the blood counts were dated and specific for an individual, each count could be linked to a specific job (exposure class and year) and through that to either of the two exposure estimates. Although information describing the hematologic sampling protocol is incomplete, a medical consultant to the operation published his recommended surveillance program (*10*), which was reviewed in our earlier publication (*7*). The hematology data included complete differential counts; however, in the present studies, only red count, white count, and hemoglobin were completely analyzed. Mean corpuscular volume (MCV) and platelet counts were not performed. All statistical analyses were performed using SAS software (*11*).

Preliminary Analyses

Initially we performed regression analysis against the linked exposures for each of the two exposure schemes using all 17,279 blood counts over all 35 years. We found very low correlation coefficients for these exposures (e.g., for WBC $r = -0.036$ for exposure B and $r = -0.038$ for exposure A). Lagging the exposure data so that blood counts were linked to the individual's exposure 45 days previous to the sample did not noticeably improve these poor correlations. However, examniation of the data revealed that many individuals in the cohort had worked for a short period of time and consequently had given relatively few blood samples.

In an effort to enhance the reliability of the study, all further analyses were conducted only on those individuals who had at least five legible blood samples recorded. This decreased the number of workers included in the analysis by 42%, from 459 to 264; however, the number of blood counts analyzed decreased by only 2.5% to 16,841. For the 264 workers who are included in our analyses, the average length of employment was 9.31 years (SD = 10.1 years) with a range of 0.19 to 36 years.

A further complication in our studies was the fact that we had widely varying numbers of samples from individuals and that there was covariance in the preliminary regression analysis due to multiple blood samples per person. This led us to go beyond analysis of individual blood samples and use data sets which relied on annual means of the exposures and their linked blood counts. Analyses were performed on the 264 subjects with more than 5 counts by computing an arithmetic mean for each parameter in a given calendar year. This yielded 1879 data points, each data point representing the annual mean of all values for any one hematologic parameter on one person. Thus, there were 1879 annual person averages for WBC, for RBC, etc. Actual numbers of observations often deviated slightly from 1879 (the number of WBC counts), as various values were missing due to illegibility.

Table 1. Descriptive statistics for annual averages of hematology variables and exposure estimates.[a]

Variable	*n*	Mean	SD	Minimum	Maximum
WBC	1879	9353	2033	3933	46,475
RBC	1872	5.15	0.34	3.57	6.50
Hemoglobin	1879	101.4	6.35	75	124
Approach A exposures, ppm	1835	16	10.6	0	45
Approach B exposures, ppm	1835	26	33.5	0	259

[a]See text for an explanation of annual averages.

Descriptive statistics on this mean data set are shown in Table 1. Initially we correlated blood counts with time and then with exposure levels. Annual exposure means were calculated as a weighted mean using the linked exposures corresponding to each blood sample in that particular year, from each of the two exposure estimate schemes.

Results

The histograms of the hematologic data show apparently lower values for all three of the major blood parameters, especially WBC (Fig. 1), during the first decade of surveillance. However, as noted, earlier analysis of the entire 17,000 counts did not reveal any consistent or substantial correlation between date and blood count.

Average annual benzene exposures for all members of the cohort who were included in the surveillance for each year are shown in Figures 2*A* and 2*B*. The average approach B estimate was approximately 10 ppm higher than the average approach A estimate for all years (Table 1); however, the differences between the two are much more marked in the 1940s, averaging over 50 ppm annually.

Although preliminary analyses using the hematologic data did not show a strong correlation between blood counts and either exposure estimate over all 35 years, we undertook further exploration of the first decade of work.

Early Effects

From 1940 through 1948 inclusive, 128 individuals who had at least 5 total counts were used in the analysis, for a total of 299 person annual averages and about 1800 blood counts. 1948 was chosen as the cutoff after review of the hematologic and exposure histograms, as this was

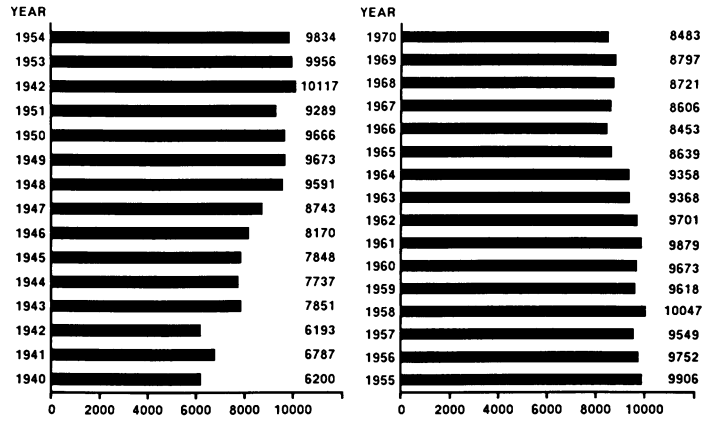

FIGURE 1. Mean annual WBC value for all individuals sampled in a given year, and having over five lifetime counts. Note increasing annual means in the 1940s and more stable means with smaller fluctuations in subsequent years.

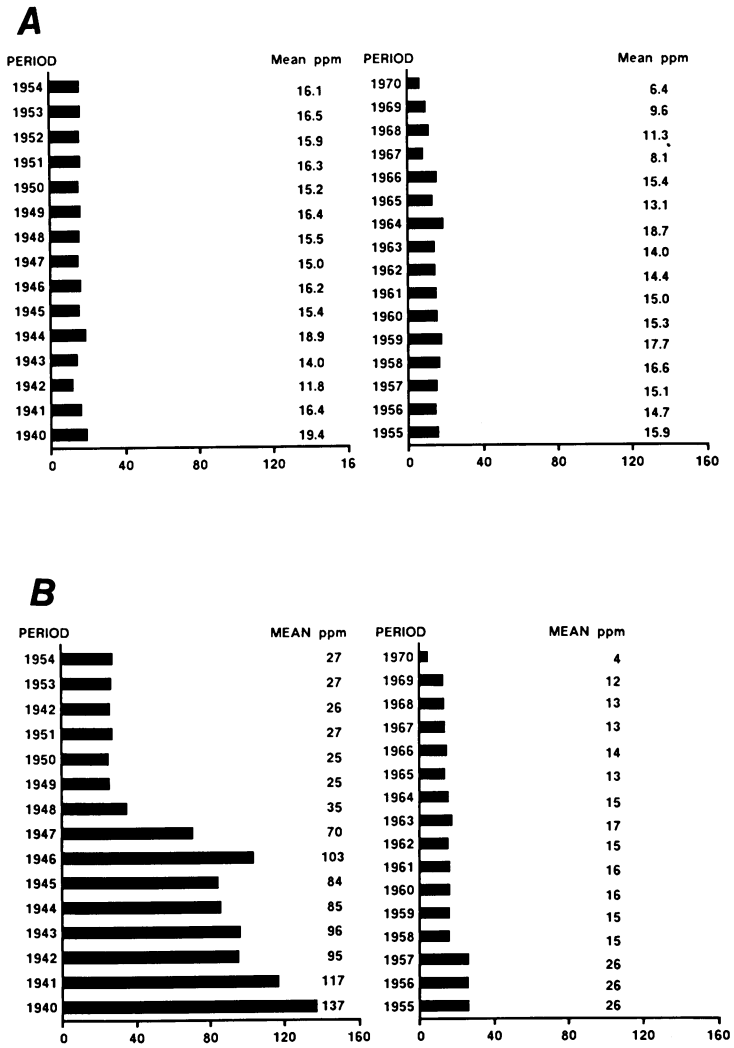

FIGURE 2. Histogram of mean annual estimates for all workers who had a blood sample in any given year for (*A*) approach A and (*B*) approach B. Note the leveling off that occurs in the late 1940s. Average numbers are also shown for each approach.

Table 2. Yearly means for hematology parameters and exposure estimates, 1940–1948.

Year	Workers averaged	WBC	RBC	Hb	Average of approach A, ppm	Average of approach B, ppm
1940	5	6200	4.67	97.00	19	137
1941	18	6787	4.43	89.85	16	102
1942	13	6193	4.46	90.50	12	74
1943	21	7851	4.72	92.79	14	68
1944	22	7737	4.65	90.92	19	71
1945	21	7848	4.65	92.89	15	64
1946	53	8170	4.71	105.93	16	93
1947	70	8743	4.73	108.00	15	62
1948	76	9591	5.13	108.00	17	32
Total	299	8386	4.78	102.21	16	66

the year when both distributions seemed to level off (Figs. 1 and 2B). Using the mean of each individual's counts for each calendar year in which he was sampled, Pearson and Spearman correlations were calculated. We found that WBC ($r = 0.50$), RBC ($r = 0.44$), and hemoglobin (Hb) ($r = 0.71$) were all significantly positively correlated with time, the counts rising from 1940 to 1948.

Figures 2*A* and 2*B* reveal the large discrepancies between approach A and approach B estimates during this time period. Approach B estimates correlated with time form 1940 to 1948 at $r = -0.26$ ($p < 0.001$). while there was no correlation with the approach A estimates. This difference was anticipated because the methods used for making the exposure estimates were different. When the quantitative exposure estimates were substituted for time in the correlations with blood parameters, generally much lower correlations were obtained, although most of the approach B correlations were statistically significant.

Since the highest correlations were obtained using time as the independent variable and blood counts as the dependent variable, further analyses that averaged all individual mean person averages for each of the 9 years (1940–1948) were undertaken. These analyses are statistically more cogent because they further reduce problems with covariance. Annual descriptive statistics are displayed in Table 2. Using this analysis on the years 1940 to 1948, the correlation between WBC and time was $R = 0.94$ (Fig. 3), between RBC and time was $R = 0.73$, between Hb and time was $R = 0.76$ (Table 3). Approach B estimates correlated with time, $R = -0.78$ (Fig. 4); however, approach A estimates were not significantly correlated with time (Fig. 5).

For the period 1940 to 1948, approach B exposure estimates correlated with fluctuations in average annual counts at $R = -0.76$ ($p = 0.016$) for WBC (Fig. 6), $R = -0.56$ ($p = 0.11$) for RBC, and $R = -0.30$ (nonsignificant for Hb). There was no substantial or significant correlation between approach A estimates and any annual average counts over the years 1940 to 1948 (Table 3).

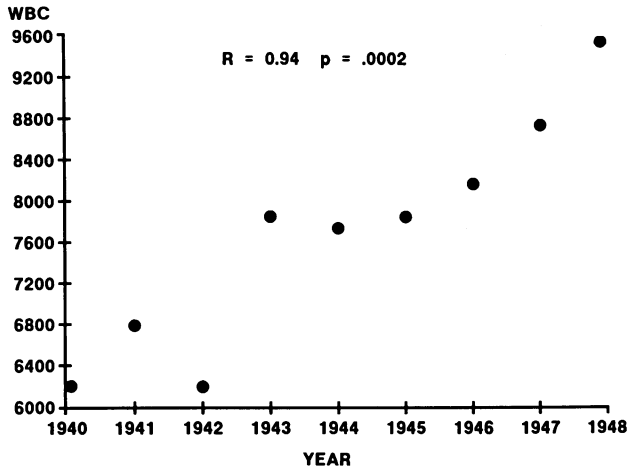

FIGURE 3. Annual average WBC count for all individuals sampled, plotted against the year of sampling, 1940–1948. Pearson correlation coefficient (R) and significance level are shown.

Discussion

This cohort of rubber workers has been among the most intensively and carefully studied cohorts in the history of occupational health (*2,3,4,8,9*). The original findings by Infante et al. of seven leukemia deaths, (1.48 expected) (*8*) led OSHA in 1977 to propose an Emergency Temporary Standard for benzene of 1 ppm instead of the current 10 ppm (TWA). The ensuing litigation led both the Emergency Temporary Standard and a subsequent proposed 1-ppm standard to be rejected by the courts for a variety of reasons. In December 1987, OSHA promulgated a 1-ppm permanent standard for benzene, after hearing risk estimates incorporating the competing approaches to exposure assessment discussed here (*5*). The more recent availability for part of the cohort of the present hematological data base has made possible validation of the approach B estimates compared with the approach A estimates.

Table 3. Correlation of hematology parameters with date and exposure estimates, grouped by yearly means, 1940–1948.

	Correlation ($n = 9$)		
	Time	Approach A estimates	Approach B estimates
WBC	0.94 (0.0002)	−0.05 (0.89)	−0.76 (0.016)
RBC	0.73 (0.03)	0.10 (0.79)	−0.56 (0.11)
Hb	0.76 (0.02)	0.03 (0.94)	−0.30 (0.43)
Approach A estimates	−0.18 (0.65)	—	—
Approach B estimates	−0.78 (0.01)	—	—

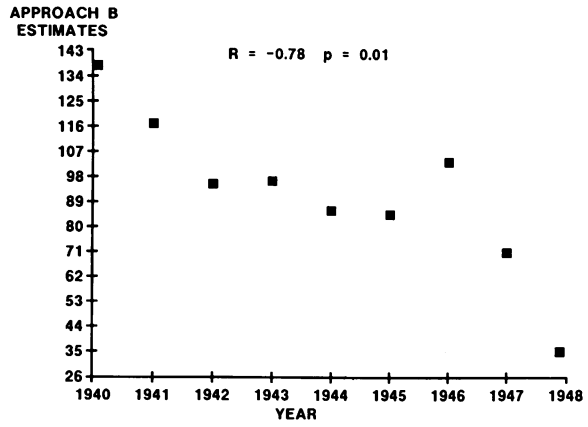

FIGURE 4. Approach B estimated average annual benzene exposure for cohort members who received blood tests, plotted against the year in which the estimated exposure occurred (blood was sampled), 1940–1948. Pearson correlation coefficient (R) and significance are shown.

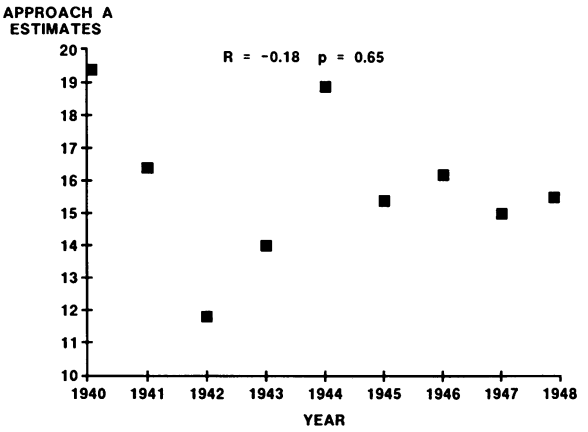

FIGURE 5. Approach A estimated average annual exposure for cohort members who received blood tests, plotted against the year in which the estimated exposure occurred (blood was sampled), 1940–1948. Pearson correlation coefficient (R) and significance are shown.

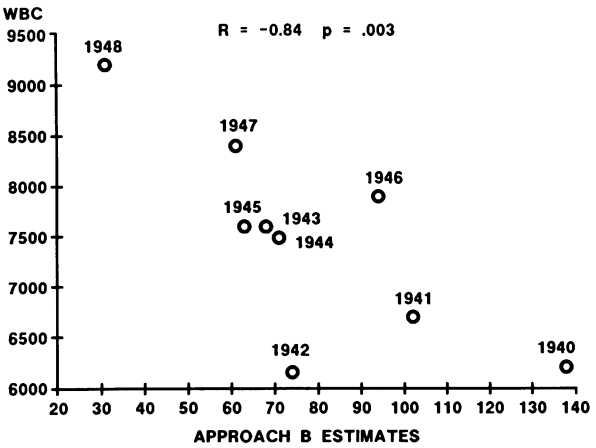

FIGURE 6. Plot of approach B estimated average annual benzene exposures against annual average WBC counts at the time of the exposures, 1940–1948. Pearson correlation coefficient (R) and significance between WBC and estimated exposure are shown.

From 1940 to 1948, approach B estimated an average benzene exposure for the sampled workers of 66 ppm, whereas approach A estimated an average exposure of 15.6 ppm, a ratio of over four to one. From 1949 onward the ratio between the two estimates, calculated on an annual basis, was less than two, and usually they were within a few parts per million of one another (Figs. 2*A* and 2*B*). These data strongly suggest the superiority of the approach B estimates of exposure for predicting observed blood count fluctuations in members of this cohort during the 1940s. Neither estimation was particularly predictive of blood counts in subsequent years from the 1950s through the 1970s.

The analyses based on the mean of each parameter for each year of the study resulted in several correlated data points per subject, since most of the subjects were in the cohort for more than 1 year. The final regression based on the means of person annual averages for 1940 to 1948 are not subject to this source of error. These regressions form the most compelling portion of the analysis that supports the concept that benzene exposure for the cohort during the 1940s was significantly higher than in subsequent years.

Nevertheless, this analysis does not conclusively establish that the approach B exposure estimates are either absolutely accurate or even superior to approach A estimates. The actual estimates could be higher or lower by any constant factor (e.g., all approach B estimates lower by a factor of 3), and the observed correlations would remain unchanged. In an extreme and unlikely case, the approach B estimates could be much less absolutely accurate than the approach A estimates, and yet have shown higher correlation coefficients. This is possible because relatively insignificant (year to year) fluctuations in the approach A estimates could have produced low coefficients of correlation (e.g., if the fluctuations although small were in the opposite direction of the observed blood count fluctuations) even though the absolute numbers estimated were fairly accurate. The approach B estimates could hypothetically be an order of magnitude too high and yet have shown a higher correlation because their fluctuations were concordant with yearly fluctuations in the blood counts. Examination of our figures, the low correlations in later years when the two estimation schemes were relatively concordant, and historical data indicating significant reductions in benzene exposures during the 1940s (*12*) all make this highly unlikely. Although the absolute approach B numbers may perhaps err by as much as a factor of two or three, the approach A estimates seem excessively low during the 1940s, and the generally higher approach B estimates are likely to be more accurate during these years.

A small number of cohort studies (*13–18*) have reported on the hematologic effects of benzene as monitored by routine counts of peripheral blood cells in groups of workers. Significant abnormalities of all three cell types were reported in individuals with high exposure from the pre-World War II era in the U.S. and in Turkey from the 1960s and 1970s (*16–18*). Subsequent studies (*13–15*) have noted only small deviations of MCV, RBC, or HB of ag-

gregate samples of workers monitored over time. Individual workers' blood counts were not followed longitudinally over time in these studies, nor were benzene exposure assessments systematically assigned to individuals over time so that fluctuations in blood counts could be related to fluctuations in exposure.

A number of limitations of the present data set and the analysis applied need to be acknowledged. This is a partial data set, and it is not known exactly how individuals were selected for surveillance nor why only data from workers at one of the two locations are available. The illegibility of some blood count data also presents potential problems. In the correlation tables, hemoglobin and RBC are only correlated at $r = 0.41$ ($r = 0.44$ for the rank correlation), and biologically this is expected to be higher since they essentially measure the same parameter, although they were also poorly correlated in other data from the same era (*16*). This implies some degree of inaccuracy and unreliability in the measurement of the blood sample data, and may be due to greater variability in manual counting techniques for RBC than for WBC or for the standard method of hemoglobin determination.

Average WBC counts for the cohort over all 35 years were over 9,300 per cubic millimeter. Currently the normal range for WBC is 5,000 to 10,000, with a mean around 7,500, although even in unexposed populations confidence intervals are wide. To the best of our knowledge this was also true in the 1940s, the 1950s, and the 1960s, and we do not have an explanation for this aberration in the data set. It does not appear to be due to the rare high counts seen in this group for people who clearly were developing leukemia. Most likely it represents bias in the manual counting procedures (perhaps performed by only one or two individuals over the entire surveillance period). If such a bias were consistent across time, it would affect the absolute counts, but not the relative increases and decreases which we report. Bias of this sort would more likely obscure a true biologically plausible effect such as we have demonstrated, rather than artificially produce it.

The earlier and higher exposures tended to be represented by fewer blood samples than did the later exposures. This was apparently due to changes in surveillance protocols, as well as shorter durations at any individual exposure level in earlier years. At times, abnormally low and occasionally abnormally high counts seemed to generate repeated samples on almost a daily basis for short periods of time. It is likely that workers also were transferred from areas of higher estimated exposure when counts were demonstrably abnormal (*10*). Both of these practices may produce bias in the sample, but are not likely to have produced the powerful chronological effect which we have demonstrated.

Plausible explanations for the demonstrated overall time trends are suggested in the published reconstructions of Pliofilm exposures which mention the installation of substantial improvements in local ventilation equipment for plant 1 in 1946, likely to have resulted in lower subsequent exposures (*9*). The historical records of the Department of Labor and the War Production Board during World War II document clinically significant blood dyscrasias and severe CNS symptoms among benzene-exposed workers at least prior to 1942, not expected to occur at exposures less than 25 to 100 ppm TWA (*12*). In addition, the records of this 1942 conference on health hazards in the rubber industry describe a shortage of toluene, a desirable nonhematotoxic benzene substitute, due to demand for it in the manufacture of munitions (trinitrotoluene). Although this was unlikely to directly affect pliofilm exposures because benzene was considered the superior solvent for this process, other nonpliofilm exposures in building tires, bullet-proof gas tank linings, and balloon fabrics, would probably have reflected substitution of benzene for toluene during the war years. The end of World War II in 1945 may have led to reintroduction of toluene in some of these processes, and thus lower benzene exposures for the cohort as a whole, even if not during their actual pliofilm work.

Thus the historical record and the hematologic record are both consistent with relatively elevated benzene exposures in this industry prior to the late 1940s. Of course, individuals or groups working in particular positions may have had average or momentary exposures far above or below those of the group as a whole. This study suggests that surveillance of blood counts to monitor populations of workers exposed to benzene may not readily detect cohort effects of exposures in the range of the current standard of 1 ppm, as during the 1950s and beyond these workers had exposures likely exceeding these values without apparent aggregate depressions in their blood counts. We are unable to say that individuals will not experience significant blood dyscrasias at these lower benzene exposures, but that based on these data, surveillance of overall population averages cannot be relied upon to detect reasonable deviations from currently permitted exposures.

The authors acknowledge the American Petroleum Institute for providing us with these data and for financial support. Special thanks to Patricia A. Hutty for help in manuscript preparation.

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