AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 29:247–257 (1996)

Risk of Low Red or White Blood Cell Count Related to Estimated Benzene Exposure in a Rubberworker Cohort (1940–1975)

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This study evaluated the relationship between benzene exposure and low white blood cell (WBC) and red blood cell (RBC) counts. Hematologic screening data collected over a 35 year period at a rubber hydrochloride manufacturing plant were analyzed; an increased risk of leukemia had been demonstrated previously among workers at the plant [Infante et al. (1977): Lancet 2:76–78; Rinsky et al. (1981): Am J Ind Med 2:217–45 (1987): NEJM 316:1044–1050]. Hematologic screening data were available for 657 of 1,037 (63.3%) individuals employed at the plant from 1939 through 1976. There was a total of 21,710 blood test records (range per individual 1–354). The study utilized a case–control design and estimated benzene exposures using the job exposure matrix developed by Rinsky et al. (1987): NEJM 316:1044–1050]. The effects of benzene exposure in the 30, 90, and 180 days before the blood test date, as well as cumulative exposure up until the blood test date, were examined using conditional logistic regression. For WBCs there was a strong exposure–response and all of the exposure metrics selected showed a significant relationship with low blood count. For RBCs there was a weak positive exposure–response, which was significant ($p = 0.03$) for one of the dose metrics. The finding of an exposure–response relationship in the range of exposures represented in this study, where the maximum daily benzene exposure estimate was 34 ppm, is consistent with findings of several animal studies demonstrating a decrease in peripheral lymphocyte counts at benzene exposures as low as 10 ppm, and a stronger effect of benzene exposure on lymphocytes (as reflected in total WBC count) than on red cells. There was no evidence for a threshold for the hematologic effects of benzene exposure, suggesting that even exposure to relatively low levels of benzene (e.g., <5 ppm) may result in hematologic suppression. © 1996 Wiley-Liss, Inc.*

KEY WORDS: benzene, white blood cells, red blood cells, hematologic suppression

INTRODUCTION

Since the late 19th century it has been recognized that exposure to high levels of benzene may result in severe hematologic suppression [Goldstein, 1988; Aksoy, 1988]. Cross-sectional studies have demonstrated decreased red, white, and platelet cell counts in benzene-exposed populations relative to population normals [Aksoy et al., 1971, 1987] or concurrently tested control groups [Greenburg et al., 1939; Goldwater, 1941; Hernberg et al., 1966]. However, there have been few studies which attempt to examine

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Accepted for publication May 8, 1995.

the relationship between a quantitative estimate of benzene exposure and hematologic response This relationship is important because hematologic monitoring is required by the OSHA for workers who are or may be exposed to benzene at or above the action level of 0.5 ppm as a time weighted average (TWA) for 30 or more days per year [OSHA, 1987]. This requirement in the OSHA standard generated controversy, with some commentators arguing that it was unlikely that hematologic suppression would occur at levels below 10 ppm.

Townsend et al. [1978] examined the relationship between peripheral blood counts and benzene exposure among 282 workers potentially exposed to benzene who participated at least once in a 7 year period in a health examination program. Examinations were offered approximately once every 2 years; if more than one exam result was available, the most recent result was used in the analysis. Referents were selected from among nonbenzene-exposed workers at the same company and matched by age, smoking status, and hire date. The regression analyses used the paired differences in blood cell count as the outcome measure. Benzene exposure for each job was assigned to one of four categories [<2 ppm; 2–9 ppm; 10–24 ppm; and ≥25 ppm time weighted average (TWA)] for each year. This cross-sectional study found that neither the red blood cell counts nor other hematologic parameters were correlated with current TWA exposure intensity, duration of exposure, or estimated cumulative exposure.

Collins et al. [1991] used regression analyses to compare peripheral blood counts between 200 workers potentially exposed to benzene and 268 workers in the same plant without potential benzene exposure. Age, sex, race, smoking, and drinking habits were controlled for in the analysis. Exposures at this plant were low, ranging from 0.01 to 1.40 ppm 8 hr TWA over a 10 year period. The most recent blood test results for each employee were used in the analysis (cross-sectional design). This study found no relationship between white blood cell count, red blood cell count, platelet count, hemoglobin concentration, or mean corpuscular volume (MCV) and cumulative benzene exposure. This study did find a small, statistically significant increase in MCV associated with current level of benzene exposure.

Kipen et al. [1988, 1989] analyzed hematologic screening data from the same rubber hydrochloride plant studied here (the data were abstracted and coded independently by ourselves and by Kipen et al. from copies of the same plant records). A subset (299 annual mean blood counts from 128 individuals with five or more blood samples 1940–1948) of a larger dataset (17,279 blood counts from 459 individuals 1940–1975) was selected for analysis. The analysis correlated mean annual blood counts in individuals with calendar time and yearly mean annual benzene exposure. The authors concluded that an observed trend of increasing WBC and RBC counts from 1940 to 1948 was due to a decline in benzene exposure levels during the time period, as estimated by one of two available exposure matrices [Crump and Allen, 1984]. These conclusions were disputed by Hornung et al. [1989], who analyzed the NIOSH-coded file of hematologic data from the same plant and found similar temporal trends in blood counts obtained from plant workers prior to their assignment to the rubber hydrochloride department. Hornung et al. also argued that Kipen et al. employed circular reasoning in concluding that the trend in blood counts from 1940 to 1948 was due to decreasing exposure after having selected the Crump and Allen exposure estimates "because they were more highly correlated with the hematologic surveillance data."

Cody et al. [1993] subsequently conducted an analysis of a different subset of the same dataset, including 161 individuals who had a pre-employment blood count and five or more total blood counts during the first year of their employment in 1946–1949. Cody et al. did not attempt to relate quantitative benzene dose with hematologic response, but instead compared mean WBC and RBC counts between "high" and "low" exposure groups defined in relation to the median exposure among workers tested at monthly time intervals after starting employment. Calendar time was not accounted for in the analyses (i.e., whether a worker began employment in 1946 or 1949, that exposure data was evaluated at "time 0" and monthly intervals thereafter). From these analyses, Cody et al. concluded that there was a relationship between exposure and blood count when the Crump and Allen [1984] and not the Rinsky et al. [1987] matrix was used to estimate exposure. Although Cody et al. state that their analyses controlled for potential temporal trends, we believe that their analytic design increased rather than controlled for the effect of this potential confounder. Because there was a substantial decline in the exposure estimates from 1946 to 1949 in the Crump and Allen matrix (the ppm estimate for every job with >1 ppm exposure in 1949 ranged from 35 to 37% of the ppm estimate for the same job in 1946), the "high exposure group" was enriched with blood samples obtained in the early part of the 1946–1949 time period, and the "low exposure group" was enriched with blood samples obtained in the latter part of the period. The differences observed in blood counts between the high and low exposure group, which are presented graphically in the Cody et al. paper, are of approximately the same magnitude as the differences in mean blood counts between samples taken in 1946 and 1948 in the data presented by Kipen et al. [1988] (mean WBC count of 8,170 cells/μl blood in 1946 and 9,591 cells/μl blood in 1948; mean RBC count of 4.71×10^6 cells/μl blood in 1946 and 5.13×10^6 cells/μl blood in 1948). We do not believe that the Cody et al. analysis provides any new information about the relationship between benzene exposure and risk of hematologic suppression in this population because their results are so heavily influenced by the temporal trends pre-

viously noted by Kipen et al. (increasing blood counts during the period 1940–1948 were correlated with the decreasing exposure estimates in the Crump and Allen matrix during that time period).

Our analysis strategy differs from previous studies of hematologic screening data in benzene cohorts in that we have used a nested case–control design. Incident cases were defined as the first occurrence of a low WBC or RBC count, and matched controls were chosen from those tested within (plus or minus) 6 months of the case's blood test date. The current study was designed to determine whether there is an exposure–response relationship between benzene exposure and the risk of developing a low WBC or RBC count. In contrast to earlier analyses of hematologic screening data from the same plant, the current analysis utilizes the entire dataset, evaluates the exposure–response relationship based on individual dose metrics, and controls for the temporal trends noted in pre-employment data.

METHODS

The plant studied here, described as location 1 in the Rinsky et al. study [1987], produced a natural rubber film (rubber hydrochloride) from 1939 until April 1976. In this process, benzene was used as a solvent for natural rubber; a detailed description of the process is provided in Rinsky et al. [1981]. The rubber hydrochloride plant was located within a larger industrial facility. Detailed job history information for each employee was obtained from company personnel records. The job–exposure matrix used to link job titles with benzene exposure has been described previously [Rinsky et al., 1987].

Hematologic screening was used to monitor workers in the rubber hydrochloride department for benzene toxicity. Hematologic screening results were reviewed by a physician and repeated if an abnormally high or low count was found. Some workers were noted to have been transferred from the rubber hydrochloride department as the result of an abnormal blood count; however, there was no indication in the records of what action level would trigger medical removal. Hematologic screening data were coded, keypunched, edited, and matched with the file of work history information used in the mortality study. Information coded included date of the blood sample, red and white cell counts, and reason for sampling (preplacement, routine, or recheck).

The type of data analyzed in this study, which involved variable numbers of blood count measurements taken at varying intervals in a large number of individuals, is difficult to analyze because measurements taken from each individual are intercorrelated. We chose to use a matched case–control design, with controls being required to have a normal blood test within (plus or minus) 6 months of the case's blood test date [Lubin, 1986]. A case was defined as the first occurrence of a blood count below the first percentile of blood counts taken during preplacement physical examinations. Only 176 of the 657 individuals with any hematologic screening data have a preplacement value. We know of no reason why only 27% of records contained a preplacement value, and cannot be sure these samples are representative of the entire work force. Nonetheless, they provide the best insight into baseline hematologic values in the population and the only means of analyzing and controlling for an apparent temporal trend in the laboratory results. All blood sample results in the "preplacement" data set were verified with the original records to ensure that the individual had no prior employment at the study plant (since some departments outside rubber hydrochloride had potential exposure to benzene).

The temporal trend was noted in the values of both WBC and RBC counts for both preplacement (unexposed to benzene) and routine (potentially exposed to benzene) samples. In order to determine the lowest first percentile cutoff, we used the lower bound of the 98% confidence interval around a regression line fit by regressing the preplacement blood samples against calendar time. Because the regression was not a simple linear function, and because changes in preplacement blood counts appeared to occur at certain points in time, a four-knot spline function was fit to the 176 pre-employment tests [Harrell et al., 1988]. The use of a spline function provides a more general and flexible approach to describing temporal trends in the pre-employment data that is free of any specific assumptions about the shape of the curve, e.g., linear, log-linear, etc. The 99% lower confidence band (CI) for the resulting curve is shown (Figs. 1, 2). Each routine blood test was then evaluated to determine if the WBC or RBC count fell below the lower CI of the spline curve on that date. Cases were removed from eligibility as either a case or a control after the date when they first became a case. Controls selected for each risk set were required to have had a normal blood test within (plus or minus) 6 months of the case date. If a potential control had more than one eligible blood test, the test with the date closest to the date of the case blood test was selected. Cases and controls were excluded if they had worked in departments outside rubber hydrochloride during the 180 days prior to the selected blood test because there were no data available to estimate potential benzene exposure in other departments. We believed that the time period in which it was most critical to accurately estimate exposure was the 180 days prior to the blood test, since the lifespan of RBCs and most WBCs is <180 days [William et al., 1983]. Estimates of benzene exposure in the 30, 60, and 180 days prior to the blood test were calculated using the job–exposure matrix coded by Rinsky et al. [1987]. Total cumulative exposure for the entire work history prior to the date of the blood test was also calculated. Exposure rate within each time interval was calculated by dividing the cumulative

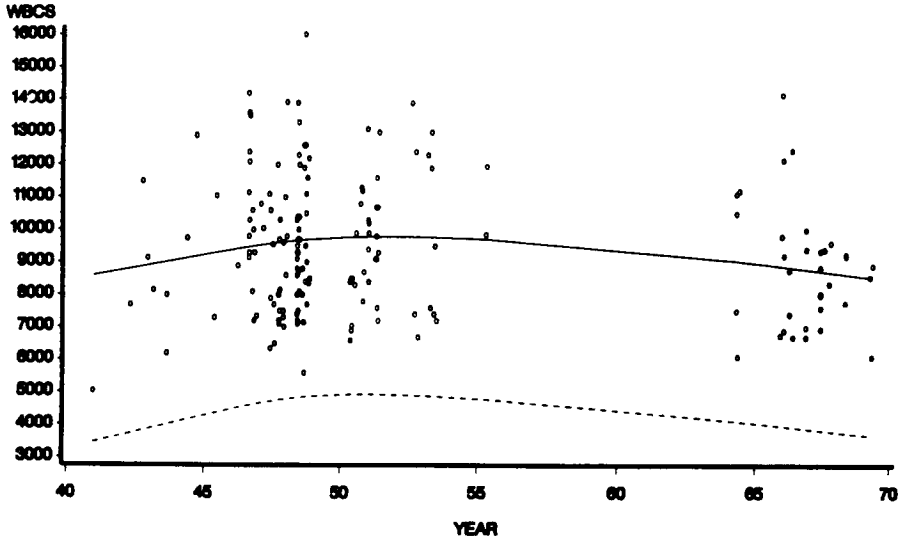

FIGURE 1. Pre-employment WBC in rubberworker cohort by calendar year: spline function and 99% lower confidence band.

exposure during the interval by the number of days in the interval with exposure >0 ppm.

Conditional logistic regression was used to examine the association between benzene exposure and risk of low WBC and RBC count using both EGRET and SAS software to select the best exposure metric [Statistics and Epidemiology Research Corporation, 1988] and illustrate the exposure–response relationship [SAS Institute Inc., 1989]. Potential confounders that were tested included age, year at starting employment, number of routine blood tests prior to the case or control blood test date (pretests), and gender. The number of prior blood tests is a function of both the duration of prior employment and the frequency of testing (which showed temporal variation for the entire population as well as interindividual variation). Eight exposure metrics (cumulative exposure and exposure rate in the 30, 60, and 180 days and at any time prior to the blood test date) were tested. The exposure metrics were tested with and without log transformation.

The greatest uncertainty in the exposure estimates utilized in this study is for the time period 1940–1946, because no measurements of benzene air concentration were made at the plant before 1946. Since the daily ppm estimates for the 1939–1946 time period are less certain than those for subsequent years, in addition to the analyses including all cases, we also analyzed the data for the subset of cases and controls hired in 1947 or later.

RESULTS

Hematologic screening data were available for 657 of 1,037 (63.3%) individuals employed at the plant from 1939 through 1976, among whom 19 were female. The frequency of monitoring varied by calendar time, with a lower proportion of employees having at least one blood test per year, and fewer blood tests per individual, in the earliest and latest decades of the sampling program. There were a total of 21,710 blood test records; the range of number of blood tests per individual was from one to 354, but the majority of individuals (359 of 657, or 54.6%) had five or fewer blood tests. There were 74 (11.3%) individuals who had 100 or more blood samples. The majority of blood samples (21,287) were routine blood tests, 176 were taken prior to placement in the rubber hydrochloride department, and 247 samples were "rechecks."

The blood tests were taken from 1940 through 1975; the annual number of blood tests is summarized in Table I along with the year of the case's blood test date for both low RBC and WBC counts. Despite adjustment for the temporal trend in blood counts in the selection of cases, cases of both low RBC and WBC counts fell disproportionately into the earlier years, during which time the estimates of daily benzene exposure by department were generally higher.

There were 78 cases and 5,637 controls included in the WBC analysis (seven of 85 cases and 935 of 6,572 controls were excluded because they had worked in departments outside rubber hydrochloride in the 180 days prior to the selected blood sample date). There were 105 cases and 8,489 controls included in the RBC analysis (13 of 118 cases and 1,985 of 10,474 referents were excluded because they had worked in departments outside rubber hydrochloride in the 180 days prior to the selected blood sample date). Table II compares WBC and RBC counts and WBC differential counts abstracted from a hematology textbook [William et al., 1983] with those observed in 176 pre-employment blood samples and among 78 cases of low WBC

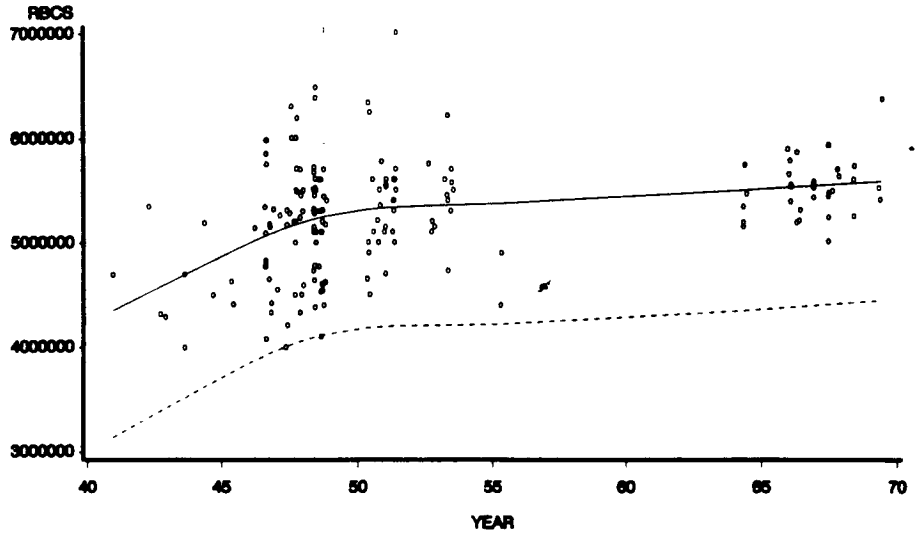

FIGURE 2. Pre-employment RBC in rubberworker cohort by calendar year: spline function and 99% lower confidence band.

TABLE I. Number of Total Blood Counts per Year and Number of Cases of Initial Low WBC and RBC Counts in Study of Rubberworker Cohort

Year	Total number of blood samples	Total number of individuals tested	Number of low WBC cases	Number of low RBC cases
1940–1944	397	73	21	5
1945–1949	3,127	283	25	50
1950–1954	4,896	251	14	19
1955–1959	5,066	187	8	10
1960–1964	4,281	127	1	14
1965–1969	3,324	134	8	7
1970–1975	619	34	1	0

count and 105 cases of low RBC count in the cohort. The mean RBC count and the differential counts in the pre-employment samples from the plant were similar to those reported in William et al. [1983], while the total WBC counts at the plant were higher. Although RBC and WBC cases were selected independently, the mean RBC count among WBC cases was lower than the mean in pre-employment samples (4.76 vs. 5.26), and RBC cases had a lower WBC count (8.48 vs. 9.44) than pre-employment samples, suggesting that for many "cases" both cell types were affected.

Table III presents the conditional logistic regression results for the risk of low WBC count related to benzene exposure and average exposure rate during four time intervals prior to the blood test date. The logistic regression results for the natural log (ln) of the exposure estimates are presented because models using log-transformed values were slightly better (greater reduction in deviance) than models using untransformed values. A variable for the number of pretests was defined as the number of routine blood tests for an individual prior to the selected blood test date. This variable was controlled for in the models as a categorical variable (intervals ≤6, 7–20, and ≥21). With the exception of "pretests," no other variables acted as confounders so final models included only exposure and pretests.

For WBCs, there was a strong exposure response and all of the dose metrics selected showed a significant relationship with low blood count. The best models (in terms of yielding both the greatest reduction in deviance, and strongest association) were for the natural log of the estimated cumulative benzene exposure in the 180 days prior to the WBC blood test date, and the Ln of the total cumulative benzene exposure (ppm-yr). Figures 3 and 4 illustrate the exposure–response relationship for these dose metrics. In these figures, odds ratios (ORs) and 95% confidence intervals calculated for specific exposure intervals are superimposed on the exposure–response curve predicted by the continuous model. These figures indicate that the continuous model used fits the data well, and that there is a monotonic increase in risk associated with increasing benzene exposure in the prior 180 days, as well as total cumulative exposure.

Table IV presents the conditional logistic regression results for RBC counts. As in the WBC analysis, using the log transformation of the exposure estimates in the models resulted in lower deviance than the untransformed values. Again, no other variables were confounders with the exception of pretests, and the variable "pretests" was controlled for in the models as a categorical variable. For RBCs, there was a weak positive exposure response which was signifi-

TABLE II. Comparison of RBC, WBC, and Differential Counts in a Hematology Textbook With Those in Pre-Employment Blood Samples and Cases of Low RBC and WBC Counts in Rubberworker Cohort

Population studied	RBC count (cells × 10^6/ μl blood) Mean ± 2 SD	WBC count (cells × 10^3/ μl blood) Mean ± SD	% Lymphocytes	% Eosinophils & basophils	% Neutrophils	% Monocytes
Population normals[a]	5.11 4.4–5.9	7.25 3.9–10.6	34	3	59	4
Pre-employment samples	5.26 4.2–6.3	9.44 5.2–13.6	32	3	61	4
WBC cases	4.76 3.5–6.0	4.89 3.5–6.3	39	4	57	5
RBC cases	3.98 3.4–4.6	8.48 3.6–13.3	35	4	58	3

[a]From William et al. [1983].

TABLE III. Determination of the Best Model for Risk of Low WBC Count Related to Estimated Benzene Dose in the 30, 60, 180, and Total Days Prior to the Date of the Low Blood Count in Rubberworker Cohort

	Model including dose and number of pretests[a]		
Dose estimate	Deviance	Coefficient	p value
Ln (cumulative dose in the 30 days prior)	582	0.15	0.02
Ln (cumulative dose in the 60 days prior)	581	0.16	0.01
Ln (cumulative dose in the 180 days prior)	573	0.25	0.001
Ln (total cumulative dose prior) (ppm-years)	576	0.30	0.001
Ln (dose rate in the 30 days prior)	584	0.21	0.04
Ln (dose rate in the 60 days prior)	583	0.23	0.03
Ln (dose rate in the 180 days prior)	580	0.31	0.006
Ln (total dose rate prior)	583	0.30	0.021

[a]Model controls for number of pretests as a categorical variable (≤6, 7–20, ≥21). The deviance for the model with only pretests as a predictor variable was 588.

cant ($p = 0.03$) for one of the dose metrics. The best model was for Ln of total cumulative exposure (ppm-yr). Figure 5 illustrates the exposure–response relationship for the natural log of the estimated cumulative benzene exposure in the 180 days prior, which did not show a significant exposure–response trend for RBCs, and Figure 6 illustrates the exposure response for total cumulative exposure. Figure 6 indicates that the continuous model used fits the data for cumulative exposure well, and that there is a monotonic increase in risk associated with increasing total cumulative benzene exposure.

In an analysis restricted to individuals hired in 1947 or later, there were 60 risk sets in the RBC analysis and 32 risk sets in the WBC analysis. Table V contrasts the results of the analyses of the full and the restricted datasets for the dose metrics used to illustrate the exposure response. In all cases, the coefficients estimated in the restricted datasets were slightly higher than those in the full datasets.

DISCUSSION

The results of this study provide evidence of an exposure–response relationship between estimated benzene exposure and risk of hematologic suppression. Only two prior studies have examined the relationship between individual blood counts and estimated benzene exposure among individuals with occupational exposure to benzene. One of these studies had a maximum exposure level substantially below

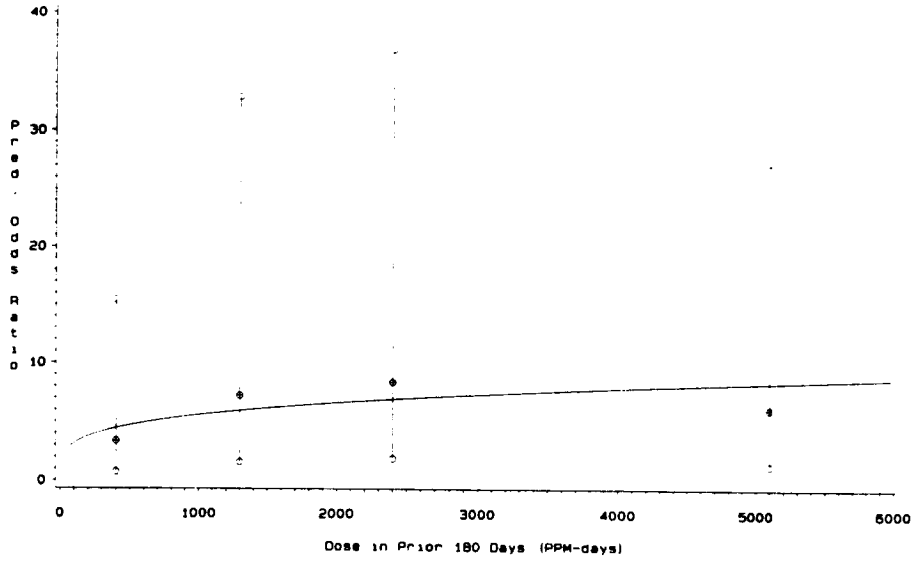

FIGURE 3. Exposure response for low WBC count in rubberworker cohort: benzene exposure in the 180 days prior to the blood test date. Odds ratios and 95% confidence intervals are superimposed on the exposure–response curve predicted by the continuous model.

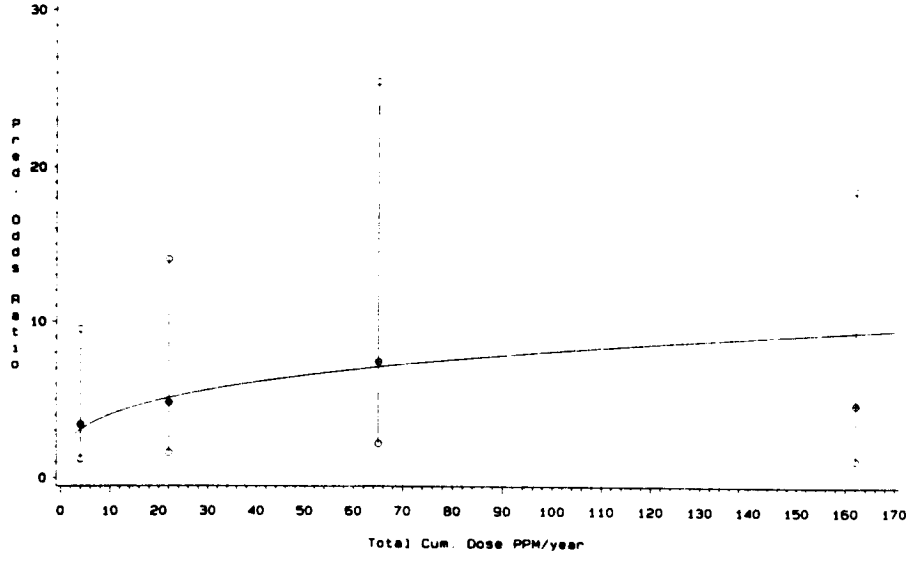

FIGURE 4. Exposure response for low WBC count in rubberworker cohort: cumulative benzene exposure prior to the blood test date. Odds ratios and 95% confidence intervals are superimposed on the exposure–response curve predicted by the continuous model.

maximum exposures in the current study (1.4 ppm daily exposure) [Collins et al., 1991]. The other study [Townsend et al., 1978] included workers in departments with potential exposures as high as 17–35 ppm estimated TWA, but the analysis was cross sectional, limited to the most recent blood test only. Our study may have been more sensitive in detecting the hematotoxic effects of benzene than that of Townsend et al. [1978] because we used a case–control design in which we focused on the first occurrence of a blood test below the normal range. This choice of outcome measure has public health relevance in that one of the purposes for which hematologic screening has been proposed is to identify subjects with overt hematologic toxicity for possible removal from exposure [Goldstein, 1988].

The hematologic screening data utilized in this study have been analyzed by other investigators, who reported finding an exposure–response relationship when an exposure matrix developed by Crump et al. [1984] was used to

TABLE IV. Determination of the Best Model for Risk of Low RBC Count Related to Estimated Benzene Dose in the 30, 60, 180, and Total Days Prior to the Date of the Low Blood Count in Rubberworker Cohort

	Model including dose and number of pretests[a]		
Dose estimate	**Deviance**	**Coefficient**	**p value**
Ln (cumulative dose in the 30 days prior)	807	0.07	0.12
Ln (cumulative dose in the 60 days prior)	807	0.07	0.13
Ln (cumulative dose in the 180 days prior)	808	0.06	0.16
Ln (total cumulative dose prior) (ppm-years)	805	0.20	0.03
Ln (dose rate in the 30 days prior)	807	0.14	0.08
Ln (dose rate in the 60 days prior)	807	0.13	0.10
Ln (dose rate in the 180 days prior)	808	0.11	0.17
Ln (total dose rate prior)	806	0.20	0.06

[a]Model controls for number of pretests as a categorical variable (≤6, 7–20, ≥21). The deviance for the model with only pretests as a predictor variable was 810.

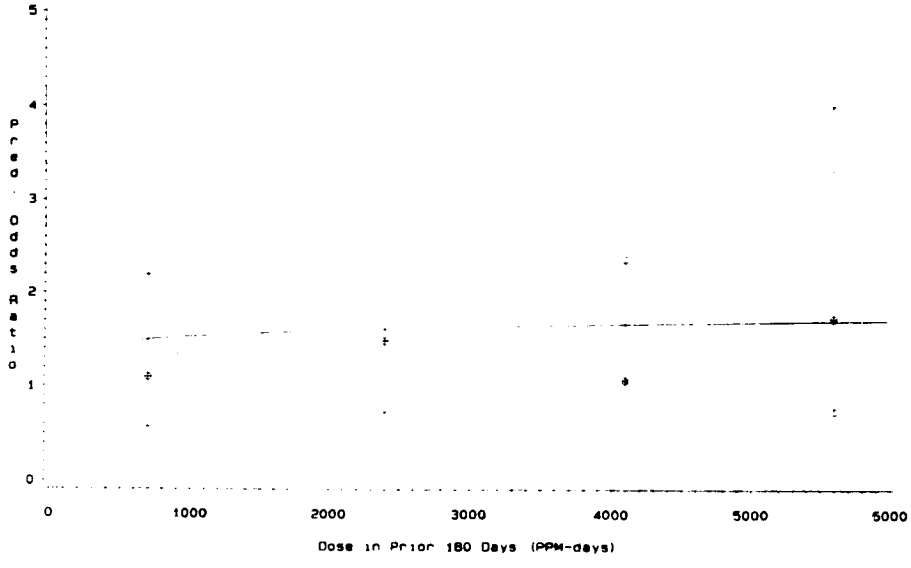

FIGURE 5. Exposure response for low RBC count in rubberworker cohort: benzene exposure in the 180 days prior to the blood test date. Odds ratios and 95% confidence intervals are superimposed on the exposure–response curve predicted by the continuous model.

estimate exposure, but not when the Rinsky et al. [1987] matrix was used [Kipen et al., 1988, 1989; Cody et al., 1993]. In contrast, our results show a strong relationship between benzene exposure and the probability of a low WBC count, and a weaker relationship between benzene exposure and the probability of a low RBC count, using the Rinsky et al. [1987] exposure matrix. As discussed in the Introduction, we believe that there were flaws in the design of prior analyses of the hematologic screening data from this plant, which may explain the discrepancy between our results and earlier papers.

There has been considerable controversy in the literature regarding historical exposure estimates at the plant under study [Utterback and Rinsky, 1995]. This controversy primarily concerns the period prior to 1946, when no air sampling data are available. Crump et al. [1984] and Paustenbach et al. [1992] have proposed alternative exposure estimates, based on different methods of extrapolating exposure during periods when no air sampling data were available, different assumptions about the accuracy of historical air sampling methods, and different reconstructions of process and plant history than were used by Rinsky et al. [1987]. Since there are no exposure data for this cohort prior to 1946, there is no direct way to validate which extrapo-

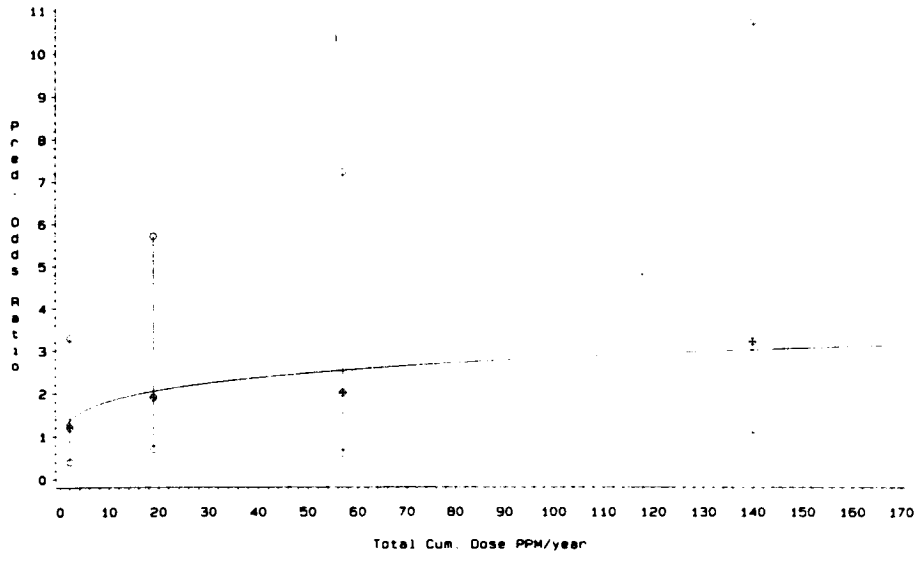

FIGURE 6. Exposure response for low RBC count in rubberworker cohort: cumulative benzene exposure prior to the blood test date. Odds ratios and 95% confidence intervals are superimposed on the exposure–response curve predicted by the continuous model.

TABLE V. Comparison of Results in Full Dataset of Rubberworker Cohort and in Dataset Restricted to Cases and Controls Hired in 1947 or Later

		Full dataset		Restricted dataset	
WBC or RBC	**Dose metric**	**Coeff.**	**p value**	**Coeff.**	**p value**
WBC	Ln (cumulative dose in the 180 days prior)	0.25	0.001	0.29	0.03
WBC	Ln (total cumulative dose prior (ppm-years)	0.30	0.001	0.31	0.17
RBC	Ln (cumulative dose in the 180 days prior)	0.06	0.16	0.11	0.10
RBC	Ln (total cumulative dose prior) (ppm-years)	0.20	0.03	0.29	0.07

lation for the 1940–1946 period most closely approximates reality. However, the results in this paper are not dependent on the method of extrapolating benzene exposure prior to 1946, since the results were similar when the analysis was restricted to cases occurring in 1947 or later.

Descriptive analyses of the pre-employment data revealed several anomalies which were probably related to laboratory variability rather than to biological differences in the plant population. These included the temporal trends in WBC and RBC counts and the increased WBC counts relative to population normal values (Table II) which are similar in the routine samples (data not shown). Kipen et al. [1987] have previously noted the increased average WBC count in their analyses of data from the same plant. Unfortunately, there is virtually no documentation of the laboratory methods used to analyze the blood samples and when, if ever, either the laboratory or the methods changed. Our methods of analysis have minimized the influence of laboratory variability by controlling for the temporal trends and selecting cases relative to the distribution of preplacement blood tests.

A number of animal studies have evaluated the hemotoxicity of benzene at daily doses of 100 ppm or greater [Snyder et al., 1978, 1980, 1984; Dempster et al., 1984], but relatively few studies have employed benzene doses below 100 ppm. Cronkite et al. [1985, 1986] exposed mice to benzene doses varying from 10 to 400 ppm, 6 hr/day, 5 days/week for 10 exposures and found lymphopenia, but no other hematologic effects, at the 25 ppm exposure level. Green et al. [1981] found no effect of benzene doses under 100 ppm (6 hr/day, 5 days/week) on hematopoietic stem and progenitor cells. Rozen et al. [1984] exposed mice to 10, 31, 100, and 300 ppm benzene for 6 hr/day for six consecutive days. Lymphocyte counts were depressed significantly below baseline at both 10 and 31 ppm. Baarson et al. [1984] investigated the effect of exposure of mice to 10 ppm benzene for 6 hr/day, 5 days/week for up to 178 days. Lymphocyte counts in peripheral blood were significantly de-

pressed at 32, 66, and 178 days of exposure, while red cell counts were significantly depressed at 66 and 178 days.

In animal studies, WBCs appear to be more sensitive to benzene hematotoxicity than RBCs, and within the WBCs lymphocytes seem to be more sensitive than other cell types. We chose total WBC count as the endpoint in this study, rather than total lymphocyte count, because of the high variability of the white blood cell differential obtained by the manual method, in which only 100 cells are counted [Goldstein, 1986; Williams, 1983; Rumke et al., 1975], and because the selective effect on lymphocytes had not been as clearly documented in humans. Our data are consistent with the animal data in showing a stronger effect of benzene exposure on WBCs than on RBCs, but do not provide evidence that the low total WBC count was due to selective depletion of lymphocytes. Although WBC cases have a mean WBC count that is only 52% of the mean WBC count in pre-employment samples, the differential counts in the WBC group do not differ from either pre-employment or textbook values. The question of the effects of benzene exposure on total lymphocyte counts and lymphocyte subsets might be better investigated in contemporary workers using modern, automated counting methods [Virella, 1992]. One study has reported a decrease in the number of T but not B lymphocytes among workers exposed to benzene and several other solvents [Moszcynski and Lisiewicz, 1983].

In summary, our study found a relationship between benzene exposure and the risk of a low WBC or RBC count which was stronger for WBCs. The finding of an exposure–response relationship in the range of exposures represented in this study, where the maximum daily benzene dose estimate was 34 ppm, is consistent with findings of several animal studies demonstrating a decrease in peripheral lymphocyte counts at benzene exposures as low as 10–30 ppm, and a stronger effect of benzene exposure on lymphocytes (as reflected in total WBC count) than on red cells. The results of our study may differ from previous analyses of hematologic screening results among benzene workers because we have studied the relationship between estimated individual benzene exposure and the incidence of low WBC or RBC count in a group of workers with substantial benzene exposure.

ACKNOWLEDGMENTS

We acknowledge the painstaking coding of the blood test results by Mrs. Janice Pedersen, the coding and verification of work history data by the Support Group of the Industrywide Studies Branch, DSHEFS, NIOSH, and statistical assistance by Dr. Jim Deddens.

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