Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort

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A reanalysis of the Pliofilm cohort was conducted incorporating six additional years of follow-up information gathered by the National Institute of Occupational Safety and Health (NIOSH) and a new set of exposure estimates developed recently. The distribution of individual worker exposures calculated with the Paustenbach exposure estimates was compared to those derived using two earlier sets of job-, plant-, and year-specific exposure estimates. A traditional standardized mortality ratio analysis and the Cox proportional hazards model were used to investigate the impact of these exposure estimates and the NIOSH updated information on evaluation of benzene’s leukemogenicity. There were no additional cases of multiple myeloma or any indication of increased incidences of solid tumors. The data added in the update did not greatly modify the estimated relative risk of all leukemias associated with benzene exposure but confirmed previous findings that occupational exposure only to very high concentrations had leukemogenic potential. Leukemia has not been observed in anyone who began employment in Pliofilm plants after 1950. Neither Paustenbach nor the Crump exposures gave dose–response estimates as steep as that resulting from the Rinsky exposures. — Environ Health Perspect 104(Suppl 6):1431–1436 (1996)

Key words: benzene, leukemia, Pliofilm

Introduction

The Pliofilm rubberworker cohort has been central to setting health-based standards for benzene, such as the U.S. Environmental Protection Agency’s (U.S. EPA) cancer potency factor, the Occupational Safety and Health Administration’s (OSHA) permissible exposure limit (PEL), and the American Conference of Governmental Industrial Hygienists’ (ACGIH) proposed threshold limit values (TLVs). The reanalysis summarized here from more detailed accounts (1,2) was motivated by the availability of new information on two aspects of the cohort’s experience. The National Institute of Occupational Safety and Health (NIOSH) had gathered six additional years of observation on the vital status of the more highly exposed portion of the cohort. The two existing sets of job-, plant-, and year-specific exposure estimates were supplemented by a third.

The detailed work histories of the individual workers composing the Pliofilm cohort represent a unique resource for estimating the dose response for leukemia that may follow occupational exposure to benzene. Detailed records of specific jobs performed at particular times within the Pliofilm plants were maintained for all workers. Although industrial hygiene data were gathered only intermittently, this information represents a better basis for estimation of individuals’ exposures than is available for most industrial situations. Rinsky et al. (unpublished data) and Crump and Allen (unpublished data) derived sets of exposure estimates corresponding to specific jobs performed at the Akron and St. Marys, Ohio, plants over the years of Pliofilm production. Paustenbach et al. (3) developed a third and more refined set of exposure estimates by performing a detailed historical reconstruction of the industrial practices at the Pliofilm plants. The cumulative exposure estimates derived by applying the new exposure estimates to the individual workers’ job histories are compared here with those obtained using previously reported exposure estimates (Rinsky et al., unpublished data; Crump and Allen, unpublished data).

The results of NIOSH’s monitoring the vital status of workers from these Goodyear plants through 1981 were published in 1987 (4). NIOSH extended its follow-up of this cohort for an additional six years from 31 December 1981 to 31 December 1987. With the last “first exposure” in 1965 and follow-up through 1987, at least 22 years have elapsed since the most recent possible “first exposure” of a worker; a sufficient latency period has passed for assessment of leukemogenicity. The impact of this update on mortality risk, especially from leukemia, following occupational exposure to benzene is presented in the form of results of standardized mortality ratios (SMR) and dose–response analyses. The proportional hazards model was used in the dose–response analysis to extend the conditional logistic analysis by Rinsky et al. (4) of the then-identified nine leukemia cases each matched ten controls.

Standardized Mortality Ratios in Updated Cohort

The Pliofilm cohort consists of 1868 nonsalaried individuals employed by Goodyear in the production of Pliofilm (Table 1, top). In Akron, 824 people worked on this process at two facilities that operated from 1936 until 1949 and from 1949 until 1965. Another 1044 people were employed.
in the production of Pliofilm in St. Marys, from 1940 until 1975. The terms "wetside" and "dryside" have been used to partition the Pliofilm cohort qualitatively into two groups: 1291 wetside workers were involved in "precasting" steps of the Pliofilm process involving direct benzene exposure and 577 dryside workers were engaged in activities in the Pliofilm process originally thought not to involve direct benzene exposure. Rinsky et al. (4) did not include the dryside workers in their SMR calculations and NIOSH did not pursue follow-up of these workers in the most recent update period through 1987, so those workers are not included in our SMR calculations. Although a female leukemia case was found in the update, women have been excluded from our SMR analyses because there were too few to allow calculation of stable estimates. This left 1212 subjects (Table 1, bottom) for computation of SMRs using the NIOSH (5) life table program.

NIOSH's update of the vital status of the wetside Pliofilm workers from 1981 to 1987 identified 123 additional deaths for a total of 481 deaths in the wetside subgroup. Table 2 delineates the changes in SMRs between the two data-gathering periods for various causes of death. The SMR for overall mortality was approximately 1 in both periods. Previously, benzene exposure was associated with an increase in nonmalignant blood disorders in this cohort; such end points are not likely to have lengthy latencies, and no new cases were reported in the 1987 update. For all types of cancer, the SMR remained nonsignificant. There were no new deaths from multiple myeloma in the 1987 update, and Wong (6) has determined that the updated SMR for multiple myeloma of 2.91, with a 95% confidence interval (CI) of 0.79 to 7.45, is no longer significant. The addition of five new deaths from leukemia and one from lymphoma left the SMR for all lymphatic and hematopoietic cancers in males little altered and still significant. For other types of cancer combined, the SMR remained less than 1. Animal studies (7) have suggested that benzene might produce solid tumors in humans, but no individual type of solid tumor showed a significant increase.

Descriptions of the old and new cases of lymphatic and hematopoietic cancer are presented in Table 3, including the first female (case 21) in the Pliofilm cohort with this form of cancer (specifically, an acute myeloid leukemia). As before, the new leukemia cases represented a variety of histologic types; unfortunately, the exact type was not specified for two of the new leukemias and this information is not readily retrievable. Note that all of the cases had held jobs exposing them to benzene by 1950.

Table 4 compares the SMRs for leukemia from the old and new updates by plant location. For the analysis through 1981, the SMR for the overall cohort was significantly elevated, but the SMR for St. Marys alone was not. After the update through 1987, the addition of five new male leukemia cases increased the SMR for the two locations combined, from 3.15 to 3.60. The addition of two more cases in Akron had little impact on the SMR, but the addition of three cases in St. Marys increased the SMR to 3.36, making it statistically significant (p<0.05).

Table 5, which gives the SMRs according to year of first Pliofilm job, shows no leukemia cases among the 299 workers who started in 1951 or later. The leukemia risk was elevated, but nonsignificant for those starting Pliofilm work between 1946 and 1950. Leukemia risk was significantly elevated only for those who started work prior to the end of World War II. In that benzene exposures in the Pliofilm process were markedly and progressively reduced after World War II, these observations are consistent with a threshold mechanism for leukemogenesis induced by benzene but might also be attributed to the low statistical power of the epidemiology data for this exposure group.

### Individual Worker Exposures from Three Sets of Exposure Estimates

For each worker, estimates of cumulative exposure in ppm-years were generated using three sets of exposure estimates corresponding to the occupational codes in the individual work histories. The original matrix of exposure estimates (the Rinsky exposure estimates) was presented in a 1985 draft (Rinsky et al., unpublished data) and used again but not presented in 1987 (4). Crump and Allen (unpublished data) developed another set of estimates (the Crump exposure estimates) based on the concept that the benzene levels in the workplace probably improved in parallel with progressively more restrictive standards for occupational exposure. Using more detailed information about the monitoring devices used at the plants, the varying

### Table 2. Summary of changes in standardized mortality ratios with update.\(^a\)

| Cause of death | 1981 | | 1987 | |
|---------------|------|------|------|------|
|               | Observed | Expected | SMR | 95% CI | Observed | Expected | SMR | 95% CI |
| Noncancer     |       |       |     |       |       |       |     |       |
| Nonmalignant  | 358   | 352.22 | 1.02 | 0.91–1.13 | 481     | 468.22 | 1.03 | 0.94–1.12 |
| diseases of   |       |       |     |       |       |       |     |       |
| blood and     |       |       |     |       |       |       |     |       |
| blood-forming |       |       |     |       |       |       |     |       |
| organs        |       |       |     |       |       |       |     |       |
| Cancer        |       |       |     |       |       |       |     |       |
| Lymphatic     | 72    | 70.98 | 1.02 | 0.79–1.28 | 111     | 102.57 | 1.06 | 0.89–1.30 |
| and           |       |       |     |       |       |       |     |       |
| hematopoietic |       |       |     |       |       |       |     |       |
| cancers       | 15    | 6.93  | 2.16\(^b\) | 1.21–3.57 | 21      | 9.51  | 2.21\(^b\) | 1.37–3.38 |
| 9 leukemias   |       |       |     |       |       |       |     |       |
| 4 multiple    |       |       |     |       |       |       |     |       |
| myelomas      |       |       |     |       |       |       |     |       |
| 2 others      |       |       |     |       |       |       |     |       |
| Other cancers | 57    | 63.95 | 0.89 | 0.68–1.17 | 90      | 93.06 | 0.97 | 0.78–1.20 |
| Buccal cavity | 2     | 2.31  | 0.87 | 0.10–3.13 | 3       | 3.07  | 0.98 | 0.20–2.86 |
| and pharynx   |       |       |     |       |       |       |     |       |
| Digestive     | 14    | 19.61 | 0.71 | 0.39–1.30 | 21      | 27.37 | 0.77 | 0.47–1.17 |
| organs and    |       |       |     |       |       |       |     |       |
| peritoneum    | 20    | 24.78 | 0.81 | 0.49–1.25 | 35      | 37.31 | 0.94 | 0.65–1.30 |
| Respiratory   |       |       |     |       |       |       |     |       |
| system        | 7     | 4.44  | 1.58 | 0.63–3.25 | 9       | 7.08  | 1.27 | 0.58–2.41 |
| Male genital  | 2     | 3.74  | 0.53 | 0.06–1.93 | 6       | 5.33  | 1.13 | 0.41–2.45 |
| organs        |       |       |     |       |       |       |     |       |
| Urinary organs| 12    | 8.96  | 1.34 | 0.89–2.34 | 16      | 12.76 | 1.25 | 0.72–2.04 |

\(^a\) n=1212 white male wetside workers; person-years start accumulating on 1/1/40. \(^b\) P-value < 0.05 by two-sided Poisson test.
length of the workweek over the years, the effect of World War II upon production, engineering controls, dermal uptake of benzene, and medical evidence that instances of very high level exposure did occur at these plants, Paustenbach et al. (3) derived a third matrix of benzene exposure estimates (the Paustenbach exposure estimates). The Paustenbach exposure estimates are "exposure equivalents" that are normalized to a 40-hr workweek and incorporate dermal, as well as inhalation, contributions; they were not designed to equate to real-time ambient measurements in the plants. Because of the comprehensiveness and detail of their derivation, the Paustenbach exposure estimates are the most appropriate for risk assessment purposes.

Figure 1 presents the cumulative distribution functions of individual cumulative exposure for all male workers at St. Marys and Akron under each of the three sets of exposure estimates. The further to the right a curve lies relative to the other curves in Figure 1, the higher the overall estimated exposure. More than 50% of the individuals have estimated cumulative exposures of less than 50 ppm-years using all three exposure matrices. The upper tails of these highly skewed distributions extend orders of magnitude above their medians, resulting in arithmetic averages (Figure 2) that are about ten times higher than their medians.

The estimated values for the leukemia cases are superimposed upon each curve in Figure 1. For St. Marys, the estimates for the six leukemia cases are spread quite evenly over the range of cumulative exposure estimates, but for Akron, the estimates for almost all the eight leukemia cases are clustered at the upper extreme of the exposure distributions. As indicated under "cause of death" in Table 3, Akron and St. Marys also differ in that the leukemia cases in Akron were predominantly acute myelogenous leukemias (AMLs), whereas in St. Marys this was not so. The lack of a dose response in St. Marys argues against benzene's being

### Table 3. Lymphatic and hematopoietic cancers in the Pliofilm cohort.

| Case no. | Plant location | First benzene exposure | Last benzene exposure | Year of death | Age at death | ICD* code | Cause of death |
|----------|----------------|------------------------|-----------------------|---------------|-------------|-----------|---------------|
| In old cohort† | St. Marys | 1940 | 1942 | 1958 | 36 | 204.2 | Monocytic leukemia |
| 2 | St. Marys | 1948 | 1948 | 1960 | 29 | 204.1 | Chronic myelogenous leukemia |
| 3 | Akron | 1945 | 1958 | 1958 | 60 | 204.3 | Acute myelocytic leukemia |
| 4 | Akron | 1944 | 1960 | 1958 | 65 | 204.3 | Acute myelogenous leukemia |
| 5 | Akron | 1939 | 1960 | 1961 | 62 | 204.3 | DiGuglielmo's acute myelocytic leukemia |
| 6 | Akron | 1941 | 1961 | 1961 | 57 | 204.3 | Acute granulocytic leukemia |
| 7 | Akron | 1942 | 1948 | 1957 | 57 | 204.2 | Acute monocytic leukemia |
| 8 | St. Marys | 1950 | 1952 | 1954 | 28 | 204.1 | Myelogenous leukemia |
| 9 | Akron | 1942 | 1960 | 1979 | 67 | 205.0 | Acute myeloblastic leukemia |
| 10* | St. Marys | 1954 | 1954 | 1980 | 69 | 203.0 | Multiple myeloma |
| 11* | Akron | 1940 | 1940 | 1963 | 52 | 203.0 | Multiple myeloma |
| 12* | St. Marys | 1943 | 1968 | 1968 | 62 | 203.0 | Plasma cell sarcoma |
| 13* | St. Marys | 1954 | 1955 | 1981 | 68 | 203.0 | Multiple myeloma |
| 14* | St. Marys | 1937 | 1970 | 1973 | 64 | 200.0 | Reticulosarcoma |
| 15* | St. Marys | 1947 | 1955 | 1978 | 55 | 202.9 | Other malignant neoplasm of lymphoid or histiocytic tissue |

*International Classification of Diseases code currently on 1987 update of NIOSH tape. †The four cases with ICD Code of 203 (multiple myeloma and immunoproliferative neoplasms) were not considered in further analyses. ‡The three cases of hematopoietic/lymphatic cancers other than leukemia, multiple myeloma, or plasma cell sarcoma were not considered in further analyses. §This one female leukemia case was not considered in the SMR analyses but was included in the dose–response analysis using the proportional hazards model.

### Table 4. Standard mortality ratios for leukemia in Pliofilm workers* by update and location.

| Location | Update through | Person-years | Observed | Expected | SMR | 95% CI |
|----------|----------------|--------------|----------|----------|-----|--------|
| All      | 1981           | 36,587       | 10       | 2.86     | 3.15** | 1.44–5.98 |
| St. Marys| 1981           | 18,945       | 3        | 1.26     | 2.38  | 0.49–6.95 |
| Akron   | 1981           | 22,807       | 6        | 1.79     | 3.36* | 1.23–7.31 |
| Akron   | 1987           | 15,642       | 6        | 1.60     | 3.76* | 1.37–6.18 |
| Akron   | 1987           | 17,533       | 8        | 2.10     | 3.61**| 1.64–7.51 |

*White male wetside workers. †Accumulation of person-years started on 1/1/40 or at the start of the first Pliofilm job, whichever was later. *p-Values by two-sided Poisson test. **p < 0.05. ***p < 0.01.

### Table 5. Standardized mortality ratios for leukemia in Pliofilm workers by date of first exposure.

| Date of first exposure | Person-years | Observed | Expected | SMR | 95% CI |
|-----------------------|--------------|----------|----------|-----|--------|
| 1945 or before        | 10,389       | 3        | 1.44     | 6.29**| 2.85–11.89 |
| 1946–1950             | 21,165       | 5        | 1.72     | 2.91 | 0.94–6.81 |
| 1951 or after         | 8,791        | 0        | 0.75     | 0   | 0–3.99 |

*White male wetside workers. †Accumulation of person-years started on 1/1/40 or at the start of the first Pliofilm job, whichever was later. *p-Value by two-sided Poisson test. **p < 0.01.
cumulative exposure for the cases using the Crump exposure estimates is greater than that derived using the Paustenbach estimates, and the Paustenbach estimates actually give lower estimated average exposure for the cases than for the controls. This deviation from the absolute increase that might have been expected with the Paustenbach exposure estimates lends credence to the objectivity and validity of the Paustenbach industrial hygiene reconstruction. One could view the Paustenbach and the Crump exposure estimates as being mutually confirmatory in that the results of Paustenbach’s detailed reconstruction lend support to the validity of the simple assumption that was the basis for the Crump exposure estimates.

Using the three sets of cumulative exposure estimates, SMRs and confidence intervals were derived for the person-years at risk in the categories: 0 to 5, 5 to 50, 50 to 500, and more than 500 ppm-years (Table 6). These findings suggest a strong dose–response relationship of risk increasing with cumulative exposure no matter which set of exposure estimates is used. For none of the three sets of exposure estimates, however, is there a statistically significant increase in the SMRs for cumulative exposures less than 50 ppm-years. This is consistent with the hypothesis that exposure in excess of some threshold value (here suggested to be greater than 50 ppm-years) is necessary for leukemogenesis. This threshold hypothesis is further supported by work at the mechanistic level (8–11). In a similar analysis of cumulative exposure partitioning these leukemia cases into acute myelocytic or acute monocytic leukemias (AMMLs) versus non-AMMLs, Crump (12) showed that the dose–response relationship is driven by AMMLs with a suggested threshold in excess of 400 ppm-years and that the frequency of the other leukemias is not associated with benzene exposure.

### Risks Estimated by Proportional Hazards Dose–Response Model

Statistical analysis with the proportional hazards dose–response model (13) relates exposure to the incidence of leukemia while controlling for demographic, socioeconomic, and other variables that might confound interpretation of the data. With this same objective, Rinsky et al. (4) had used a conditional logistic regression analysis on a subset of the Pliofilm data consisting of the nine leukemia cases (all white males), each of whom was matched on the basis of sex, race, date of birth, and date of first employment in a Pliofilm job to ten controls who were alive at the time their corresponding case died. Because it accepts all controls falling within a defined stratum (Table 7), the proportional hazards analysis includes more workers than would the conditional logistic’s matching process. It does not require the arbitrary assignment of each control to one of several cases sharing similar profiles or the utilization of very poorly matched controls when the fixed number of appropriate individuals is not available, as does the conditional logistic analysis.

The matching criteria of Rinsky et al. (4) were used to define the strata in the proportional hazards model (i.e., sex, race, date of birth, and date of first Pliofilm job). The possibility that the plants in Akron and St. Marys might have differed in the leukemogenic response they induced because of factors other than benzene exposure levels was controlled for by using location as an additional matching criterion. Although the vital status of the dryside workers had been followed up only through 1981, they

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**Figure 1.** The occurrence of leukemias in relation to cumulative exposure: (A) St. Marys; (B) Akron.

**Figure 2.** Estimated average cumulative exposures of white males.

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**Table 6.** Standardized mortality ratios for leukemia in Pliofilm workers* by cumulative exposure at all locations.

| Exposure estimates | Cumulative exposure, ppm-years | Person-years | Observed | Expected | SMR\(^2\) | 95% CI |
|--------------------|--------------------------------|--------------|----------|----------|-----------|--------|
| Rinsky             | 0-5                            | 18,178       | 3        | 1.52     | 1.97      | 0.41–5.76 |
|                    | >6-50                          | 13,456       | 3        | 1.31     | 2.29      | 0.47–6.89 |
|                    | >50-500                        | 8,383        | 7        | 1.01     | 6.93\(^*\) | 2.78–14.29 |
|                    | >500                           | 328          | 1        | 0.05     | 0.05      | 0.51–11.14 |
| Crump              | 0-5                            | 12,974       | 1        | 1.14     | 0.88      | 0.02–4.89 |
|                    | >5-50                          | 13,951       | 4        | 1.23     | 3.25      | 0.88–8.33 |
|                    | >50-500                        | 11,448       | 6        | 1.23     | 4.87\(^*\) | 1.79–10.63 |
|                    | >500                           | 1,972        | 3        | 0.29     | 10.34\(^*\) | 2.13–30.21 |
| Paustenbach        | 0-5                            | 9,645        | 1        | 0.75     | 1.33      | 0.02–7.43 |
|                    | >5-50                          | 12,882       | 2        | 1.12     | 1.79      | 0.22–6.45 |
|                    | >50-500                        | 14,095       | 4        | 1.43     | 2.90      | 0.76–7.16 |
|                    | >500                           | 3,723        | 7        | 0.59     | 11.86\(^*\) | 4.76–24.44 |

*White male wetside workers. \(^*\)p-Value by two-sided Poisson test; \(^{\ast}\)p<0.05, \(^{\ast\ast}\)p<0.01.
made suitable stratum co-occupants in the proportional hazards model for leukemia cases based on age calculations up to 1981. A female leukemia patient identified during the 1987 update was included in our proportional hazards analysis because she could be appropriately matched with female controls in a separate stratum. Therefore, all 1868 Pliofilm workers were considered eligible for inclusion in this proportional hazards analysis (Table 1, top) using BMDP software (Bio-Medical Data Processing, Los Angeles, CA) (14).

To estimate the probability of leukemia over a lifetime associated with various cumulative exposures \(x_j\) to benzene, we used \(p(0)\) the estimate of background lifetime \((t = 70)\) leukemia probability derived \((15)\) as a reference point and get

\[
p(x_{70}) = p(0)RR(x_{70};x)
\]

The increase in risk for a cumulative benzene exposure of \(x_{70}\) was estimated as

\[
p(x_{70}) - p(0).
\]

Table 7 describes the composition of the informative strata used in regression analysis based on the proportional hazards dose–response model for the cohort as updated through 1987. Our proportional hazards analysis used 665 (35.6%) of the 1868 members of the entire Pliofilm cohort compared to the 165 (8.8%) that would have been used if the conditional logistic approach of Rinsky et al. \((4)\) had been applied to the 15 leukemia cases found through 1987.

The estimates of the slope parameter in this dose–response model before and after the 1987 update under the three sets of exposure estimates are presented in Table 8. For either update period, the slope of dose–response relationship was estimated to be about 20 to 40% as steep using the Crump or the Paustenbach estimates of exposure as when the Rinsky exposure estimates were used. Updating the cohort’s leukemia status through 1987 resulted in a lowering of the estimated slope parameters under all three sets of exposure estimates.

The predictions of additional leukemia deaths and associated 95% confidence intervals are plotted in Figure 3. Risks for occupational exposure are given for working lifetimes (8 hr/day, 5 days/week, 50 weeks/year for 45 years) for continuous exposure at 0.1, 0.3, 1, 5, or 10 ppm. In the current analysis, using the preferred exposure estimates of either Crump or Paustenbach predicts about 0.3 to 0.5 additional leukemia deaths per thousand workers in the concentration range around 1 ppm. Overall, the results of this update and reanalysis suggest that the previous estimate of 5.1 additional leukemia deaths for that exposure scenario \((16)\), based on the approach of Rinsky et al. \((4)\), is about an order of magnitude too high. More detailed investigation of the dose–response relationships in the Pliofilm cohort using all the workers and focusing on the most pertinent end point, AMLs only, may be found in the sensitivity analysis of Crump \((12)\) summarized at this conference.

### Table 7. Composition of strata analyzed with proportional hazards model for update through 1987.

| Stratum | Location | Sex \(a\) | Decade of birth | Decade of first Pliofilm employment | Number in stratum Cases | Controls |
|---------|----------|-----------|----------------|-----------------------------------|-------------------------|----------|
| 1       | St. Marys | Male      | 1900–1899      | 1940–1949                         | 1                       | 2        |
| 2       | St. Marys | Male      | 1910–1919      | 1940–1949                         | 2                       | 80       |
| 3       | St. Marys | Male      | 1920–1929      | 1940–1949                         | 2                       | 305      |
| 4       | St. Marys | Male      | 1920–1929      | 1950–1959                         | 1                       | 137      |
| 5       | Akron    | Male      | 1886–1895      | 1936–1945                         | 1                       | 18       |
| 6       | Akron    | Male      | 1896–1905      | 1936–1945                         | 4                       | 40       |
| 7       | Akron    | Male      | 1906–1915      | 1936–1945                         | 1                       | 27       |
| 8       | Akron    | Male      | 1916–1925      | 1946–1955                         | 2                       | 34       |
| 9       | Akron    | Female    | 1886–1895      | 1936–1945                         | 1                       | 7        |
|         | Total    |           |                |                                   | 15                      | 650      |

*Nonblack wetside and dryside cohort members alive at the time of a case’s death were eligible for matching to the cases, who were all white.

### Table 8. Proportional hazards estimates of probability of leukemogenic response as a function of cumulative exposure

| Update through | Exposure estimates | \(\beta\) | Standard error | \(p\)-Value |
|---------------|--------------------|----------|----------------|-------------|
| 1981\(^a\)    | Rinsky             | 0.0047   | 0.0015         | 0.0002      |
|               | Crump              | 0.0009   | 0.0004         | 0.0016      |
|               | Paustenbach        | 0.0020   | 0.0007         | 0.0006      |
| 1987\(^a\)    | Rinsky             | 0.0056   | 0.0014         | 0.0023      |
|               | Crump              | 0.0008   | 0.0004         | 0.0602      |
|               | Paustenbach        | 0.0015   | 0.0005         | 0.0015      |

*Because the underlying models differ, these \(\beta\)s are not directly comparable to those derived by Rinsky et al. \((4)\) and by Brett et al. \((16)\) using the conditional logistic model. \(^a\)Based upon the original 9 leukemia cases and the 527 controls in their strata. \(^b\)Based upon the updated information on all 15 leukemia cases and the 650 controls in their strata.

### Conclusion

The additional information assembled in updating the Pliofilm cohort strengthens but does not greatly alter the thrust of the data through 1981 concerning leukemia risk in this occupational setting \((4,16)\). The absence of any additional cases of multiple myeloma in the update through 1987 weakens to nonsignificance the previous statistical association of this end point with benzene exposure. There continues to be no evidence of any increase in the incidence of any type of solid tumors. The more rigorously defined exposure estimates derived by Paustenbach et al. \((3)\) are consistent with those of Crump and Allen (unpublished data) in giving estimates of the slope of the leukemogenic dose response that are not as steep as the slope resulting from the exposure estimates of Rinsky et al. (unpublished data).

The newly gathered information continues to be consistent with a threshold model for leukemogenesis by benzene. The leukemia deaths in the entire cohort occurred exclusively among individuals who commenced their work in Pliofilm production in 1950 or earlier. The simplest explanation would be that industrial hygiene improved over the years at both Akron and St. Marys and achieved a critical level of reduced benzene exposure in the early 1950s, so that workers entering the workplace after that time were no longer at risk for developing leukemia.
REFERENCES

1. Paxton MB, Chinchilli VM, Brett SM, Rodricks JV. Leukemia risk associated with benzene exposure in the Pliofilm cohort. I: Mortality update and exposure distribution. Risk Anal 14:147–154 (1994).

2. Paxton MB, Chinchilli VM, Brett SM, Rodricks JV. Leukemia risk associated with benzene exposure in the Pliofilm cohort. II: Risk estimates. Risk Anal 14:155–161 (1994).

3. Paustenbach DJ, Price PS, Ollison W, Blank C, Jernigan JD, Bass RD, Peterson HD. Reevaluation of benzene exposure for the Pliofilm (rubberworker) cohort (1936-1976). Toxicol Environ Health 36:177–231 (1992).

4. Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. Benzene and leukemia: an epidemiologic risk assessment. N Engl J Med 316:1044–1050 (1987).

5. NIOSH. User Documentation: Life Table Analysis System, Version F. Cincinnati, OH: National Institute for Occupational Safety and Health, 1991.

6. Wong O. Risk of acute myelogenous leukemia and multiple myeloma in workers exposed to benzene. Occup Environ Med 52:380–384 (1995).

7. NTP. Toxicology and Carcinogenesis Studies of Benzene (CAS No. 71-43-2) in F344/N Rats and B6C3F1 Mice (Gavage Studies) NTP TR 289. Research Triangle Park, NC: National Toxicology Program, 1986.

8. Irons RD, Stillman WS. Cell proliferation and differentiation in chemical leukemogenesis. Stem Cells 11:235–242 (1993).

9. Schattenberg DG, Stillman WS, Gruntmeier JJ, Helm KM, Irons RD, Ross D. Peroxidase activity in murine and human hematopoietic progenitor cells: potential relevance to benzene-induced toxicity. Mol Pharmacol 46:346–351 (1994).

10. Hazel BA, O'Conner A, Niculescu R, Kalf GF. Benzene and its metabolite, hydroquinone, induce granulocytic differentiation in myeloblasts by interacting with cellular signaling pathways activated by granulocyte colony-stimulating factor. Stem Cells 13:295–310 (1995).

11. Cox LA. More accurate estimates of dose-response functions using Monte Carlo uncertainty analysis: the data cube approach. Human Ecol Risk Assess 2:146–170 (1996).

12. Crump KS. Risk of benzene-induced leukemia: a sensitivity analysis of the ploofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health 42:219–242 (1994).

13. Cox DR. Regression Models and Life-tables. J Royal Statist Soc Series B 34:187–202 (1971).

14. Hopkins A. 2L: Survival analysis with covariates. In: BMDP Statistical Software Manual (Dixon WJ, ed). Berkeley, CA: University of California Press, 1990; 769–806.

15. White MC, Infante PF, Chu KC. A quantitative estimate of leukemia mortality associated with occupational exposure to benzene. Risk Anal 2:195–204 (1982).

16. Brett SM, Rodricks JV, Chinchilli VM. Review and update of leukemia risk potentially associated with occupational exposure to benzene. Environ Health Perspect 82:267–281 (1989).