Risk of Benzene-induced Leukemia Predicted from the Pliofilm Cohort

Kenny S. Crump
ICF Kaiser International, Ruston, Louisiana

This report updates the risk assessment by Crump and Allen for benzene-induced leukemia that was based on a cohort exposed to benzene in the manufacture of Pliofilm. The present study derives new risk estimates using data from follow-up through 1987 (whereas the earlier assessment only had follow-up available through 1978) and uses new exposure information for this cohort developed by Paustenbach et al. that accounts for a number of factors that were unknown or not fully evaluated in earlier exposure assessments. There was a significant excess of acute myelocytic or acute monocytic leukemia (AMML) (8–10 observed, 1.61 expected) in this cohort, and this end point also exhibited a strong dose–response trend. No other types of lymphatic or hematopoietic cancer were clearly linked to benzene exposure. Quantitative risk estimates were robust with respect to whether AMML or all leukemia was being modeled. They were also robust with respect to whether the Paustenbach et al. Crump and Allen exposure estimates were used (differences in risk estimates of no greater than 2-fold) as long as linear dose–response models were applied. However, whereas the Crump and Allen exposures predicted a linear dose response, the Paustenbach et al. exposures predicted a quadratic dose response. This departure from linearity was borderline significant (p=0.08). Estimates of additional lifetime from 45 years of occupational exposure (lifetime exposure) to 1 ppm derived using the Paustenbach et al. exposure matrix and best-fitting (quadratic) models ranged from 0.020 to 0.036 per thousand, whereas corresponding estimates based on a linear dose response ranged from 1.6 to 3.1 per thousand. — Environ Health Perspect 104(Suppl 6):1437–1441 (1996)

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Introduction

Crump and Allen (1) developed estimates of the benzene-related risk of leukemia using data from a cohort of workers exposed to benzene during the manufacture of Pliofilm, a glossy membrane made from rubber hydrochloride and used chiefly for packaging and other water-resistant materials (2–5). This risk assessment was used by the U.S. Occupational Safety and Health Administration (6) to support a reduction of the permissible exposure limit (PEL) for benzene from 10 ppm to 1 ppm; it also formed the basis for the “unit risk estimate” for inhaled benzene developed by the U.S. Environmental Protection Agency (7).

Since the Crump and Allen risk assessment (1), significant new information has become available on the Pliofilm cohort. First, follow-up of the cohort has been extended by the National Institute of Occupational Safety and Health (NIOSH) from 1978 through 1987. Second, Paustenbach et al. (8) made a detailed reevaluation of exposures in the Pliofilm cohort that incorporated information obtained recently from historical records and from interviews with former workers. This assessment accounted for, among other things, dermal exposures, short-term, high-level exposures, respirator use, biases of sampling devices used in earlier years, and a previously unaccounted for shutdown of the St. Marys plant during World War II. The present article summarizes an update of the Crump and Allen risk assessment (1) that incorporates 9 years of additional follow-up and the new exposure estimates developed by Paustenbach et al. (8). Crump (9) presents a more detailed description of this work.

Methods

The present analysis used mortality data from follow-up by NIOSH of a cohort of 1717 white male workers employed in Pliofilm operations for at least 1 day at either the St. Marys or the Akron, Ohio manufacturing facility (6). The total included 577 workers in jobs not considered by Rinsky et al. (3-4) to involve benzene exposure [although both Crump and Allen (1) and Paustenbach et al. (8) estimated some exposure to benzene in these jobs] and for whom follow-up did not extend beyond 31 December 1981. The mortality experience of the 1140 remaining workers was followed through 31 December 1987. Paxton et al. (5) provided a detailed description of the status of the cohort through the most recent follow-up.

The analysis focuses upon lymphatic and hematopoietic cancer (International Classification of Diseases, 9th Revision, codes 202–209), all leukemias, and a category of acute leukemia defined as acute myelogenous or acute monocytic leukemia (AMML). AMML includes all of the acute nonlymphocytic leukemias that have been identified in the Pliofilm cohort. A lifetable analysis is conducted for all three cancer categories and, based on the results of the lifetable analysis, dose–response modeling is conducted for all leukemias and for AMML. The type of leukemia is not known for 2 of the 14 cases found in the most recent follow-up, and these cases were excluded from the dose–response modeling of AMML.

Following the approach used by Crump and Allen (1), both absolute risk and cumulative risk models were used. An additive risk model assumes that benzene increases the background mortality rate by an additive amount that depends on prior benzene exposure; a multiplicative risk model assumes that benzene increases the background mortality rate by a multiplicative factor that depends on prior benzene exposure. Both linear and nonlinear versions of each of these models were considered. For the linear additive risk model, the mortality rate at age t for the cancer of interest is assumed to be in the form

\[ b(t) = a(t) + BX(t), \]

where \( a(t) \) is the background mortality rate at age \( t \) (which was estimated from
appropriate mortality rates for white males in the United States). $X(t)$ is a summary measure of benzene exposure before age $t$, and $\beta$ is a parameter that gauges the carcinogenic potency of benzene. The corresponding expression for the linear multiplicative model is

$$h(t) = a(t) \left[1 + \beta X(t)\right].$$

The study also involved analyses that incorporated a parameter that multiplied $a(t)$ to account for the possibility that the background mortality rates in the Pliofilm cohort differed systematically from total U.S. rates (9). However, there was no evidence that U.S. rates were not appropriate, and those analyses are not discussed here.

The summary exposure measure, $X(t)$, discussed in the present report, is cumulative exposure (ppm-years/m$^2$) to age $t$, with a 5-year lag (i.e., omitting exposures during the 5 most recent years). Lags of 0 and 3 years were also considered, but they did not describe the data as well as a lag of 5 years.

We also considered a form of weighted exposure that was based on the leukemia-response pattern observed following X-ray treatment (10). With weighted exposure, the impact of benzene exposure occurring during a small time slice on future cancer mortality increases with increasing elapsed time from zero impact to a maximum level of impact and decreases thereafter. The effect of the complete pattern of benzene exposure is obtained by integrating the effects of exposures during each time slice. In general, weighted exposure did not describe the mortality data as well as cumulative exposure and it produced risk estimates roughly comparable to those obtained using cumulative exposure. Estimates of lifetime risk based on weighted exposure could be either higher or lower than those based on cumulative exposure, but generally the differences were less than a factor of 2 (9). Only results based on cumulative exposure are presented here.

To investigate the possibility of a nonlinear relationship between benzene exposure and mortality rate, the linear models described above were expanded to include nonlinear terms. Two types of nonlinearity were considered. In nonlinearity that was dependent on the area under exposure-duration curve (AUC), additional terms were incorporated that varied as the square or cube of cumulative exposure. That is, AUC-dependent, nonlinear models were defined by replacing $\beta X(t)$ in the linear additive and multiplicative models by $\beta X(t) + \beta_2 X^2(t) + \beta_3 X^3(t)$. Intensity-dependent nonlinear models were described the same way except that cumulative exposure raised to a power, $X(t)$, was replaced by

$$X(t) = \int_0^t x(v) dv$$

where $x(v)$ is the intensity of exposure (ppm) at age $v$, $X(t)$ is the accumulation [integral] of instantaneous exposure raised to the $i$th power, where $i = 2$ or $i = 3$. With intensity-dependent nonlinearity, the intensity of exposure was given greater weight than the duration of exposure. For example, at the completion of the exposure period, $X^2(t) = 100$ (ppm-years)$^2$ both for exposure to 100 ppm for 1 year and exposure to 10 ppm for 10 years. However, $X_3(t) = 10,000$ ppm$^2$-years for the former exposure pattern and 1000 ppm$^2$-years for the latter pattern, which represents a 10-fold difference. Intensity-dependent nonlinearity may be more appropriate than AUC-dependent nonlinearity for modeling biological effects brought about by acute toxicity.

Analyses were performed using both the Paustenbach et al. exposure matrix [the set of exposure estimates recently developed for the Pliofilm cohort by Paustenbach et al. (8)] and, for comparison purposes, the Crump and Allen exposure matrix [the set of exposures developed by Crump and Allen (7)].

The method of maximum likelihood was used to fit models to data and to test hypotheses. Estimates of the potency parameters ($\beta$ and $\beta_i$) were translated into estimates of the additional lifetime risk of cancer from specific patterns of benzene exposure (lifetime occupational exposure and continuous lifetime exposure) using a formula for the lifetime probability of cancer based on United States mortality rates [males and females combined] for total mortality and for the cancer of interest.

In converting from occupational exposure to continuous exposure, it was assumed that Pliofilm workers were exposed for 8 hr/day, 250 days/year, and breathed 10 m$^3$ of air per 8-hr workday. It was further assumed that persons exposed continuously breathe 20 m$^3$ of air per 24-hr day. Additional details regarding methods of analysis are provided in Crump (9).

**Results**

Table 1 contains a list of the 21 cases of lymphatic and hematopoietic cancer in the cohort along with the cumulative benzene exposures (zero lag) at time of death computed using both the Paustenbach et al. and the Crump and Allen exposure matrices. This table also indicates which of these 21 cases were AMML (8-10 cases) or leukemia of any type (14 cases). All the model fits for AMML included only the eight confirmed cases and omitted the two questionable cases. Both questionable cases involved relatively low exposures to benzene.

Table 2 presents the results of the lifetable analysis of the association of various categories of hematopoietic cancer, with cumulative exposure defined using the Paustenbach et al. exposure matrix. A similar analysis (not shown) based on the Crump and Allen exposure matrix gave comparable results. A dose response was observed for each of the three categories, AMML, all leukemias, and total lymphatic and hematopoietic cancer. However, neither the dose response for all leukemias nor that for total lymphatic and hematopoietic cancer was as strong as that for AMML; and a dose response was not apparent for either of these categories if AMML was excluded. For the category defined as total lymphatic and hematopoietic cancer excluding leukemia, there was a slight deficit of cancer deaths (observed $= 7$, expected $= 7.3$), and there was no indication of a dose response (other than a single case in the high-exposure group). There was a nonsignificant excess for non-AMML leukemias [expected $= 3.1$, observed $= 4$ ($p = 0.38$) to $6$ ($p = 0.10$)]. However, all of the non-AMML leukemias were associated with exposures <400 ppm-years, whereas five of the AMMLs were associated with exposures >1000 ppm-years (only 0.06 expected). Thus, AMML was the only response clearly related to benzene exposure.

Table 3 contains results from fitting linear versions of the additive and multiplicative risk models to responses of AMML and all leukemias. Potency estimates (estimates of $\beta$) derived from the Paustenbach et al. (8) exposure matrix are smaller by a factor of $<2$ compared to the corresponding estimates based on the Crump and Allen exposure matrix (7). Potency estimates derived from AMML and all leukemias using the additive model are in close agreement. Corresponding estimates derived from multiplicative models are not strictly comparable because the increase in relative risk derived from all leukemias multiplies a larger background than the increase derived from only AMML alone. Potency estimates derived...
Table 1. Summary of information on 21 cases of lymphatic and hematopoietic cancer in males.

Patient identification no. | Rinsky et al. (1) case no. | Birth | Death | Year of diagnosis | First employment | Last employment | Cumulative exposure, ppm-years | Leukemia | AMML
---|---|---|---|---|---|---|---|---|---
19 | 2 | 1921 | 1950 | 1948 | 1948 | 3 | 3 | X
65 | 6 | 1925 | 1954 | 1950 | 1952 | 23 | 54 | X
69 | 7 | 1999 | 1957 | 1942 | 1949 | 307 | 670 | X | Y
136 | 1 | 1921 | 1956 | 1940 | 1942 | 381 | 127 | X | Y
41 | 3 | 1988 | 1958 | 1945 | 1958 | 251 | 1054 | X | X
160 | 1 | 1984 | 1956 | 1944 | 1958 | 1497 | 1242 | X | X
176 | 6 | 1904 | 1961 | 1941 | 1961 | 2155 | 1771 | X | X
233 | 5 | 1989 | 1961 | 1939 | 1960 | 939 | 1122 | X | Y
260 | 11 | 1910 | 1963 | 1940 | 1940 | 1514 | 1109 | ? | ?
896 | 12 | 1905 | 1968 | 1943 | 1948 | 1148 | 3075 | X | X
154 | 1987 | 1973 | 1957 | 1970 | 54 | 651 | X | X
148 | 1923 | 1978 | 1947 | 1955 | 175 | 138 | X | X
184 | 9 | 1912 | 1979 | 1942 | 1960 | 325 | 1129 | X | X
48 | 10 | 1912 | 1980 | 1954 | 1986 | 31 | 51 | X | X
949 | 13 | 1912 | 1981 | 1954 | 1955 | 16 | 12 | X | X
624 | 17 | 1917 | 1984 | 1950 | 1957 | 85 | 330 | X | X
432 | 1918 | 1956 | 1940 | 1956 | 145 | 233 | X | X
379 | 1918 | 1965 | 1948 | 1958 | 18 | 598 | X | X
75 | 1914 | 1986 | 1945 | 1946 | 50 | 20 | X | X
671 | 1905 | 1987 | 1949 | 1949 | 6 | 8 | X | X
561 | 1926 | 1987 | 1947 | 1947 | 0 | 19 | X | X

*Includes acute myelocytic (X) and acute monocytic (Y) leukemia.

Table 2. Observed and expected numbers of cancer deaths by cumulative exposure (Paustenbach exposure matrix) for different categories of lymphatic and hematopoietic cancers.

| Cumulative exposure, ppm-years range (mean) | Person-years | AMML | Leukemia | Total lymphatic and hematopoietic | Total excluding leukemia | Leukemia excluding AMML | Total excluding AMML |
|---|---|---|---|---|---|---|---|
| | Obs | Exp | RR | Obs | Exp | RR | Obs | Exp | RR | Obs | Exp | RR | Obs | Exp | RR |
| 0–45 (11) | 30482 | 0–2 | 0.02 | 0.0–2.4 | 3 | 2.4 | 1.2 | 6 | 3.6 | 1.0 | 3 | 3.75 | 0.8 | 1–3 | 1.59 | 0.63–1.9 | 4–6 | 5.34 | 0.75–1.1 |
| 45–150 (151) | 16320 | 1 | 0.51 | 2.0 | 4 | 1.5 | 0.7 | 6 | 3.8 | 1.8 | 2 | 2.33 | 0.9 | 3 | 0.99 | 3.0 | 5 | 3.32 | 1.5 |
| 100–1000 (602) | 467 | 1 | 0.22 | 9.1 | 2 | 0.65 | 3.1 | 3 | 1.6 | 0.4 | 1 | 0.99 | 1.0 | 0 | 0.43 | 0.0 | 1 | 1.43 | 0.7 |
| >1000 (1341) | 915 | 5 | 0.06 | 82.8 | 5 | 0.18 | 28.1 | 6 | 0.44 | 13.5 | 1 | 0.27 | 3.8 | 0 | 0.12 | 0.0 | 1 | 0.38 | 2.6 |
| Total (132) | 52584 | 8–10 | 1.61 | 5.0–6.2 | 14 | 4.75 | 2.9 | 21 | 12.0 | 1.7 | 7 | 7.34 | 1.0 | 4–6 | 3.14 | 1.3–1.9 | 11–13 | 10.48 | 1.05–1.2 |

Abbreviations: obs, number of observed cancer deaths; exp, number of expected cancer deaths based on U.S. sex- and age-specific rates; RR, obs/exp (relative risk). *AMML and AML (ICD codes 209.0 and 208.0); leukemia (ICD codes 204–207); total lymphatic and hematopoietic cancers (ICD codes 200–209).

Table 3. Results from fits of linear models.

| Exposure matrix | β (βSE) | Maximum likelihood |
|---|---|---|
| Crump and Allen (1)* | | |
| AMML | Additive model | 2.0E-5 (8.2E-7) | –64.00 |
| Multiplicative model | 4.5E-2 (1.8E-2) | –61.84 |
| All leukemias | Additive model | 1.9E-6 (8.8E-7) | –115.18 |
| Multiplicative model | 1.7E-2 (6.8E-3) | –111.68 |
| Paustenbach et al. (18)* | | |
| AMML | Additive model | 1.3E-6 (5.1E-7) | –64.96 |
| Multiplicative model | 2.7E-2 (1.0E-2) | –61.68 |
| All leukemias | Additive model | 1.3E-6 (5.6E-7) | –115.98 |
| Multiplicative model | 1.1E-2 (3.9E-3) | –111.57 |

*References indicate the method used for calculation of data in table.
multiplicative risk model is also presented. The risk estimate obtained by Crump and Allen (6.6/thousand) agrees closely with the corresponding estimate obtained from the current analysis using the Crump and Allen exposure matrix (1) (5.1/thousand). Estimates derived from data on AMML and on all leukemias also agree closely. Estimates from linear models based on the Paustenbach et al. exposure matrix (8) are roughly one-half of the corresponding estimates based upon the Crump and Allen exposure matrix (1). Risk estimates derived from nonlinear models are far smaller with the Paustenbach et al. exposure matrix (8) than the Crump and Allen exposure matrix (1). This is because the Paustenbach et al. exposure matrix (8) produces a purely quadratic dose response, whereas the Crump and Allen exposure matrix (1) produces an essentially linear dose response.

Table 6 contains estimates of the number of additional deaths per 1 million persons exposed continuously throughout life to 1 ppb benzene. Estimates based on linear models range from 15 per million using the Paustenbach et al. (8) exposure matrix to 21 to 24 per million based on the Crump and Allen (1) exposure matrix. Estimates based on nonlinear models and the Paustenbach et al. (8) exposure matrix are about 100,000 times smaller than estimates based on linear models.

**Discussion**

The two exposure matrices lead to quite different conclusions concerning the shape of the dose response. Whereas dose responses were essentially linear when the Crump and Allen (1) exposure matrix was used, there was evidence of intensity-dependent nonlinearity in dose responses derived using the Paustenbach et al. exposure matrix (Table 4); based on this matrix, each of the three best-fitting models was quadratic, and departures from linearity were borderline significant in each case. Estimates of risk from 45 years of exposure at 1 ppb based on these quadratic models were about 100-fold smaller than corresponding estimates derived from linear models.

The Paustenbach et al. (8) exposure matrix was based on a much more detailed investigation than that conducted by Crump and Allen (1). Based on review of their work and personal knowledge of methods used by Crump and Allen, we believe that the Paustenbach et al. matrix is likely to provide a better representation of exposures in the cohort. Nevertheless, considerable uncertainty exists with regard to exposures during the earliest period of plant operation. Paxton et al. (5) showed that the average exposure in the cohort based on the Paustenbach et al. exposure matrix was about 2-fold higher than that based on the Crump and Allen exposure matrix and about 4-fold higher than that based on the Rinsky et al. (4) exposure matrix.

The Rinsky et al. (4) exposure matrix, which was not used in this analysis, did not conform with blood count data for this cohort or with the Crump and Allen (1) exposure matrix. Based on a study of over 17,000 peripheral blood counts collected from 459 workers at St. Marys between 1940 and 1975, Kipen et al. (11) showed that assignment of relatively higher benzene exposures to this cohort during the 1940s, with a substantial and rapid decline in these exposures after 1946 (as assumed by Crump and Allen (1)), was consistent with temporal increases in blood counts. Using a different method of analysis, Horning (unpublished data) showed that the exposures predicted by the Rinsky et al. exposure matrix also were correlated with blood counts. However, Horning did not use his method to evaluate the other two exposure matrices.

The large differences in risk obtained in this study between linear and nonlinear models are extremely important to the regulation of benzene. Unfortunately, it is not possible to accurately determine the amount of nonlinearity present in the dose response based on the information available from the Pliofilm cohort. Perhaps continued follow-up of the much larger Chinese cohort (R Hayes, unpublished data) will help further narrow the range of risks associated with human exposure to benzene.

**REFERENCES**

1. Crump K, Allen B. Quantitative estimates of risk of leukemia from occupational exposure to benzene. Unpublished report prepared for the Occupational Safety and Health Administration, 1984.

2. Infante PF, Rinsky RA, Wagoner JK, Young RJ. Leukemia in benzene workers. Lancet 2:76–78 (1977).

3. Rinsky RA, Young RJ, Smith AB. Leukemia in benzene workers. Am J Ind Med 2:217–245 (1981).
4. Rinsky RA, Smith AB, Hornung R, Filloon RG, Young RJ, Okun AH, Landrigan PJ. Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 316:1044–1050 (1987).
5. Paxton MB, Chinchilli VM, Brett SM, Rodricks JV. Leukemia risk associated with benzene exposure in the pliofilm cohort. Risk Anal 14:147–162 (1994).
6. Occupational Safety and Health Administration. Occupational exposure to benzene; final rule. Fed Reg 52:50512–50586 (1987).
7. U.S. EPA. Interim Quantitative Cancer Unit Risk Estimates Due to Inhalation of Benzene. EPA-600/X-85-022. Washington: U.S. Environmental Protection Agency, 1985.
8. Paustenbach DJ, Price PC, Ollison W, Blank C, Jernigan JD, Bass RD, Peterson HD. Reevaluation of benzene exposure for the pliofilm (rubberworker) cohort (1936–1976). J Toxicol Environ Health 36:177–231 (1992).
9. Crump K. Risk of Benzene-induced leukemia: a sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health 42:219–242 (1994).
10. Darby SC, Doll R, Gill SK, Smith PG. Long-term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer 55:179–190 (1987).
11. Kipen HM, Cody RP, Crump KS, Goldstein B. Hematologic effects of benzene: a thirty-five year longitudinal study of rubber workers. Toxicol Ind Health 4:411–430 (1988).