

Risk of Benzene-induced Leukemia Predicted from the Pliofilm Cohort

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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. or 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

$$h(t) = a(t) + \beta X(t),$$

where $a(t)$ is the background mortality rate at age t (which was estimated from

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Abbreviations used: AMML, acute myelogenous/monocytic leukemia; AUC, area under curve; NIOSH, National Institute of Occupational Safety and Health; PEL, permissible exposure limit.

appropriate mortality rates for white males in the United States), $X(t)$ is a summary measure of benzene exposure before age t , and β is a parameter that gauges the carcinogenic potency of benzene. The corresponding expression for the linear multiplicative model is

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

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^3) 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, $X^i(t)$, was replaced by

$$X_i(t) = \int_0^{t-5} x^i(v) dv$$

where $x(v)$ is the intensity of exposure (ppm) at age v (i.e., $X_i(t)$ 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, $X_{c2}(t) = 10,000$ ppm²-years for the former exposure pattern and 1000 ppm²-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 (1)].

The method of maximum likelihood was used to fit models to data and to test hypotheses. Estimates of the potency parameters (β and β_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 risk and multiplicative risk models to responses of AMML and all leukemias. Potency estimates (estimates of β) 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 (1). 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. (4) case no.	Birth	Death	Year of		Cumulative exposure, ppm-years		Leukemia	AMML ^a
				First employment	Last employment	Crump and Allen (7)	Paustenbach (8)		
19	2	1921	1950	1948	1948	3	3	X	
859	8	1925	1954	1950	1952	23	54	X	
689	7	1899	1957	1942	1948	307	670	X	Y
136	1	1921	1958	1940	1942	381	127	X	Y
49	3	1898	1958	1945	1958	251	1054	X	X
180	4	1894	1960	1944	1958	1497	1242	X	X
176	6	1904	1961	1941	1961	2155	1771	X	X
233	5	1899	1961	1939	1960	939	1122	X	X
280	11	1910	1963	1940	1940	0	0		
826	12	1905	1968	1943	1968	1148	3075		
154		1908	1973	1937	1970	54	651		
459		1923	1978	1947	1955	175	138		
184	9	1912	1979	1942	1960	325	1129	X	X
48	10	1912	1980	1954	1956	31	51		
949	13	1912	1981	1954	1955	16	12		
824		1917	1984	1950	1957	65	338	X	
432		1918	1985	1940	1956	145	293	X	
379		1918	1985	1948	1958	18	598	X	X
95		1914	1986	1945	1946	50	12	X	?
871		1905	1987	1949	1949	6	8	X	?
581		1926	1987	1947	1947	0	19		

^aIncludes 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	Obs	Exp	RR
0–45 (11)	30482	0–2	0.82	0.0–2.4	3	2.41	1.2	6	6.16	1.0	3	3.75	0.8	1–3	1.59	0.63–1.9	4–6	5.34	0.75–1.1
45–400 (151)	16320	1	0.51	2.0	4	1.50	2.7	6	3.83	1.6	2	2.33	0.9	3	0.99	3.0	5	3.32	1.5
400–1000 (602)	4867	2	0.22	9.1	2	0.65	3.1	3	1.65	1.8	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	12.09	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). ^aAMML and AML (ICD, codes 205.0 and 206.0); leukemia (ICD, codes 204–207); total lymphatic and hematopoietic cancers (ICD, codes 200–209).

from additive and multiplicative models also are not comparable. It appears that in each case the multiplicative model fits the data considerably better than the additive model (because higher likelihoods are associated with multiplicative models, although a formal statistical test is not possible because the models are not nested). Consequently, results based on the multiplicative risk models will be emphasized in the remainder of the paper.

Table 4 contains results from fitting nonlinear versions of the multiplicative risk model. There was no evidence of nonlinearity in models that employed AUC-dependent nonlinearity. Similarly, no evidence of nonlinearity was evident from application of models incorporating intensity-dependent nonlinearity models to the Crump and Allen exposure matrix. However, the two analyses that combined

intensity-dependent nonlinearity with the Paustenbach et al. exposure matrix detected a marginally significant departure from a purely linear model ($p = 0.081$ and 0.085). Using this combination, the best-fitting models were quadratic for both AMML and all leukemias. Although standard errors are not provided in Table 4, the fact that both of these p -values are slightly greater than 0.05 implies that the 95% upper confidence limits on the linear term in these nonlinear models will be slightly greater than the potency estimates derived from the linear versions of these fits (Table 3).

Table 5 contains estimates of the number of additional deaths per thousand persons exposed occupationally to 1 ppm benzene for 45 years (from age 20–65). For comparison purposes, the estimate obtained by Crump and Allen (7) from this cohort based on a linear, cumulative exposure,

Table 3. Results from fits of linear models.

Exposure matrix	β (SE), ppm-years ⁻¹	Maximum likelihood
Crump and Allen (7) ^a		
AMML		
Additive model	2.0E-6 (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. (8) ^a		
AMML		
Additive model	1.3E-6 (5.1E-7)	–64.46
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

^aReferences indicate the method used for calculation of data in table.

Table 4. Results from fits of nonlinear multiplicative models.

Exposure matrix	AUC-dependent nonlinearity					Intensity-dependent nonlinearity				
	β_1	β_2	β_3	Maximum likelihood	p-value ^a	β_1	β_2	β_3	Maximum likelihood	p-value ^a
Crump and Allen (1) ^b										
AMML	4.0E-2	0.0	6.0E-9	-61.75	NS ^c	4.5E-2	0.0	0.0	-61.84	NS
All leukemias	1.7E-2	0.0	6.1E-10	-111.67	NS	1.7E-2	0.0	0.0	-111.68	NS
Paustenbach et al. (8) ^b										
AMML	9.5E-3	2.4E-5	0.0	-61.34	NS	0.0	3.1E-4	0.0	-60.74	0.085
All leukemias	9.7E-3	1.0E-6	0.0	-111.57	NS	0.0	1.2E-4	0.0	-110.60	0.081

AMML, acute myelogenous/monocytic leukemia. ^ap-Value for test for a significantly nonlinear dose response.

^bReferences indicate the methods used for calculation of data in the table. ^cNS, p-value > 0.1.

Table 5. Additional deaths expected per thousand persons from occupational exposure to 1 ppm benzene from age 20 through 65.

Exposure matrix	Linear model	Intensity-dependent nonlinear model
Crump and Allen (1) ^a		
AMML	4.3	4.3
All leukemias	5.1	5.1
All leukemias, 1978 follow-up	6.6	
Paustenbach et al. (8) ^a		
AMML	2.6	0.030
All leukemias	3.1	0.036

Estimates based on multiplicative model, cumulative exposure with a 5-year lag. ^aReferences indicate the methods used for calculation of data in the 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

Table 6. Additional deaths expected per million persons from continuous exposure to 1 ppb benzene.

Exposure matrix	Linear model	Intensity-dependent nonlinear model
Crump and Allen (1) ^a		
AMML	21.0	21.0
All leukemias	24.0	24.0
Paustenbach et al. (8) ^a		
AMML	15.0	0.00014
All leukemias	15.0	0.00017

Estimates based on multiplicative model, cumulative exposure with a 5-year lag. ^aReferences indicate the methods used for calculation of data in the table.

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 ppm 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, Hornung (unpublished data) showed that the exposures predicted by the Rinsky et al. exposure matrix also were correlated with blood counts. However, Hornung 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.

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