The Contribution of Benzene to Smoking-Induced Leukemia

Jeffrey E. Korte,[1,*] Irva Hertz-Picciotto,[1] Mark R. Schulz,[1] Louise M. Ball,[2] and Eric J. Duell[1,]**

[1]Department of Epidemiology, [2]Department of Environmental Sciences and Engineering, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Cigarette smoking is associated with an increased risk of leukemia; benzene, an established leukemogen, is present in cigarette smoke. By combining epidemiologic data on the health effects of smoking with risk assessment techniques for low-dose extrapolation, we assessed the proportion of smoking-induced total leukemia and acute myeloid leukemia (AML) attributable to the benzene in cigarette smoke. We fit both linear and quadratic models to data from two benzene-exposed occupational cohorts to estimate the leukemogenic potency of benzene. Using multiple-decrement life tables, we calculated lifetime risks of total leukemia and AML deaths for never, light, and heavy smokers. We repeated these calculations, removing the effect of benzene in cigarettes based on the estimated potencies. From these life tables we determined smoking-attributable risks and benzene-attributable risks. The ratio of the latter to the former constitutes the proportion of smoking-induced cases attributable to benzene. Based on linear potency models, the benzene in cigarette smoke contributed from 8 to 48% of smoking-induced total leukemia deaths [95% upper confidence limit (UCL), 20–66%], and from 12 to 58% of smoking-induced AML deaths (95% UCL, 19–121%). The inclusion of a quadratic term yielded results that were comparable; however, potency models with only quadratic terms resulted in much lower attributable fractions—all < 1%. Thus, benzene is estimated to be responsible for approximately one-tenth to one-half of smoking-induced total leukemia mortality and up to three-fifths of smoking-related AML mortality. In contrast to theoretical arguments that linear models substantially overestimate low-dose risk, linear extrapolations from empirical data over a dose range of 10- to 100-fold resulted in plausible predictions. *Key words*: benzene, environmental exposure, epidemiology, leukemia, life tables, occupational exposure, risk assessment, smoking. *Environ Health Perspect* 108:333–339 (2000). [Online 23 February 2000]
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Based on the results of several large cohort studies (*1–3*), cigarette smoking is associated with an increased risk of leukemia. The relative risks (RRs) range from 1.5 to 2.0. Although cigarette smoke contains a multitude of toxic chemical compounds, researchers have not yet established which chemicals are responsible for the leukemogenicity of this complex mixture.

Benzene is present in mainstream cigarette smoke at concentrations of approximately 45 µg/cigarette, and in sidestream smoke at concentrations about 10 times higher. Personal exposure assessment research has indicated that the average cigarette smoker inhales 6–10 times the benzene inhaled by the average nonsmoker, and that approximately 90% of a smoker's benzene exposure is from smoking (*4*). For nonsmokers, most benzene exposure comes from automobile exhaust, environmental tobacco smoke, and exposure to consumer products (*5*). Benzene induces leukemia both in humans with occupational exposures (*6,7*) and in experimental animals (*8,9*). Some research indicates the strongest association of benzene to be with acute myeloid leukemia (AML) (*10,11*), but effects on other types of leukemia have not been ruled out (*12*). The purpose of this investigation was to determine what proportion of smoking-induced leukemia is likely to be caused by the benzene in cigarette smoke.

Several regulatory agencies, including the U.S. Environmental Protection Agency (EPA), have established procedures for estimating risks from low- or moderate-level chemical exposures (*13*). These risk assessment methods, which assume low-dose linearity, have been used for over a decade to set regulatory standards, and we used these methods to calculate leukemia risks from benzene in cigarette smoke. The EPA has proposed new guidelines for risk assessment (*14*), which are still under debate. Our use of the earlier standard permitted an assessment of its adequacy for benzene. Some authors have argued that the true low-dose relationship for this compound is sublinear, and that the default assumptions will therefore result in a substantial overestimation of benzene's potency (*15*). This investigation was specifically designed to quantitatively test whether these assumptions do, in fact, result in the prediction of more leukemia deaths than actually occur in smokers.

In general, risk assessment uses quantitative dose–response data that associate a chemical exposure with the risk of cancer mortality to obtain a potency, and low-dose extrapolation models to estimate the risk at lower doses. Often the dose levels of interest are experienced through environmental exposure in the general population or through occupational exposure in groups of workers. In this case, we examined the benzene doses inhaled by smokers. Unlike many exposure scenarios, the risks to smokers have been well characterized. Thus, the predicted leukemia risks attributable to low-doses of benzene can be compared with the actual leukemia risk observed in epidemiologic studies of smoking.

Materials and Methods

We used five steps to estimate the proportion of smoking-induced leukemia caused by benzene in cigarette smoke: *a*) a calculation of the lifetime risk of leukemia due to smoking; *b*) a determination of the leukemogenic potency of benzene; *c*) the quantification of benzene dose for smokers at two levels of smoking; *d*) the characterization of the low-dose risk of leukemia due to the benzene in cigarette smoke [using the results of *b*) and *c*)]; and *e*) a comparison of the predicted lifetime leukemia risk due to benzene in cigarette smoke [from *d*)] to the observed lifetime leukemia risk due to smoking [from *a*)].

Lifetime risk of leukemia due to smoking. We constructed life tables to calculate cumulative lifetime risks of dying from leukemia, stratified by smoking status (never, former, light, or heavy). Life tables were truncated at 75 years of age to avoid instability in the oldest age groups. We conducted this exercise first for all leukemia and then repeated it for AML alone [some authors argue that AML has generally shown stronger associations with benzene exposure than other leukemia types (*10*)]. We used the life table results to calculate the smoking-induced

Address correspondence to I. Hertz-Picciotto, Department of Epidemiology, CB #7400, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7400 USA. Telephone: (919) 966-7445. Fax: (919) 966-2089. E-mail: ihp@unc.edu

*Current address: Unit of Environmental Cancer Epidemiology, IARC, 150 Cours Albert Thomas, 69008, Lyon, France.

**Current address: Department of Cancer Cell Biology, Harvard School of Public Health, Boston MA 02115 USA.

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excess lifetime risk of death (ELR) (*16*) from leukemia for each smoking category as follows: $ELR_{smoking}$ = (cumulative lifetime risk among smokers) - (cumulative lifetime risk among never-smokers).

We conducted life table analyses separately for males and females; the data used to construct the male cause-specific AML life tables are shown in Table 1. The mortality rates for 1990 were taken from U.S. vital statistics (*17*). Because age- and sex-specific AML rates were not available, we used scaling factors derived from the Surveillance, Epidemiology, and End Results (SEER) mortality data (*18*) to convert myeloid leukemia death rates (*17*) to AML death rates. In the life table calculations, we partitioned age-specific leukemia and all-cause death rates by smoking status (never, former, light, and heavy) using smoking prevalences and smoking-related RRs. Partitioning formulas have been published previously (*19*). We calculated smoking prevalences from the September 1989 Current Population Survey dataset (*20*) (Table 2). Age-specific all-cause mortality RRs (*21*) for former, light (weighted average of 10–19 and 20–39 cigarettes/day), and heavy (≥ 40 cigarettes/day) smokers were taken from published studies: for all leukemia combined, and for myeloid leukemia alone, we used the Cancer Prevention Studies I and II, respectively (*2*). RRs for all leukemia in males were 1.36, 1.32, and 1.61 among former, light, and heavy smokers, respectively; RRs for myeloid leukemia in males were 1.17, 1.65, and 1.75. Because age-specific RRs were not reported and because RRs for females were unstable as a result of sparse data, RRs for males were applied to both men and women and to all age groups from 35 to 75 years of age.

Potency calculation. We obtained several benzene potency estimates for acute nonlymphocytic (myeloid or monocytic) leukemia and for all leukemia. These included potency estimates published by Crump (*22*), whose risk assessment of benzene-induced leukemia was based on the Pliofilm cohort (*23*); estimates that we calculated using summary data from the analysis by Crump; and estimates that we calculated using data from a recently published study of workers in China (*24*). Crump's analysis (*22*) of the Pliofilm cohort included 1,717 white male workers from Pliofilm manufacturing plants in Akron, Ohio, and St. Mary's, Ohio. The workers were considered to have no other substantial workplace exposures; therefore, the possibility of biased potency estimates due to other leukemogens was small. The cohort from China (*24*) was assembled from 672 factories in 12 cities, and included 74,828 exposed workers and 35,805 unexposed workers. Hayes et al. (*24*) did not adjust for exposures to other chemicals, although an examination of previous reports reveals that most of the workers in China were exposed to toluene and xylene in addition to benzene (*25,26*). Studies of both the China cohort and the Pliofilm cohort utilized exposure assessments that were based on occupational histories, ambient benzene expo-sure measurements, and detailed production information.

The risk assessment of Crump (*22*) updated a previous risk assessment (*27*) by extending mortality data to the most recent follow-up (*28*), and by expanding the analyses to include an exposure matrix developed by Paustenbach et al. (*29*). Crump (*22*) provided sensitivity analyses of risk estimates under various dose–response models for each of the two exposure matrices, including linear and nonlinear forms of both additive and multiplicative risk models. We chose potency estimates from linear multiplicative models fit using the Paustenbach et al. (*29*) exposure matrix, unweighted cumulative exposure, and a 5-year lag.

We converted the potencies of Crump (*22*) to per-cumulative-gram units to provide compatibility with the units of exposure to cigarette smoke—a nonoccupational but chronic exposure.

$$\begin{aligned} 1 \text{ ppm-year} = {} & (1/10^6) \times (1 \text{ year}) \\ & \times (250 \text{ workdays/year}) \\ & \times (10 \text{ m}^3\text{/workday}) \\ & \times (10^3 \text{ cm}^3\text{/m}^3) \\ & \times (\text{mL/cm}^3) \\ & \times (\text{L/1,000 mL}) \\ & \times (\text{mol/24.45 L}) \\ & \times (78.11 \text{ g benzene/mol}) \\ & = 7.987 \text{ g,} \end{aligned}$$

where workers are assumed to breathe 10 m^3/workday, 24.45 L/mol represents the molar volume constant, and 78.11 g/mol is the molecular weight of benzene. Accordingly, a carcinogenic potency of 1 per ppm-year is equivalent to 1 per 7.987 g, or 1.252×10^{-1} per cumulative gram benzene.

For our potency calculations based on the Pliofilm data, we fit linear multiplicative models of the form:

$$obs = \alpha \times exp(1 + \beta \times d), \quad [1]$$

where *obs* = the number of deaths in the specified exposure category, *exp* = the expected number of deaths based on the age and sex distribution of the exposed group and the death rates of the referent group, d = the cumulative benzene dose in grams, β represents the leukemogenic potency parameter of benzene in per-cumulative-gram units, and α represents the ratio of the background leukemia risk in the industrial cohort to that of the general population referent group (e.g., the healthy worker effect). Crump (*22*) did not make an adjustment for the healthy worker effect in his final models. Equation 1 is a simplified version of the fundamental relation between observed and expected rates; Equation 1 is obtained by multiplying both sides of this relation by the person-years in the denominators of both rates. As is standard practice for quantitative risk assessment, we calculated a 95% upper confidence limit (UCL) for each potency.

For the China data, we fit a linear model without the α term because the analysis was based on an internal comparison:

$$obs = exp(1 + \beta \times d). \quad [2]$$

Because the Pliofilm data suggest a nonlinear dose–response curve, we repeated the Pliofilm analysis using two quadratic multiplicative models:

$$obs = \alpha \times exp(1 + \beta \times d^2) \quad [3]$$

$$obs = \alpha \times exp(1 + \beta_1 \times d + \beta_2 \times d^2). \quad [4]$$

Table 1. Example of life table data: male AML.

5-year age group	All-cause death rate per 100,000	Myeloid leukemia death rate per 100,000	Age-specific scaling factor[a]	AML death rate per 100,000[b]	All-cause RR for smoking		
					Former	Light	Heavy
0	1,135.2	1.143	0.820	0.937	1	1	1
5	25.6	0.249	0.820	0.204	1	1	1
10	31.6	0.252	0.820	0.206	1	1	1
15	127.2	0.523	0.820	0.429	1	1	1
20	166.3	0.718	0.679	0.488	1	1	1
25	184.9	0.878	0.679	0.596	1	1	1
30	223.4	1.004	0.679	0.682	1	1	1
35	280.7	1.312	0.613	0.804	1.02	1.78	2.57
40	344.2	1.556	0.613	0.953	1.02	1.78	2.57
45	491.1	2.092	0.630	1.317	1.21	2.90	4.39
50	756.5	3.350	0.630	2.109	1.21	2.90	4.39
55	1,208.5	5.770	0.683	3.940	1.27	1.85	2.59
60	1,902.7	7.298	0.683	4.983	1.27	1.85	2.59
65	2,847.6	12.557	0.733	9.202	1.30	1.85	2.32
70	4,345.4	19.004	0.733	13.926	1.30	1.85	2.32

[a]Proportion of myeloid leukemias that are AML. [b]Calculated using scaling factor.

In the Pliofilm data, neither of the two leukemias in the lowest Paustenbach exposure group were cell typed; therefore, we present AML results under several assumptions for this exposure category: zero, one, or two deaths. For brevity, we present results under the assumption of one AML death using linear (Equation 1) and quadratic models (Equation 3), but only partial results for zero and two AML deaths.

Data on mean exposures for each category were available for the Pliofilm cohort, but not for the cohort from China. We therefore assigned the mid points for the lower two categories (< 40 and 40–100 ppm-years) in this cohort, and a value of 130 ppm-years (1,038.31 cumulative grams) for the open-ended category of ≥ 100 ppm-years (based on the lower limit plus one-half the width of the next lower category).

Quantification of benzene dose in smokers. The International Agency for Research on Cancer (IARC) reported a range of benzene values between 12 and 48 µg/cigarette in mainstream smoke (*30*). Two studies (*31,32*) published since the IARC report, both of which used standard Federal Trade Commission methods (*33*) and Kentucky Reference filter cigarettes (1R4F; Tobacco and Health Research Institute, University of Kentucky, Lexington, KY), reported benzene values of 45 and 51 µg/cigarette. One of these studies (*32*) also tested a Kentucky Reference nonfilter cigarette (1R1) and a low-tar cigarette; benzene levels were 73 µg/cigarette in the nonfilter cigarette and 8 µg/cigarette in the low-tar cigarette.

Given this range and the documentation of the smoking methods in the studies by Byrd et al. (*31*) and Brunnerman et al. (*32*), we selected 45 µg/cigarette as our estimate of the benzene dose in mainstream smoke. This estimate represents a reasonable average dose per cigarette across the lifetimes of those persons represented in our life tables (i.e., those who died in 1990).

Table 2. Age-specific smoking prevalences.

	Prevalence of smoking			
Age	None	Former	Light	Heavy
0	1	0	0	0
5	1	0	0	0
10	1	0	0	0
15	0.85	0.02	0.12	0.01
20	0.68	0.07	0.22	0.03
25	0.57	0.11	0.27	0.05
30	0.50	0.17	0.25	0.07
35	0.43	0.23	0.24	0.09
40	0.39	0.27	0.23	0.11
45	0.33	0.33	0.21	0.12
50	0.31	0.36	0.22	0.11
55	0.30	0.39	0.21	0.01
60	0.28	0.45	0.19	0.07
65	0.28	0.51	0.15	0.05
70	0.30	0.54	0.13	0.03

It is more difficult to choose an estimate of the amount of benzene in sidestream smoke because measurement methods are not standardized. Given the uncertainty, we chose 500 µg/cigarette, the mid point of the range (300–700 µg/cigarette) reported by Guerin et al. (*33*).

We assumed that 100% of the benzene in mainstream smoke is inhaled. We searched the literature but were unable to find direct data on the proportion of sidestream smoke inhaled by a smoker. We therefore used data on the proportion of nicotine inhaled from sidestream smoke. We calculated that if each cigarette requires 10 min to smoke and generates an environmental nicotine concentration of 1,000 µg/m^3 for the smoker [the maximum reported by the National Research Council (*34*)], then that smoker breathes, at most, 100 µg sidestream nicotine from each cigarette:

$$1{,}000\ \mu g/m^3 \times 1\ m^3/1{,}000\ L \times 10\ L\ breathed/min \times 10\ min/cigarette = 100\ \mu g/cigarette.$$

The total nicotine in sidestream smoke is 3.0 mg/cigarette (*34*). Therefore, the smoker, by inhaling 100 µg of 3,000 µg, breathes 3.3% of sidestream nicotine. Accordingly, we estimated that the smoker inhales 3.3% of the benzene in sidestream smoke. By including 100% of the mainstream smoke and 3.3% of the sidestream smoke, we estimated that each cigarette delivers 61.5 µg benzene [45 + (0.033 × 500)]. At 20 cigarettes/day (light smoker), the inhaled dose is 1,230 µg benzene/day; at 40 cigarettes/day (heavy smoker), the inhaled dose is 2,460 µg benzene/day.

Calculation of excess risk due to benzene. Similar to the ELR due to smoking, the benzene-induced ELR in smokers (*16*) is defined as: $ELR_{benzene}$ = (cumulative lifetime risk in smokers) - (cumulative lifetime risk in smokers with the benzene effect removed). To obtain cumulative lifetime risks of death from leukemia without the benzene effect, we constructed life tables in which leukemia death rates among smokers for each age group were divided by $1 + \beta \times d$ for linear models, by $1 + \beta \times d^2$ for models with a second-order term only, and by $1 + \beta_1 \times d + \beta_2 \times d^2$ for models with both a linear and a second-order term. In this way, using the inverse of our dose–response models, we obtained the expected death rates and cumulative lifetime risk for a population of smokers unexposed to benzene.

Benzene-attributable fraction of smoking-induced leukemia deaths. The proportion of smoking-induced leukemia deaths due to the benzene in cigarette smoke is denoted the benzene-attributable fraction [AF(benzene)] of leukemia mortality in smokers. This fraction was calculated by dividing the benzene-induced ELR by the smoking-induced ELR:

$$AF(\text{benzene}) = (ELR_{benzene})/(ELR_{smoking}).$$

Results

Acute myeloid leukemia. The cumulative lifetime risk (to 75 years of age) of AML death in never-smokers was 0.095% for females and 0.128% for males. The lifetime risk was lower in heavy smokers than in light smokers for both males and females: for females, the lifetime risk was 0.135% in light smokers and 0.132% in heavy smokers; for males, the lifetime risk was 0.168% in light smokers and 0.156% in heavy smokers. Life table results, showing calculations for the lifetime risk of AML death in male never-smokers, are provided in Table 3.

The benzene-associated risks among smokers for AML alone are shown in Table 4. The AML potencies ranged from 2.0×10^{-3} to 3.4×10^{-3} per cumulative gram benzene for the linear models (95% UCL, 3.4×10^{-3} to 8.2×10^{-3}). Using maximum likelihood estimates for the linear models, the proportion of smoking-induced AML deaths attributable to the benzene in cigarette smoke was estimated to range from 15 to 46% using potencies that we derived from the Hayes et al. (*24*) results (Equation 2); from 19 to 58% using the potencies published by Crump (*22*) [based on the Pliofilm cohort data (*23*)]; and from 12 to 36% using our own potency estimates based on the published Pliofilm cohort results (Equation 1). Based on 95% UCL potencies of these linear models, the AF(benzene) ranged from 19 to 121%.

The potency for the second-order model (Equation 3) of the Pliofilm data (assuming one death in the lowest exposure group) was 3.9×10^{-7} per cumulative gram squared (95% UCL, 7.8×10^{-7}), and resulted in AF(benzene) ranging from 0.05 to 0.29% (95% UCL, 0.08–0.62%). Equation 4, with unconstrained parameters, produced a negative maximum likelihood estimate for β_1.

We conducted sensitivity analyses (male light smokers only) under different assumptions regarding the histologic type of the untyped leukemia deaths in the Pliofilm cohort. For the linear dose–response model (Equation 1) with two AML deaths in the lowest exposure category ($\beta = 5.9 \times 10^{-4}$ per gram), the benzene-attributable fraction was 4.3% (95% UCL, 16%). Using the second-order model (Equation 3), with zero ($\beta = 2.8 \times 10^{-6}$ per gram squared) or two ($\beta = 1.9 \times 10^{-7}$ per gram squared) AML deaths, the benzene-attributable fractions were 0.40% (95% UCL, 2.7%) and 0.03% (95% UCL, 0.05%), respectively.

Total leukemia. The cumulative lifetime risk (to 75 years of age) of death from any

type of leukemia in never-smokers was 0.300% for females and 0.421% for males. For females, the lifetime risks in light and heavy smokers were 0.344 and 0.379%, respectively; for males, lifetime risks were 0.451 and 0.474%, respectively.

Results for all leukemia are shown in Table 5. The leukemia potencies ranged from 6.6×10^{-4} to 1.7×10^{-3} per cumulative gram benzene for the linear models (95% UCL, 1.6×10^{-3} to 2.4×10^{-3}). Using maximum likelihood potency estimates for the linear models, the AF(benzene) of smoking-induced leukemia deaths was estimated to range from 21 to 48% using the potencies that we estimated from the China cohort results; from 17 to 39% using potencies published by Crump based on the Pliofilm cohort data (*22*); and from 8 to 19% using potencies that we estimated from the Pliofilm cohort. Based on 95% UCL potencies, the attributable fractions ranged from 20 to 66%.

For analyses of the Pliofilm cohort data based on Equation 3 (second-order term only), we estimated that the potency was 1.0×10^{-7} per cumulative gram benzene squared (95% UCL, 2.7×10^{-7}), and that the attributable fractions ranged from 0.02 to 0.11% (95% UCL, 0.07–0.32%). For analyses based on Equation 4 (linear and second-order terms), we estimated the coefficients for β_1 and β_2 to be 6.2×10^{-4} per gram (95% UCL, 2.8×10^{-3}) and 7.6×10^{-9} per gram squared (95% UCL, 3.9×10^{-7}), respectively. The attributable fractions ranged from 8 to 18% of smoking-related leukemia; the fractions ranged from 35 to 76% when using UCL potency estimates.

Discussion

In this investigation, we estimated the contribution of benzene in cigarettes to excess leukemia mortality observed among smokers. At an estimated dose of 61.5 µg benzene/cigarette, the calculated potency based on the assumption of a second-order dose–response curve was too low to explain even 1% of smoking-induced leukemia or AML. As expected, linear models resulted in much higher attributable fractions; however, linear models did not result in implausibly high attributable fractions (e.g., > 100%), with the single exception of the UCL for AML among male heavy smokers, using the Pliofilm cohort data. The dose–response model including both linear and quadratic terms resulted in predictions comparable to those based on the linear model, at benzene doses inhaled by smokers.

Other known or suspected leukemogens are present in cigarette smoke, including urethane (*30,35*), 1,3-butadiene (*32,36*), radioactive elements (*37,38*), *N*-nitrosodi-*n*-butylamine (*30,39*), and styrene (*30,40*); benzene is therefore unlikely to be independently responsible for all smoking-induced leukemia. However, based on current knowledge of the leukemogenicity of these compounds and their relative concentrations in tobacco smoke, it seems likely that benzene's contribution is substantial. Thus, in this analysis, dose–response models including a linear term resulted in much more plausible AF(benzene) than the model including a second-order term only.

As in all risk assessments, we made assumptions when necessary. First, we assumed that the potency of benzene inhaled in the occupational setting is equivalent, gram for gram, to the potency of benzene vapor emitted from combusted cigarettes. In both situations, the route of exposure is by inhalation. As air travels into the lung, rapid increases in the cross-sectional area result in a slowing of the air velocity; in addition, rapid increases in the total surface area of the airway walls contribute to extremely efficient heat exchange. The temperature of cigarette smoke therefore decreases rapidly to body temperature once it is inhaled, and potency differences due to temperature are unlikely in these two exposure settings. It is possible, however, that the carcinogenic potency of benzene exposure in the industrial workplace differs from the potency of benzene in complex mixed exposures such as cigarette smoke. The overall effect of these numerous coexposures, some of which may provide potentiating or inhibiting effects on benzene, is difficult to predict. In addition, it may be impossible with current methods to determine any benzene potency difference between these exposure scenarios because of the low exposure levels experienced by smokers and the complexity of the cigarette smoke mixture.

Our second assumption reflects our choice of multiplicative models for potency calculations. These models assume that the effect of a carcinogen is dependent on the background rate of the disease and are appropriate when a carcinogen operates on the same pathway or pathways that produce the background cancer rate (*41*). Although researchers have found that benzene-induced leukemia is often preceded by benzene-induced pancytopenia (*10*), the mechanism of benzene-induced leukemia (*42*) is insufficiently understood to support a causal pathway distinct from the significant background rate of leukemia. The additive models fit by Crump (*22*) would have produced somewhat lower risk estimates for benzene-induced leukemia and therefore a smaller contribution to smoking-induced leukemia. Our final conclusions, however, would not have been substantially altered, i.e., that linear models give rise to plausible risk estimates.

A third assumption in our extrapolation of potencies from the occupational cohorts was that the studies were substantially free of confounding, misclassification, and other biases. The Pliofilm cohort is well suited to minimize the possible confounding effects of

Table 3. Example of life table results: male never-smoker, AML.

5-year age group	All-cause death rate per 100,000	P(survival to next age interval)[a]	Cumulative P(survival to beginning of interval)	AML death rate per 100,000	P(AML death during interval) given survival to beginning of interval	Unconditional P(AML death during interval)	Cumulative P(AML death)
0	1,135.2	0.94482	1.00000	0.937	0.00004556	0.00004556	0.0000456
5	25.6	0.99872	0.94482	0.204	0.00001021	0.00000965	0.0000552
10	31.6	0.99842	0.94361	0.206	0.00001031	0.00000972	0.0000649
15	127.2	0.99366	0.94212	0.429	0.00002138	0.00002015	0.0000851
20	166.3	0.99169	0.93615	0.488	0.00002437	0.00002282	0.0001079
25	184.9	0.99077	0.92837	0.596	0.00002978	0.00002765	0.0001355
30	223.4	0.98885	0.91980	0.682	0.00003402	0.00003129	0.0001668
35	210.0	0.98956	0.90955	0.637	0.00003167	0.00002880	0.0001956
40	255.2	0.98732	0.90005	0.750	0.00003724	0.00003352	0.0002292
45	260.0	0.98708	0.88864	1.026	0.00005095	0.00004528	0.0002744
50	407.1	0.97985	0.87717	1.646	0.00008145	0.00007144	0.0003459
55	842.0	0.95877	0.85949	3.098	0.00015169	0.00013038	0.0004762
60	1,364.7	0.93404	0.82406	3.983	0.00019250	0.00015863	0.0006349
65	2,109.2	0.89991	0.76970	7.526	0.00035715	0.00027490	0.0009098
70	3,326.1	0.84679	0.69266	11.667	0.00053744	0.00037226	0.0012820

[a]Probability of survival is equal to e^{-rt}, where r = death rate and t = time.

other leukemogens because the industrial process did not involve exposure to other potential carcinogens. Most benzene-exposed workers in the China cohort were also exposed to toluene and xylene. These compounds are not established human carcinogens, although by competing for P450 they may reduce the metabolism rate of benzene, resulting in an underestimation of the benzene potency. Possible bias due to the healthy worker effect has been controlled in our potency calculations for both cohorts: our model for the Pliofilm data adjusted for differences in background rates between workers and the general population, and the China results were based on a comparison with unexposed workers.

In this study, we conducted a sensitivity analysis of the relationship between benzene and AML under different assumptions regarding the untyped leukemia cases in the lowest exposure category presented by Crump (*22*). Although Crump indicates no confirmed cases in the lowest exposure category (< 45 ppm-years), a separate analysis of the Pliofilm cohort by Wong (*11*) indicated the presence of one AML death in the lowest exposure category (< 40 ppm-years benzene exposure). This apparent contradiction is likely explained by the fact that Crump presented results based on the Paustenbach et al. (*29*) exposure matrix, whereas Wong (*11*) presented results based on the Rinsky et al. (*43*) exposure matrix.

With regard to the validity of our results, our linear multiplicative model potencies based on the Pliofilm cohort are somewhat smaller than those of Crump. There are several possible reasons for the differences. Crump used individual data in his analysis, whereas we calculated potencies based on published summary data from the cohort. Crump evaluated several possible lag times between exposure and the development of leukemia; we used the potency that he obtained based on a 5-year lag, but the summary data that were available for our analysis did not incorporate lag times. Finally, we adjusted for the differences in expected mortality between workers and the general population; Crump did not find the α term to be statistically significant and excluded it from his final models.

As noted in "Results," the lifetime risk of AML mortality is slightly higher in light smokers than in heavy smokers. This counterintuitive finding reflects the increased risk to heavy smokers of death from competing causes, such as other cancers and heart disease. Although the AML death rates for each age category are higher for heavy smokers than for light smokers, the lifetime cumulative risk rises less in the later age categories among heavy smokers because of their dramatically higher all-cause death rate. This effect is also observed in our results for all leukemia; however, the cross-over occurs too late to be reflected in a reversal of the lifetime cumulative probabilities of leukemia death.

Another issue is the potential for sex differences in benzene leukemogenicity. In our study, we assumed the same potency for males as for females. Nevertheless, the difference in overall and smoking-induced rates of leukemia led to a lower attributable fraction for females as compared to males. Background rates of leukemia are higher for men than for women. Evidence supporting a sex difference in benzene leukemogenicity includes recent results of physiologically based pharmacokinetic modeling, which show that under the same exposure conditions, women may metabolize more benzene than men despite lower benzene blood concentrations (*44*). However, other recent data show that levels of protein adducts formed by benzene metabolites do not differ by sex (*45*).

In the construction of life tables for AML and for all leukemia, we were unable to locate age-specific RRs for former, light, and heavy smokers. Therefore, for each smoking category we used the overall smoking RR obtained from Cancer Prevention Studies I and II (*2*). The use of the same RR for all groups from 35 to 74 years of age is unlikely to cause substantial bias. For lung cancer, in comparison, RRs derived from Kahn (*21*) and Doll and Peto (*46*) for light smokers vary only between 6.8 and 9.4 across age groups—a variation of < 50%.

In our life tables, we used U.S. population data for smoking prevalence from September 1989 (*20*) and for vital statistics mortality rates (*17*) from 1990. The latency period for benzene-induced leukemia is typically < 10 years (*10*), although it may be > 40 years (*26*); therefore, the cigarettes of interest in our analysis are those smoked between 1950 and 1990. A fairly wide range has been reported for the quantity of benzene in mainstream smoke: 8.0–73.4 µg, according to the type of cigarette (low-tar filter or nonfilter) (*32*). If the average benzene content of cigarette smoke, either mainstream or sidestream, was higher than we assumed, then we underestimated the proportion of smoking-induced leukemia attributable to benzene. Conversely, if the benzene content of cigarettes has increased over time, or if we overestimated the proportion of sidestream smoke inhaled by a smoker, then we overestimated the contribution of benzene to leukemia in smokers. In fact, 3.3% of sidestream could be a maximum. If the true contribution from sidestream smoke is closer to zero, our attributable fractions should be reduced approximately 25%.

Violations of these assumptions are unlikely to have a major impact on our results. A significantly more influential assumption is the shape of the dose–response curve at low exposures. Several authors have argued that the dose–response curve of benzene in particular must be sublinear (*10,47*), with the implication that linear models result in substantial overestimation of the low-dose carcinogenic potency. The carcinogenic potency and the dose–response curve of benzene have been the subject of both extensive discussion in the literature and controversy among policy makers. In 1978, the Occupational Safety and Health Administration reduced the permissible 8-hr workplace exposure from 10 to 1 ppm (*48*); this decision was overturned by the U.S. Supreme Court in 1980 (*49*). A more

Table 4. Percent of smoking-induced AML deaths attributable to benzene in cigarette smoke, with 95% UCL.

Model[a]	Cohort	Potency[b] (UCL)	20 cigarettes/day		40 cigarettes/day	
			Male	Female	Male	Female
Linear	China (*22*)	2.6×10^{-3} (3.4×10^{-3})	18.4 (23.5)	14.7 (18.8)	45.9 (57.9)	29.3 (37.1)
Linear[c]	Pliofilm (*20*)	3.4×10^{-3} (5.8×10^{-3})	23.6 (38.9)	18.9 (31.1)	58.1 (92.4)	37.1 (59.1)
Linear	Pliofilm (*20*)	2.0×10^{-3} (8.2×10^{-3})	14.4 (52.4)	11.5 (42.0)	36.2 (120.7)	23.2 (77.3)
Quadratic	Pliofilm (*20*)	3.9×10^{-7} (7.8×10^{-7})	0.05 (0.10)	0.05 (0.08)	0.29 (0.62)	0.19 (0.38)

[a]All models are multiplicative (see text). [b]Carcinogenic potency per cumulative gram, or, for quadratic model, per cumulative gram squared. [c]Potency published by Crump (*20*).

Table 5. Percent of smoking-induced leukemia deaths attributable to benzene in cigarette smoke, with 95% UCL.

Model[a]	Cohort	Potency[b] (UCL)	20 cigarettes/day		40 cigarettes/day	
			Male	Female	Male	Female
Linear	China (*22*)	1.7×10^{-3} (2.4×10^{-3})	41.0 (57.2)	21.4 (29.8)	47.6 (65.5)	25.4 (34.9)
Linear[c]	Pliofilm (*20*)	1.4×10^{-3} (2.3×10^{-3})	33.1 (55.1)	17.3 (28.7)	38.6 (63.3)	20.6 (33.7)
Linear	Pliofilm (*20*)	6.6×10^{-4} (1.6×10^{-3})	16.1 (38.4)	8.4 (20.0)	19.0 (44.6)	10.1 (23.8)
Linear + Quadratic	Pliofilm (*20*)	$\beta_1 = 6.2 \times 10^{-4}$ (2.8×10^{-3}) $\beta_2 = 7.6 \times 10^{-9}$ (3.9×10^{-7})	15.2 (66.6)	7.9 (34.7)	18.0 (76.0)	9.6 (40.5)
Quadratic	Pliofilm (*20*)	1.0×10^{-7} (2.7×10^{-7})	0.07 (0.13)	0.02 (0.07)	0.11 (0.32)	0.06 (0.16)

[a]All models are multiplicative (see text). [b]Carcinogenic potency per cumulative gram; excepting β_2 (potency per cumulative gram squared). [c]Potency published by Crump (*20*).

detailed quantitative risk assessment was subsequently conducted, and the 1 ppm standard was reinstated in 1987 (*48*). That risk assessment utilized the default assumption (*50*) of linearity for low-dose quantitative risk assessment. The argument for this default is the goal of achieving health protection; the implicit assumption is that most curves are sublinear, and that linearity provides an upper limit of carcinogenic potency.

Researchers have established DNA adduct formation by benzene metabolites (*51–55*). It is not yet clear which metabolite(s) of benzene are involved in leukemogenesis, although some evidence suggests that hydroquinone may be important in DNA adduct formation (*56*). Benzene and its phenolic metabolites are less active than many other chemical carcinogens in binding to DNA (*57*); nevertheless, recent studies showed DNA adducts persisting up to 21 days after the administration of benzene (*51*). This DNA damage, resulting from a chemical reaction with a carcinogen, may initiate cell transformation leading to carcinogenesis at any level of exposure. Proof of DNA adduct formation after exposure to benzene therefore provides evidence against a threshold effect, and would tend to support the use of a linear extrapolation model.

In our risk assessment, the range of extrapolation from the cumulative occupational benzene exposure down to the cumulative exposure of smokers is approximately 1 order of magnitude for the China cohort and approximately 2 orders of magnitude for the Pliofilm cohort. A light smoker (20 cigarettes/day) inhales approximately 0.45 g benzene/year, whereas a heavy smoker (40 cigarettes/day) inhales approximately 0.9 g benzene/year. The lifetime cumulative exposure to benzene from smoking is therefore approximately 3 ppm-years (i.e., work-years) for a light smoker and 6 ppm-years for a heavy smoker. An industrial worker exposed to the current standard of 1 ppm benzene in air inhales approximately 8 g benzene/year. The smaller range of extrapolation from exposure in the China cohort, combined with the substantially larger number of leukemia deaths and person-years, suggests that more weight might reasonably be placed on the findings from this cohort. With attributable fractions based on linear models ranging from 21 to 66% for total leukemia, these results from the China cohort do not suggest that the shape of the dose–response curve in this range is sublinear. However, if the comparison of our potencies to those of Crump are informative, it is possible that our use of published data rather than an analysis of the original data from the China cohort could have resulted in underestimates of attributable fractions.

Notably, the linear–quadratic dose–response model yielded results similar to those based on the linear model. At the low doses of benzene inhaled by smokers, the linear term in the model is more influential than the second-order term, providing similarly plausible estimates of the proportion of smoking-induced leukemia deaths attributable to the benzene in cigarette smoke. The dose–response model including a second-order term only, however, resulted in implausibly low estimates of benzene's contribution to smoking-induced leukemia and AML.

The present analysis provides little evidence for exclusion of linear terms in extrapolation models: the linear models extrapolated across 1–2 orders of magnitude of exposure did not predict implausibly high proportions of smoking-related leukemia, or smoking-related AML, attributable to the benzene in cigarettes. Rather, under the default assumptions, benzene appears to be responsible for approximately one-tenth to one-half of smoking-induced leukemia and up to three-fifths of smoking-induced AML. A more direct determination of the role of benzene in inducing smoking-related leukemia may be possible in future studies through comparisons of the genetic characteristics of leukemia cases in smokers and nonsmokers. Previous research has identified several chromosomal aberrations and other genetic damage in humans and animals exposed to benzene (*51,56–59*). Future research may therefore identify benzene-specific markers that will allow a direct assessment of the proportion of leukemias attributable to benzene exposure among smokers and nonsmokers.

The attributable fractions calculated in our study, however, seem reasonable and not unrealistically high in light of the other recognized or suspected leukemogenic compounds present in cigarette smoke (including urethane, 1,3-butadiene, radioactive elements, *N*-nitrosodi-*n*-butylamine, and styrene). These additional leukemogens may provide synergistic effects as well as independent contributions to smoking-related leukemia mortality. In addition, as-yet unidentified leukemogens, or potentiation by nonleukemogens, may be important in explaining smoking-induced leukemia. Nevertheless, the results presented here for benzene alone provide evidence supporting the use of linear models to extrapolate substantially below occupational exposures. This conclusion is bolstered by evidence of DNA adduct formation by benzene metabolites (*51–55*).

Although we provided UCLs in this paper, U.S. regulatory agencies do not use them when extrapolating from epidemiologic data. The use of maximum likelihood potency estimates may limit the margin of safety.

In conclusion, we estimate that benzene is responsible for 8–48% of smoking-induced leukemia and for 12–58% of smoking-induced AML. The use of cancer mortality data for smokers and never-smokers provides a real-world upper bound for the estimated low-dose carcinogenicity of cigarette smoke constituents and permits an empirical check on the plausibility of risks extrapolated from benzene exposures in industrial settings 10- to 100-fold higher. Our findings show that models with linear terms produce estimates consistent with known smoking-induced risks and with the presence of other leukemogens in mainstream and sidestream smoke.

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