Risk Analysis, Vol. 16, No. 6, 1996

7749

Determination of Leukemogenic Benzene Exposure Concentrations: Refined Analyses of the Pliofilm Cohort

A. Robert Schnatter,[1,2] Mark J. Nicolich,[1] and Michael G. Bird[1]

key leukemia benzene risk assessment

Received March 18, 1996; revised August 9, 1996

Biologic data on benzene metabolite doses, cytotoxicity, and genotoxicity often show that these effects do not vary directly with cumulative benzene exposure (i.e., concentration times time, or $c \times t$). To examine the effect of an alternate exposure metric, we analyzed cell-type specific leukemia mortality in Pliofilm workers. The work history of each Pliofilm worker was used to define each worker's maximally exposed job/department combination over time and the associated long-term average concentration associated with the maximally exposed job (LTA-MEJ). Using this measure, in conjunction with four job exposure estimates, we calculated SMRs for groups of workers with increasing LTA-MEJs. The analyses suggest that a critical concentration of benzene exposure must be reached in order for the risk of leukemia or, more specifically, AMML to be expressed. The minimum concentration is between 20 and 60 ppm depending on the exposure estimate and endpoint (all leukemias or AMMLs only). We believe these analyses are a useful adjunct to previous analyses of the Pliofilm data. They suggests that (a) AMML risk is shown only above a critical concentration of benzene exposure, measured as a long-term average and experienced for years, (b) the critical concentration is between 50 and 60 ppm when using a median exposure estimate derived from three previous exposure assessments, and is between 20 and 25 ppm using the lowest exposure estimates, and (c) risks for total leukemia are driven by risks for AMML, suggesting that AMML is the cell type related to benzene exposure.

KEY WORDS: Benzene; leukemia; exposure concentration; threshold; epidemiological data.

1. INTRODUCTION

The leukemogenic potential of benzene has been well-documented.[1–15] Biologic evidence suggests that the timing, duration, and concentration of exposure are important independent factors in predicting benzene's hematotoxic, genotoxic, and possibly leukemogenic effects. Specifically, Green *et al.*[16] reported that severe toxicity to the bone marrow, spleen, and peripheral blood was observed in CD-1 mice following a 5-day, 6-hour/day, 100-ppm exposure (125 ppm-days) while no toxicity was observed to the bone marrow or peripheral blood following an equivalent cumulative exposure of 10-week, 6-hour/day, 5-day/week exposure at 10 ppm. Toft *et al.*[17] exposed male NMRI mice to various exposure regimens and reported several examples of dose rate effects for cellularity, granulopoietic stem cells (CFU-GM), and micronuclei in polychromatic erythrocytes (MN-PCE's). As an example, a MN-PCE were significantly higher for a 95-ppm, 2-day regimen (190 ppm-days) compared to a 21-ppm, 10-day (210-ppm-days) regimen. Exposure intermittency may also have a role in benzene-induced myelotoxicity. Luke *et al.*[18] showed that for 300-ppm exposure to benzene, suppression of polychromatic erythrocyte (PCE) counts in mice was more persistent for 3-day consecutive exposures rather than 5-day consecutive exposures.

Some pharmacokinetic models have examined po-

[1] Exxon Biomedical Sciences, Inc., Mettlers Road, CN 2350, East Millstone, New Jersey 08875-2350.
[2] To whom all correspondence should be addressed.

0272-4332/96/1200-0833$09.50/1

tential dose rate effects of benzene exposure.[19–24] Bois and Paxman,[20] and Watanabe *et al.*[22] predict greater internal metabolite levels for short-term, high-level administered doses compared to longer term, lower level exposures. Cox[23,24] showed that the same cumulative exposure regimen can have different hematotoxic effects depending upon how benzene is administered over time. This model predicts that a high level discontinuous exposure has a greater effect on bone marrow proliferation. Premature bone marrow stem cell proliferation is a critical step in recently proposed models of leukemogenesis.[25,26]

The above research suggests that benzene dose rate effects may be important, which we define as an effect which relies on exposure concentration in a manner other than as a simple, linear product term of cumulative exposure (concentration × time). The above data apply to internal benzene metabolite doses, cytotoxicity, and some measures of genotoxicity. Comparable data on leukemogenesis is lacking. However, since the induction of leukemia (specifically, acute nonlymphocytic leukemia, or ANLL) is likely a long term, multifactorial process involving metabolism,[27] and both cytotoxicity and genotoxicity,[25,26] a reasonable supposition is that these effects also play a role in benzene-induced leukemogenesis. Another corollary of the multifactorial leukemogenesis model borne out by empirical data[3,5] is that long term exposure at such critical concentrations is necessary, and it is unlikely that exposures of hours, days, or weeks have any practical relevance to leukemogenesis.

Most epidemiologic studies, including those on benzene-exposed populations, estimate cumulative exposure in ppm-years ($c \times t$). When leukemic risk is estimated by cumulative exposure, it is implicitly assumed that c (in ppm) and t (in years) are equal contributors to an exposure index (ppm-years) which is then used to predict leukemic risk. While some refinements have been used such as using a nonlinear combination of concentration and duration ($c^n \times t$),[8] and entering simultaneous terms for c, t, and $c \times t$[5] these maneuvers have not been fully investigated, and still rely on model extrapolations to predict low-level effects.

To further explore the possible impact of exposure rate effects on leukemogenesis, we used the Pliofilm data,[5–8] which is the basis of most risk assessments and regulatory decisions.[9–14] Effects of specific benzene LTA exposure concentrations, rather than the estimated cumulative exposure of benzene were analyzed. The exposure concentrations investigated were those used by previous authors[1,9,15] and represent long-term averages for jobs held by employees in the Pliofilm cohort.

2. METHODS

2.1. Subjects/Statistical Analysis

The employees included in this evaluation are described in detail elsewhere.[5,6] Vital status of the cohort was determined through 1987 for most workers, and 1981 for one subgroup. Age and time period specific rates of total leukemias and acute myelocytic and monocytic leukemia (AMML) were obtained for the U.S. and the state of Ohio. Since similar results were obtained using both sets of rates, only results for U.S. rates are reported here. Expected deaths were calculated by multiplying distributions of person years (through 1981 or 1987) by these rates, specific to time period, age, and gender. The population was restricted to non-Black non-female employees, consistent with previous publications. Standardized Mortality Ratios (SMRs) were calculated in a conventional manner using the Occupational Mortality Analysis Program (OCMAP) program.[28]

2.2. Exposure Determination

Three different sets of LTA exposure estimates have been developed for the Pliofilm workers.[1,9,15] Analyses have been performed with each set of exposure estimates, plus an estimate derived by considering the median of the three sets of estimates. The median exposure estimate was calculated by simply selecting the middle-ranked estimate for each cell in the job/department/time exposure matrix. One advantage of this estimate is that it disregards extreme exposure estimates (either high or low), which have been the subject of previous criticism.[8,29] Each worker's maximally exposed job/department combination over time and the long term average concentration associated with the maximally exposed job (LTA-MEJ) was calculated for the median as well each series[1,9,15] of exposure estimates. This enabled the enumeration of subgroups of workers and person-years who were always exposed *less than or equal to* specific concentrations of benzene.[3] By varying the exposure concentration cutpoint in small increments and calculating SMRs for workers exposed below each cutpoint, exposure concentrations which are

[3] To avoid immortal person-years, the maximally-exposed job (MEJ) was determined over an entire workers career. A worker's MEJ could change over time. If he first experienced jobs with low exposures, and subsequently experienced jobs with a higher LTA concentration, the worker would contribute person-years first to lower, then higher concentrations.

Table I. Number of Workers and Person Years for Selected Cutpoints and Four Exposure Estimates

Exposure concentration (ppm)	Median		Rinsky		Crump		Paustenbach	
	N at risk	Person years	*N* at risk	Person years	*N* at risk	Person years	*N* at risk	Person years
1	248	4555.1	1047	19252.3	267	4894.2	65	795.2
5	427	8314.1	1135	21232.6	480	9326.3	85	857.3
10	508	9503.8	1206	24737.9	554	10303.6	105	1073.5
15	552	10570.5	1206	24794.9	636	12405.6	188	1878.1
20	890	17516.6	1267	29348.5	993	20382.7	210	2754.8
25	1109	24528.3	1381	35175.4	1056	23379.7	704	10955.2
30	1126	25004.6	1439	39166.9	1204	27246.0	730	12377.3
35	1158	26310.6	1560	44819.2	1222	28082.1	771	14995.6
40	1321	34090.2	1597	45830.2	1264	32482.4	910	18196.0
45	1367	36616.3	1695	49610.1	1293	34963.6	1021	21433.6
50	1388	38414.5	1706	51648.5	1293	34963.6	1087	24950.8
55	1458	40380.2	1706	51648.5	1419	38398.9	1088	24976.3
60	1501	42932.6	1710	52453.9	1465	40984.4	1166	26398.0
70	1530	44449.9	1710	52453.9	1493	42012.7	1267	29245.3
80	1596	46696.5	1710	52453.9	1568	44593.6	1389	34725.9
90	1596	46696.5	1710	52453.9	1568	44593.6	1457	38417.2
100	1600	46744.8	1710	52453.9	1568	44593.6	1494	40672.4
120	1653	49989.8	1710	52453.9	1609	47064.8	1548	43258.1
140	1710	52453.9	1710	52453.9	1609	47064.8	1610	45915.5
150	1710	52453.9	1710	52453.9	1609	47064.8	1610	45933.5
175	1710	52453.9	1710	52453.9	1609	47064.8	1673	46993.0
200	1710	52453.9	1710	52453.9	1609	47064.8	1681	50465.1
250	1710	52453.9	1710	52453.9	1616	47516.3	1695	51483.9
260	1710	52453.9	1710	52453.9	1710	52453.9	1710	52453.9

related to risk can be examined. This method is useful for identifying "empirical thresholds," i.e., critical concentrations which are not associated with any excess risk in the database.

3. RESULTS

Table I displays the aggregate number of workers and person-years exposed at or below selected cutpoints. Table I clearly shows that the estimates developed by Rinsky[1] are, on average, lower than those developed by Crump and Allen,[9] which in turn are slightly lower than those developed by Paustenbach *et al.*[15]

Table II displays SMRs for total leukemia in Pliofilm workers exposed at or below specific concentrations. For all sets of exposure estimates, Table II shows total leukemia SMRs are not different from 1.0 among those workers always exposed to benzene concentrations less than 20 ppm. However, for workers exposed to concentrations between 20 and 40 ppm, a nonstatistically significant elevation of total leukemia mortality is evident for all estimates, except those of Paustenbach *et al.*[15]

Table III displays the more relevant SMRs for AMML[4] by exposure concentration. These results indicate no AMMLs (except for the Crump and Allen[9] estimates) in workers only exposed to concentrations of 20 ppm and below. The Rinsky *et al.*[1] estimates support the notion of a critical concentration which must be attained for increased risk, in that exposures between 20–25 ppm show a high SMR, while those below 20 ppm show no cases (SMR = 0, 95% C.I. = 0, 4.53). The median exposure estimates and the Crump and Allen[9] exposure estimates are also indicative of this critical concentration in that exposures below 50 ppm do not result in excess risk (SMR = 0.86, 95% C.I. = 0.01, 4.80), while those between 55 and 60 ppm do. The Paustenbach[15] exposure estimates, also show an increasing SMR trend for higher concentrations, but the estimates do not show markedly excess risks, until concentrations of 140 ppm are reached.

Figure 1 graphically depicts the results for both the median exposure estimates and the Rinsky *et al.*[1] exposure estimates. This plot suggests that exposures under

[4] In the Pliofilm workers, there were no forms of ANLL other than acute myelocytic leukemia and acute monocytic leukemia. Following the Crump[8] terminology, these cell types are referred to as AMML.

Table II. Observed Total Leukemias, Expected Leukemias, and SMR for Selected Cutpoints and Four Exposure Estimates

Exposure concentration (ppm)	Median			Rinsky			Crump			Paustenbach		
	Obs. leuk.	Exp. leuk.	SMR	Obs. leuk.	Exp. leuk.	SMR	Obs. leuk.	Exp. leuk.	SMR	Obs. leuk.	Exp. leuk.	SMR
1	0	0.43	0.00	1	1.53	0.65	0	0.53	0.00	0	0.07	0.00
5	0	0.83	0.00	1	1.72	0.58	0	1.01	0.00	0	0.10	0.00
10	0	0.89	0.00	1	2.00	0.50	0	1.04	0.00	0	0.11	0.00
15	0	0.98	0.00	1	2.00	0.50	0	1.28	0.00	0	0.15	0.00
20	0	1.50	0.00	3	2.30	1.30	2	1.92	1.04	0	0.21	0.00
25	2	1.88	1.06	7	2.92	2.40	2	2.13	0.94	1	0.80	1.25
30	2	2.01	1.00	7	3.24	2.16	3	2.35	1.28	1	0.90	1.11
35	2	2.19	0.91	10	3.90	2.56	3	2.43	1.23	1	1.07	0.93
40	5	2.84	1.76	10	4.04	2.48	5	2.73	1.83	1	1.33	0.75
45	5	3.11	1.61	11	4.52	2.43	5	2.98	1.68	1	1.67	0.60
50	5	3.30	1.52	14	4.79	2.92	5	2.98	1.68	3	1.96	1.53
55	7	3.59	1.95	14	4.79	2.92	6	3.38	1.78	3	1.96	1.53
60	8	3.85	2.08	14	4.87	2.87	7	3.62	1.93	3	2.11	1.42
70	9	4.02	2.24	14	4.87	2.87	8	3.74	2.14	3	2.41	1.24
80	9	4.21	2.14	14	4.87	2.87	8	3.98	2.01	4	2.97	1.35
90	9	4.21	2.14	14	4.87	2.87	8	3.98	2.01	4	3.31	1.21
100	9	4.21	2.14	14	4.87	2.87	8	3.98	2.01	5	3.55	1.41
120	11	4.55	2.42	14	4.87	2.87	9	4.20	2.14	7	3.83	1.83
140	14	4.87	2.87	14	4.87	2.87	9	4.20	2.14	10	4.14	2.42
150	14	4.87	2.87	14	4.87	2.87	9	4.20	2.14	10	4.14	2.42
175	14	4.87	2.87	14	4.87	2.87	9	4.20	2.14	14	4.63	3.02
200	14	4.87	2.87	14	4.87	2.87	9	4.20	2.14	14	4.70	2.98
250	14	4.87	2.87	14	4.87	2.87	9	4.24	2.12	14	4.77	2.94
260	14	4.87	2.87	14	4.87	2.87	14	4.87	2.87	14	4.87	2.87

20 ppm do not result in risk, regardless of the endpoint (AMML or all leukemias) or the exposure estimates used.

When the median exposure estimate is used, this critical concentration appears to be 50–60 ppm when AMML is the endpoint, and could be as low as 38 ppm (based on two cases exposed at that level) for total leukemias. With the Rinsky *et al.*[1] exposure estimates and both AMML and total leukemias, concentrations of 23 ppm are the lowest associated with excess risk, based on four and seven cases, respectively. For all exposure estimates, risks are consistently higher for AMML compared to total leukemias, and it is apparent that risks for AMML are driving the results for total leukemia.

4. DISCUSSION

Several lines of evidence indicate that benzene concentration is a particularly relevant determinant of its toxicity. While this exposure metric is usually deemed relevant for acute effects, it has also received attention for chronic effects such as lung cancer due to radon and other alpha emitters.[30] Analyses presented in this paper shed light on what specific benzene exposure concentrations may actually result in excess leukemogenic risk.

Some previous epidemiologic analyses have examined the importance of exposure concentration vs. the more traditional cumulative exposure metric in the Pliofilm cohort. Specifically, Rinsky *et al.*[5] examined cumulative exposure (ppm-years), average exposure rate (average concentration over a career in ppm), and duration of exposure (years), in a logistic regression model and reported that cumulative exposure "was the strongest single predictor of death from leukemia." Addition of concentration and time terms did not improve the fit of the overall logistic model. However, it was noted that the various exposure terms were correlated, which may have violated model assumptions. Crump[8] investigated several metrics and reported that the risk of leukemia was explained better by concentration-dependent nonlinear exposure metrics for the Paustenbach,[15] but not the Crump and Allen[9] exposure estimates. The suggestion of concentration-dependent nonlinear risk was a guarded one since it depended on the set of exposure estimates used.

Both of the above approaches inherently consider the full range of exposure concentrations represented in

Table III. Observed AMMLs, Expected AMMLs, and SMR for Selected Cutpoints and Four Exposure Estimates

Exposure concentration (ppm)	Median			Rinsky			Crump			Paustenbach		
	Obs. AMML	Exp. AMML	SMR	Obs. AMML	Exp. AMML	SMR	Obs. AMML	Exp. AMML	SMR	Obs. AMML	Exp. AMML	SMR
1	0	0.15	0.00	0	0.54	0.00	0	0.18	0.00	0	0.02	0.00
5	0	0.27	0.00	0	0.60	0.00	0	0.33	0.00	0	0.03	0.00
10	0	0.30	0.00	0	0.70	0.00	0	0.34	0.00	0	0.03	0.00
15	0	0.33	0.00	0	0.70	0.00	0	0.43	0.00	0	0.05	0.00
20	0	0.52	0.00	0	0.81	0.00	1	0.66	1.52	0	0.07	0.00
25	1	0.66	1.52	4	1.02	3.92	1	0.74	1.35	0	0.28	0.00
30	1	0.71	1.41	4	1.13	3.54	1	0.83	1.20	0	0.31	0.00
35	1	0.76	1.32	5	1.34	3.73	1	0.85	1.18	0	0.37	0.00
40	1	1.00	1.00	5	1.39	3.60	1	0.97	1.03	0	0.47	0.00
45	1	1.09	0.92	5	1.55	3.23	1	1.06	0.94	0	0.59	0.00
50	1	1.16	0.86	8	1.64	4.88	1	1.06	0.94	0	0.70	0.00
55	3	1.24	2.42	8	1.64	4.88	2	1.17	1.71	0	0.70	0.00
60	4	1.34	2.99	8	1.67	4.79	3	2.80	1.07	0	0.75	0.00
70	4	1.38	2.90	8	1.67	4.79	3	1.30	2.31	0	0.85	0.00
80	4	1.45	2.76	8	1.67	4.79	3	1.38	2.17	1	0.33	3.03
90	4	1.45	2.76	8	1.67	4.79	3	1.38	2.17	1	1.15	0.87
100	4	1.45	2.76	8	1.67	4.79	3	1.38	2.17	1	1.23	0.81
120	5	1.57	3.18	8	1.67	4.79	4	1.45	2.76	2	1.34	1.49
140	8	1.67	4.79	8	1.67	4.79	4	1.45	2.76	5	1.33	3.76
150	8	1.67	4.79	8	1.67	4.79	4	1.45	2.76	5	1.43	3.50
175	8	1.67	4.79	8	1.67	4.79	4	1.45	2.76	8	1.58	5.06
200	8	1.67	4.79	8	1.67	4.79	4	1.45	2.76	8	1.60	5.00
250	8	1.67	4.79	8	1.67	4.79	4	1.46	2.74	8	1.64	4.88
260	8	1.67	4.79	8	1.67	4.79	8	1.67	4.79	8	1.67	4.79

the data in one model. While these approaches are useful, they may miss the effects if exposure concentration has variable effects along the entire gradient. For example, if it is thought that concentration of exposure is important, a model which gives concentration more weight could adjust for this concept by applying a ($c^n \times t$) term, where n is often 2 or more. However, if there is a critical concentration (c) which must be reached for excess risk, low concentrations would be given undue weight. Thus, the use of a continuous function ($c^n \times t$) could mask relevant vs. irrelevant values of c. Similarly, nonlinearities which manifest as S-shaped risk curves (i.e., sublinear and supralinear components) may not be detected. While we regard these techniques as useful, we sought an alternate method which examined the effect of exposure concentration more directly.

The approach used in this paper did not depend on a model which simultaneously evaluates the entire exposure range for nonlinearities or rate effects. Instead, the approach is based on life table methodology and categorical exposure classification. The life table method is widely used and understood in occupational mortality studies. While this approach has limitations related to the fact that severe imbalances in person-year distributions between subcohorts can yield biased results,[31] the practical effect of this bias is often negligible. Among the advantages are that the external rates used for comparison purposes are stable since they are based on large numbers. The approach also lends itself to categorizing exposure data to directly examine risk in relevant exposure categories, although this advantage is not unique to the life table approach.

These analyses suggest that a critical concentration of benzene exposure must be reached in order for the risk of leukemia or, more specifically, AMML to be expressed. When the median exposure estimate is used, this concentration appears to be between 50 and 60 ppm for both AMML and leukemia. For the Rinsky *et al.*[1] exposure estimates, critical concentrations were lower for both AMML and total leukemias, ranging between 20 and 25 ppm. Both analyses support previous analyses[8,32] suggesting that acute myelocytic and acute monocytic leukemia (and, by inference, related forms of ANLL) as cell types which are uniquely related to benzene exposure.

While the duration of exposure is not explicitly accounted for in these analyses, the effects of exposure duration can be investigated in these data. Using the Rin-

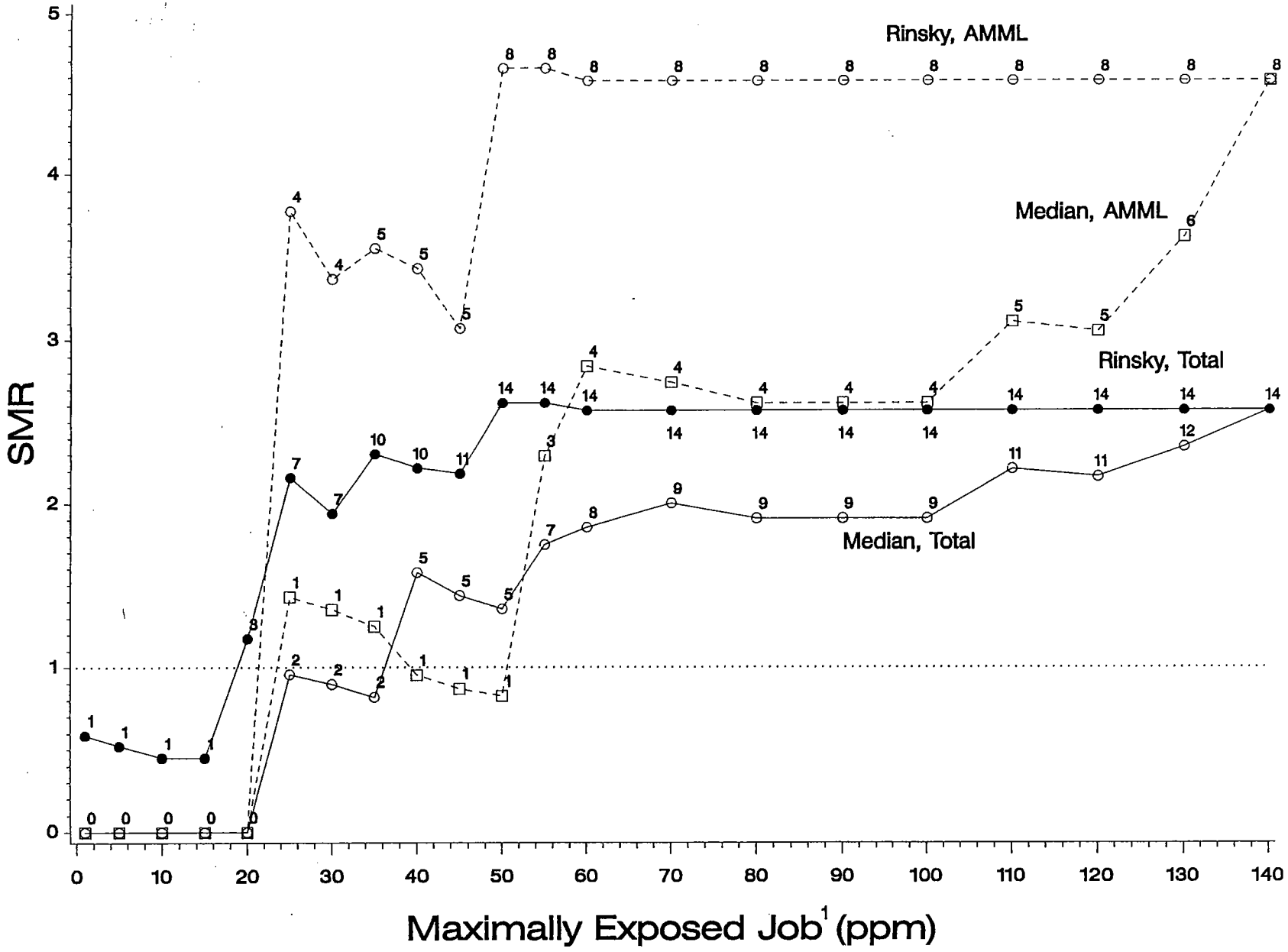

Fig. 1. SMR based on maximally exposed job Pliofilm data, total leukemia, and AMML, two exposure estimates. Numbers represent observed cases. [1]See text for definition.

sky *et al.*[1] estimates, workers who were exposed to concentrations above 20 ppm (i.e., where excess risk was noted) were exposed for an average of approximately 6.2 years, while AMML cases were exposed an average of 13 years. In either case, the exposure duration associated with excess risk is several years (rather than days or weeks). Thus, these results should not be taken to imply that instantaneous, or short duration exposures of 20 ppm could be leukemogenic.

The results of recent epidemiologic studies and analyses on benzene and leukemia are consistent with the notion that benzene concentrations of at least 20–25 ppm experienced over years, are necessary for leukemogenesis. When AMML is considered as the appropriate endpoint in reassessments of the Pliofilm cohort, no risk was evident for exposure below 200 ppm-years using the Rinsky *et al.*[1] estimates,[32,33] or 400 ppm-years using the Paustenbach *et al.* estimates.[8] Using the latter analysis, CONCAWE[34] estimated a no observed effect level of 42 ppm, using the average duration of exposure for all workers exposed below 400 ppm-years. Similar analyses on the Rinsky *et al.*[1] exposure estimates are not available, but such an analysis would likely estimate a somewhat lower no observed effect level. Furthermore, in recent petroleum worker studies[35,36] where lower benzene exposures (<1 ppm as a LTA concentration) occur, no consistently elevated risks have been observed.

In summary, we believe this analysis is a useful adjunct to previous analyses of the Pliofilm data. It suggests that (a) AMML risk is shown only above a critical concentration of benzene exposure, measured as a long-term average and experienced for years, (b) the critical concentration is between 50 and 60 ppm when using a median exposure estimate derived from three previous exposure assessments, and is between 20 and 25 ppm using the lowest exposure estimates, and (c) risks for total leukemia are driven by risks for AMML, suggesting that AMML is the cell type related to benzene exposure.

REFERENCES

1. R. A. Rinsky, R. J. Young, and A. B. Smith, "Leukemia in Benzene Workers," *American Journal of Industrial Medicine* **2**, 217–245 (1981).
2. E. C. Vigliani, and G. Saita, "Benzene and Leukemia," *New England Journal of Medicine* **271**, 872–876 (1964).
3. M. Aksoy, S. Erdem, and G. Dincol, "Leukemia in Shoe-Workers Exposed Chronically to Benzene," *Blood* **44**, 837–841 (1974).
4. P. K. Infante, R. A. Rinsky, J. K. Wagoner, and R. J. Young, "Leukemia in Benzene Workers," *Lancet* **2**, 76–78 (1977).
5. R. A. Rinsky, A. B. Smith, R. Hornung, T. G. Filloon, R. J. Young, A. H. Okun, and R. J. Landrigan, "Benzene and Leukemia: An Epidemiologic Risk Assessment," *New England Journal of Medicine* **316**(17), 1044–1050 (1987).
6. M. B. Paxton, V. M. Chinchilli, S. M. Brett, and J. V. Rodricks, "Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort. I. Mortality Update and Exposure Distribution," *Risk Analysis* **14**(2), 148–154 (1994).
7. M. B. Paxton, V. M. Chinchilli, S. M. Brett, and J. V. Rodricks, "Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort. II. Risk Estimates," *Risk Analysis* **14**, 155–157 (1994).
8. K. Crump, "Risk of Benzene-Induced Leukemia: A Sensitivity Analysis of the Pliofilm Cohort with Additional Follow-up and New Exposure Estimates," *Journal of Toxicology and Environmental Health* **43**, 219–242 (1994).
9. K. S. Crump, and B. C. Allen, Quantitative Estimates of Risk of Leukemia from Occupational Exposure to Benzene. U.S. Department of Labor, Washington, D.C., (OSHA Docket H-059b, Exhibit 152, Annex B) (1984).
10. Occupational Safety and Health Administration (OSHA), "Final Rule on Occupational Exposure to Benzene," *Federal Register* **54**, 34660–34762 (1987).
11. H. Austin, E. Delzell, and P. Cole, "Benzene and Leukemia: A Review of the Literature and a Risk Assessment," *American Journal of Epidemiology* **127**, 419–439 (1988).
12. S. M. Brett, J. V. Rodricks, and V. M. Chinchilli, "Review and Update of Leukemia Risk Potentially Associated with Occupational Exposure to Benzene," *Environmental Health Perspectives* **82**, 267–281 (1989).
13. CEC: Commission of the European Communities. Occupational Exposure Limits-Criteria Document for Benzene. Luxembourg. Directorate-General Employment, Industrial Relations and Social Affairs (EUR 14491 EN) (Health and Safety Series) (1993).
14. Health Canada and Environment Canada, CEPA PSL Supporting Document-Benzene (1993).
15. D. J. Paustenbach, P. S. Price, W. Ollison, C. Blank, J. D. Jernigan, R. D. Bass, and H. D. Peterson, "Reevaluation of Benzene Exposure for the Pliofilm (Rubberworker) Cohort (1936–1976)," *Journal of Toxicology and Environmental Health* **36**, 177–231 (1992).
16. J. D. Green, C. A. Snyder, J. LoBue, B. D. Goldstein, and R. E. Albert, "Acute and Chronic Dose/Response Effect of Benzene Inhalation on the Peripheral Blood, Bone Marrow, and Spleen Cells of CD-1 Male Mice," *Toxicology and Applied Pharmacology* **59**, 204–214 (1981).
17. L. Toft, T. Olofsson, and A. Tunek, "Toxic Effects on Mouse Bone Marrow Caused by Inhalation of Benzene," *Archives of Toxicology* **51**, 295–302 (1982).
18. C. A. Luke, R. R. Tice, and R. T. Drew, "The Effect of Exposure Regimen and Duration on Benzene-Induced Bone Marrow Damage in Mice II. Strain Comparisons Involving B6C3F1, C57B1/6 and DBA/2 Male Mice," *Mutation Research* **203**, 273–295 (1988).
19. C. Travis, J. L. Quillen, and A. D. Arms, "Pharmacokinetics of Benzene," *Toxicol. Appl. Pharmacol.* **102**, 400–420 (1990).
20. F. Y. Bois, and D. G. Paxman, "An Analysis of Exposure Rate Effects for Benzene Using a Physiologically Based Pharmacokinetic Model," *Regulatory Toxicology and Pharmacology* **15**, 122–136 (1992).
21. L. A. Cox, Jr. and P. F. Ricci, "Reassessing Benzene Cancer Risks Using Internal Doses," *Risk Analysis* **12**(3), 401–409 (1992).
22. K. H. Watanabe, F. Y. Bois, J. M. Daisey, and D. M. Auslander, "Benzene Toxicokinetics in Humans: Exposure of Bone Marrow to Metabolites," *Occupational and Environmental Medicine* **51**, 414–420 (1994).
23. L. A. Cox, Jr., Reassessing Benzene Cancer Risks Using Interval

Dose. Forthcoming in *Environmental Health Perspectives*. (Paper presented at Benzene '95 International Conference) (1996).
24. L. A. Cox, Jr., "Dynamic Dose–Time-Response Models of Chemical Leukemogenesis Cell Proliferation" (in press) (1996).
25. R. D. Irons, and W. S. Stillman, The Process of Leukemogenesis. Forthcoming in *Environmental Health Perspectives*. (Paper presented at Benzene '95 International Conference) (1996-preprint).
26. R. D. Irons, and W. S. Stillman, Impact of Benzene Metabolites on Differentiation of Bone Marrow Progenitor Cells. Forthcoming in *Environmental Health Perspectives*. (Paper presented at Benzene '95 International Conference) (1996-preprint).
27. R. Snyder and G. Kalf, "A Perspective on Benzene Leukemogenesis," *Critical Reviews in Toxicology* **24**(3), 177–209 (1994).
28. G. Marsh, J. Ehland, M. Paik, *et al.*, "OCMAP/PC: A User-Oriented Occupational Cohort Analysis Program for the IBM PC," *American Statistician* **40**, 308 (1986).
29. D. F. Utterback and R. A. Rinsky, "Benzene Exposure Assessment in Rubber Hydrochloride Workers: A Critical Evaluation of Previous Estimates," *American Journal of Industrial Medicine* **27**, 661–676 (1995).
30. BEIR IV, *Health Risks of Radon and Other Internally Deposited Alpha-Emitters* (National Academy Press, Washington, D.C., 1988).
31. S. P. Tsai and C. P. Wen, "A Review of Methodological Issues of the Standardized Mortality Ratio (SMR) in Occupational Cohort Studies," *International Journal of Epidemiology* **15**, 8–21 (1986).
32. O. Wong, "Risk of Acute Myeloid Leukemia and Multiple Myeloma in Workers Exposed to Benzene," *Occupational and Environmental Medicine* **52**, 380–384 (1995).
33. O. Wong and G. K. Raabe, "Cell-Type-Specific Leukemia Analyses in a Combined Cohort of More than 208,000 Petroleum Workers in the United States and the United Kingdom, 1937–1989," *Regulatory Toxicology and Pharmacology* **21**, 307–321 (1995).
34. CONCAWE, Scientific Basis for an Air Quality Standard on Benzene. Report No. 95/58R (1995).
35. L. Rushton and H. Romaniuk, "Results of a Case-Control Study to Investigate the Risk of Leukemia Associated with Exposure to Benzene in Petroleum Marketing and Distribution Workers in the United Kingdom," *Submitted to Occupational and Environmental Medicine* (1996).
36. A. R. Schnatter, T. W. Armstrong, M. J. Nicolich, F. S. Thompson, W. W. Huebner, A. M. Katz, and E. D. Pearlman, "Risk of Lymphohematopoietic Malignancies and Quantitative Estimates of Benzene Exposure in Canadian Marketing/Distribution Workers," *Occupational and Environmental Medicine* (in press) (1996).