X: ART/API/Benzene
T.F.

American Petroleum Institute
1220 L Street, Northwest
Washington, D.C. 20005

memo

Date: August 24, 1993

From: Mary Paxton

To: Benzene Task Force (BTF)

Re: Minutes of August 11 Meeting and ACGIH Submission

Enclosed are draft minutes of our BTF meeting on August 11.

The final version of our submission to ACGIH is enclosed. You will also find the remarks from Sheryl Bartlett of Dan Krewski's office, which unexpectedly arrived in time to include with our submission.

Pat Beatty is preparing the overheads for his presentation at ACGIH on September 13. They will be distributed at the beginning of next week in time for our conference call on Thursday, September 2, at 2:30 EDT. Pat will be holding a "dress (or shorts?) rehearsal" of his presentation at 1:00 on Sunday, September 12, at the Holiday Inn Crowne Plaza in Rockville, MD; if you are able to attend, your input would be appreciated.

The next full meeting of the BTF will be on Thursday, September 30, in San Francisco. Details and an agenda will follow.

Also included is a newly published article by Cody, Strawderman, and Kipen, which we helped support.

If you have comments on the draft by Tony Cox that was distributed at the BTF meeting, please convey them to me to pass along to him.

att: minutes.805
acgih.813
Bartlett letter
Cody et al.

BENZENE TASK FORCE (BTF)
Wednesday, August 11, 1993

American Petroleum Institute,
Room 939
1220 L Street, NW
Washington, DC 20005

Wednesday, August 11, 1993

Meeting Minutes - Subject to Approval

Attendees	Affiliation
Pat Beatty	Chevron
Peter Craig	Mobil
Barbara Divine	Texaco
Anita Ducca	API
Carol Fairbrother	Exxon
David Mongillo	API
Ramona Panson	SUN
Mary Paxton	API
Gerry Raabe	Mobil
Dave Steup	Shell
Dale Strother	BP America
Li Yang	ARCO

Introduction

Pat Beatty convened this meeting of the Benzene Task Force (BTF) at 9:10. The minutes for the last meeting (6/22/93) were accepted without change. The primary purpose of this meeting was to finalize the submission to be sent to ACGIH on Friday, so other matters were briefly reviewed first.

Regulatory Affairs

U.S. EPA: A journalist had informed us that EPA had reactivated its reconsideration of the benzene potency factor. [Responses to inquiries received the day after the meeting indicated that EPA is developing a position statement on the need for updating the benzene potency factor. This should be available by the end of the year.]

California EPA: Pat Beatty reported that he will be requesting funding in 1994 from WSPA to fund a workshop and a review paper of developments since the Cal. EPA developed their benzene potency factor.

Project Updates

ITRI: If a contract has not been settled within two weeks, the $150K requested in ITRI's revised proposal will be sent in the form of a gift.

Kalf: Kalf has been told that we will support a graduate student in researching the hydroquinone receptor. Bob Drew is looking for money to cover the full three years of support from this year's budget.

Cox: His draft and summary comments of a journal article summarizing his feasibility study of biologically-based risk assessment (BBRA) modeling of leukemia using data for the well-studied chemotherapeutic agent cyclophosphamide (CP) were distributed for comment. It was formatted for a special issue of *Risk Analysis* to which he was asked to contribute.

Richard Paul, staffer of the American Automobile Manufacturers Association (AAMA), sent their integrated summary of how the biological data support a threshold for benzene's leukemogenic effect. Mary Paxton will arrange for a few BTF members to meet with AAMA representatives to determine how AAMA might contribute support to the BBRA modeling effort.

Genotoxicity: Irene Jones of Lawrence Livermore National Laboratory reviewed the two articles from Legator's lab (Au et al. 1991 and Ward et al. 1992). Mary Paxton discussed possibilities for research in this area with her at the Gordon Research Conference on genetic toxicology. The Gordon Conference was largely concerned with defining the background mutation rate and developing a profile of spontaneous effects. The attendees focused their risk assessment concerns primarily on somatic effects (cancer) and discussed why quantitation of heritable damage would probably entail much more effort than the actual dangers merited. Mary Paxton also noted that she met Ken Turteltaub of Lawrence Livermore Labs, who is applying ultrasensitive detection (e.g., one molecule of ^{14}C in 10^{-18} mole) by tandem accelerator mass spectrometry to DNA adducts. His work to date has included some work with benzene exposures.

Paper on biological basis for model selection: In planning to have this paper written, note should be taken of an extensive review of dose-response modeling by Zeise et al. (1987 *Environ. Health Perspect.* 73:259-308) supported by API, CMA, and Monsanto.

Benzene exposure in gasoline studies: The summary of the Nottingham workshop is now available. The study of the Imperial Oil cohort will be presented at a meeting in Nice in September. API's participation in the May 1994 IARC meeting will be limited, but Lesley Rushton will be making a presentation.

David Mongillo will inform the Industrial Hygiene Oversight Group about this issue at its meeting at the end of August. Jack Hinton will then develop a scope-of-work statement that reflects

the objective of reconstructing benzene exposure from gasoline in a generic fashion.

Financial Impact Study: Anita Ducca suggested doing this study in two parts, rather than just revising our previous RFP for the full study. Phase I will identify potential federal and state modifications in benzene regulation and what changes would be triggered by events (such as a reduction in the TLV to 0.1 ppm) and prioritize the likely magnitude of their impact on the industry. In the next 4-6 weeks, Anita will prepare a scope-of-work and approach several contractors for cost estimates; the anticipated cost is in the range of $10-20K for about a month's project. After this effort to more precisely define the problem, we should be better able to determine exactly what should be included in our RFP for the study itself (Phase II).

ACGIH Strategy

After a break from 10:25-10:50, the group reconvened to discuss plans for the meeting with ACGIH on September 13 in Rockville, MD.

Jennifer Galvin learned from Dr. Sharma that, if ACGIH does not approve the 0.1-ppm TLV and does not wish to fall back to the current 10-ppm TLV, the entire process will have to be repeated for any alternative figure they select, i.e., there would be a formal published Notice of Proposed Change followed by a year-long comment period before another value for the TLV could go into effect.

Submission for September 13: A letter with comments for attachment to our submission has been received from Vern Chinchilli, and one is expected next week from Dan Krewski and Sheryl Bartlett, which we will send along after the submission. Exxon Biomedical has made available a critique of the Brown and Spirtas analysis, which will also be attached to our submission.

The group went over the prepared draft and noted several points that needed to be added or expanded. After breaking for lunch at noon, the BTF members composed the necessary insertions.

Plans for September 13: Pat Beatty will give a dry run of his presentation for all who can attend at 1:00 on the afternoon before at the meeting hotel. API's delegation to the meeting will be Pat Beatty, Jack Hinton, Vern Chinchilli, Bob Drew, and Mary Paxton. Kenny Crump and Gerry Raabe have also been invited independently by ACGIH.

Future meetings

A conference call will be held 2:30 EDT on Thursday, September 2, to go over the overheads Pat Beatty will use in his presentation at the September 13 ACGIH meeting.

All interested BTF members may attend a practice session for the presentation to be held the afternoon of Sunday, September 12, at the Holiday Crown Plaza in Rockville, Maryland.

The full BTF will convene Thursday, September 30, in San Francisco.

The meeting was adjourned at 2:00.

Respectfully submitted,

Mary Burr Paxton

Mary Burr Paxton, Ph.D.

Health and Welfare Canada | Santé et Bien-être social Canada
Health Protection Branch | Direction générale de la protection de la santé

Room B43
Environmental Health Centre
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

July 26, 1993

Dr. Mary Paxton
American Petroleum Institute
1220 L Street, Northwest
Washington, D.C. 20005

Dear Mary,

As requested, I have read over the material you sent us on benzene risk estimation by C. Brown and R. Spirtas as well as the reply by K. Crump. My comments follow.

Spirtas and Brown[1] were asked to review Paxton et al.[2] Specifically, they addressed three issues: (1) the risk-group stratification, (2) the dose-response function and (3) combining data from Akron and St. Mary's locations. K. Crump[3] commented on the differences between analyses by Paxton et al.[2], Crump[4] and Brown and Spirtas[1].

As pointed out by Crump[3], a higher log-likelihood does not necessarily mean a better fit. It only means that in total, the curve is closer to the observed points. However, this does not address potential lack-of-fit, particularly systematic departures of the estimated model from the observed data, and there could be other models with even higher log-likelihoods. One method for assessing lack of fit is to add more parameters to the model. If there is a significant increase in the log-likelihood, then the original model is not fitting the data as well as the new model. It would also be helpful if Crump[3] had provided standard errors for the parameter estimates of the expanded models.

---

1 Brown C. and Spirtas R. (1993) A re-analysis of the leukemogenic risk associated with occupational benzene exposure in th pliofilm cohort. Unpublished.

2 Paxton M., Chinchilli V., Brett S, Rodricks J. (1993) Leukemia risk associated with benzene exposure in the pliofilm cohort. I. Mortality updata and exposure distribution, and II. Risk estimates, to appear in Risk Analysis.

3 Crump K. (1993) Reconciliation of results of three statistical analyses of the risk of benzene exposure based on data from the pliofilm cohort. Unpublished.

4 Crump K. (1993) Risk of benzene-induced leukemia derived from pliofilm cohort: effect of additional follow-up and new exposure estimates. J. Tox. Environ. Health, submitted.

Canada

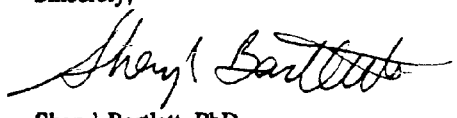
Mike Walker of the Biostatistics Section graphed the five curves fit by K. Crump[3] for cumulative doses up to 50 ppm-years to view the differences for low doses and up to 3000 ppm-years to obtain a more global view. In the first figure, three of the models are quite similar. The exponential curve is somewhat flatter than these three though starts rising quickly at around 1000 ppm-years. The power curve raises quickly from the beginning and is much higher than the other four until 2500 ppm-years when the exponential curve overtakes it. It is puzzling that the power curve is so different from the others especially since the cumulative exposure for cases is not likely to exceed 3000 ppm-years. A graph of data would go a long way to clarify this issue. What about a plot of the relative risk in 500 ppm-year dose intervals? If you can provide this data, we would be happy to do some graphical comparisons. My FAX number is (613) 952-9798.

The method of stratifying risk-group did not lead to appreciable differences in parameter estimates for the exponential model and some small differences for the power function model (Paxton[5], 1993). For all three sets of exposure estimates and for both models, the Spirtas strata yielded higher maximum log-likelihoods. It would be useful to know how the differences in parameter estimates translate into differences in estimated relative risks at specific cumulative exposures.

The only comment we have about the Akron and Combined analyses is that we believe that acute myelogenous leukaemia is the response of interest and would prefer to focus on that response.

I hope these comments are helpful to you. Please give me a call with any questions that arise.

Sincerely,



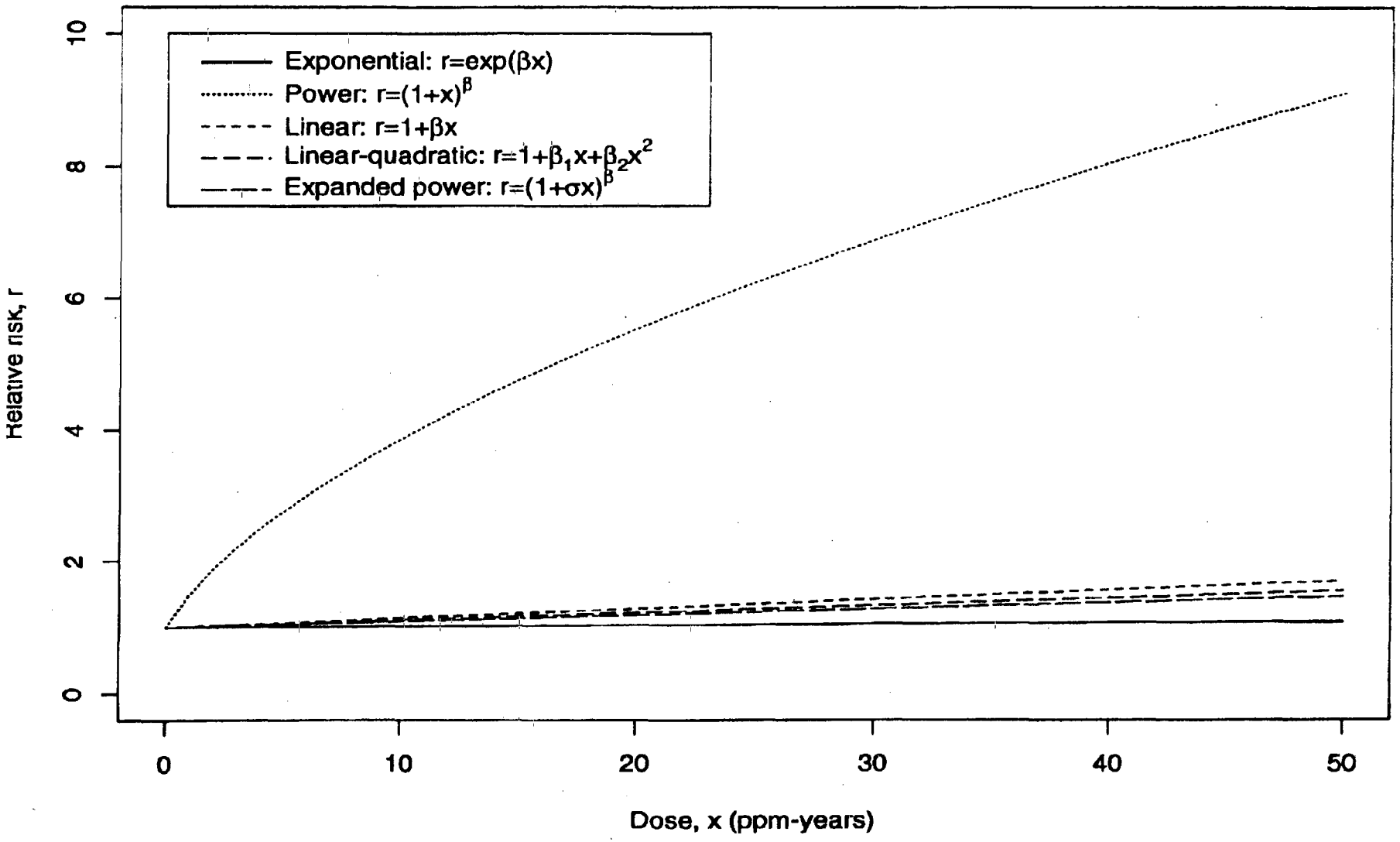
Sheryl Bartlett, PhD
Head, Biostatistics
Section
Environmental Health
Directorate
(613) 954-7787

cc. Dr. D. Krewski

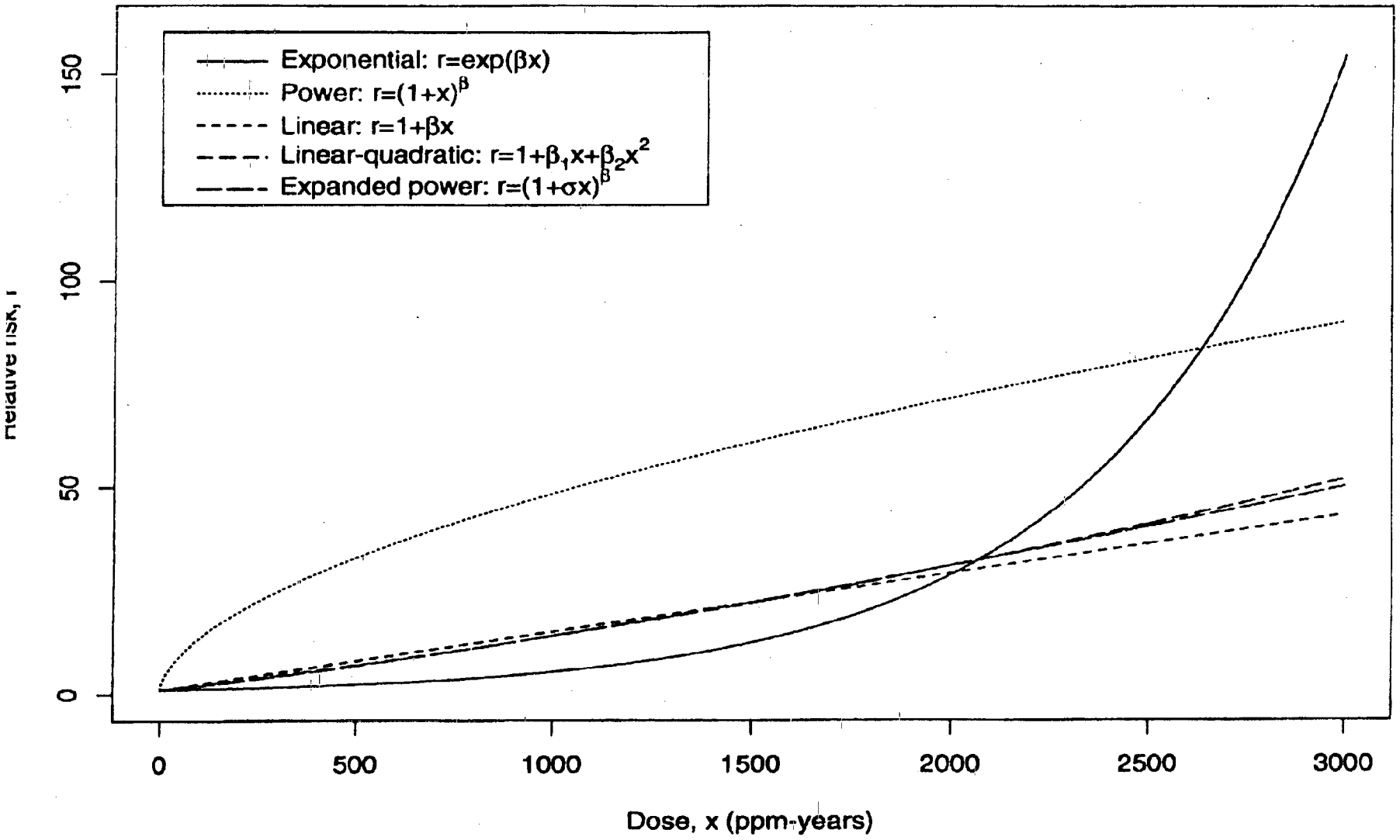
---

[5] Paxton, M. (1993) Exponential vs. Power function as dose-response in proportional hazards model. Unpublished table.

Benzene: relative risk vs. dose



Benzene: relative risk vs. dose



Hematologic Effects of Benzene

Job-Specific Trends during the First Year of Employment among a Cohort of Benzene-Exposed Rubber Workers

Ronald P. Cody, EdD
William W. Strawderman, PhD
Howard M. Kipen, MD, MPH

Hematologic surveillance data from 1940 to 1975 were analyzed for a benzene-exposed cohort of 459 rubber workers. The present analyses are restricted to 161 workers with "preemployment" counts done before exposure and rely on their subsequent counts from the first 12 months of employment. While blood cell counts declined approximately 1000 cells/mm³ over the first 4 months of exposure. Using repeated-measures analysis of variance, workers exposed above the median benzene exposure at the plant had significantly lower average white and red blood cell counts at each month during the first year of work when compared with workers exposed below the median. These decreased counts suggest that clinically detectable bone marrow depression accompanied the onset of work in this plant during the 1940s and support exposure assessments that favor higher benzene levels in the 1940s when compared with subsequent decades. The general utility of repeated-measures analytic techniques for medical surveillance data is also demonstrated by this analysis.

Benzene is a bone marrow depressant that, after significant exposure, may eventually cause peripheral blood cytopenias due to bone marrow depression in occupationally exposed humans.[1-4] The data that demonstrate this in humans are mostly from individual members of industrial cohorts of the 1920s and 1930s or from uncontrolled exposures without even basic protective measures. Exposures were regularly in excess of 100 ppm. Except for individual cases, surveillance of modern cohorts followed for the clinical effects of benzene exposure in refineries and chemical plants have not yielded significant nonmalignant hematologic findings, perhaps because of relatively lower benzene exposures.[5-8] We have retrospectively analyzed hematologic monitoring data from 1940 to 1975 on an Ohio cohort of benzene-exposed rubber workers known as the Pliofilm Cohort. They are acknowledged to have approximately a fivefold excess of leukemia mortality and to be the best cohort upon which to base risk assessments for the malignant effects of benzene exposure.[9,10] These analyses of hematologic effects are not only unique in their depiction of the widespread bone marrow depressant effects of benzene, but provide insight into discrepancies in quantitative estimates of the quantity of benzene exposure that the cohort experienced in its early years.

Our previous publications on the St Mary's Pliofilm cohort[10,11] showed a significant increase in white blood cell (WBC) and red blood cell (RBC) counts of the entire group of surveyed workers in the 1940 to 1948 time period, corresponding to apparently declining benzene exposures in the

From the UMDNJ-Robert Wood Johnson Medical School Department of Environmental and Community Medicine, Piscataway, New Jersey (Dr Cody, Dr Kipen); Rutgers, The State University of New Jersey, Department of Statistics, Piscataway, New Jersey (Dr Strawderman); and the Environmental and Occupational Health Sciences Institute, Piscataway, New Jersey (Dr Kipen).

Address correspondence to: Environmental and Community Medicine, EOHSI, 681 Frelinghuysen Road, PO Box 1179 (Dr Kipen), Piscataway, NJ 08855-1179

0096-1736/93/3508-0776$03.00/0

[illegible] increase in WBC [illegible] manifest as a trend of increasing preemployment (preexposure) blood counts.[12,13] Analysis of each worker's individual experience beginning with a preemployment count seemed to be a useful approach to further explore and define any exposure–blood count relationship.

The main analyses reported here describe blood count depressions in the months following new-onset benzene exposure in previously unexposed workers. Blood counts for groups of individuals are followed prospectively for 12 months after each worker's onset of exposure, in contrast to our previous cross-sectional approaches, which did not account for a worker's prior exposure history. These analyses are based on repeated-measure analysis of variance for counts starting from an unexposed baseline in previously unexposed workers. To minimize interindividual variability, this technique establishes unique baselines for each subject and then serially tracks subsequent measurements. This has not been used previously in serial analysis of medical monitoring data for correlation with toxicant exposure and may provide a valuable approach to future analysis of longitudinally collected medical monitoring data.

Methods

For our analyses, described in greater detail previously,[10,13] we used hematologic surveillance records of 459 rubber hydrochloride workers from the Pliofilm production departments of an Ohio rubber products manufacturer.

For each person, we obtained a cover sheet that showed demographic data and a chronologic work history of his rubber hydrochloride jobs with beginning and ending dates, as well as records of his blood counts. This data set consisted of handwritten medical department records of 17,800 blood counts performed on the 459 men. The date of sampling (from 1940 to 1975) and handwritten results were legible for 17,279 of the counts. Sampling was performed at approximately [illegible] individual each count could be linked through that person's work history to a specific job at a specific time and through that to either of two different exposure estimate schemes: one developed by the National Institute for Occupational Safety and Health[17] and the other for the Occupational Safety and Health Administration by Crump and Allen.[18] Each estimate scheme assigned a certain number of parts per million of benzene to each job for each different year the plant was in operation. In the present studies, only WBC and RBC counts were completely analyzed because they provided the most reliable data for the time period in question before automated analyzers. Platelet counts were not performed on the original sample. All statistical analyses were performed using SAS software.[19]

Further examination of the hard-copy hematologic monitoring records resulted in a total of 161 workers on whom actual preemployment blood tests were performed and recorded on the material provided to us. This is 120 (preemployment) counts more than we used in our original analysis of 17,279 counts. The additional blood counts had been recorded on hiring and personnel forms rather than on "medical data recording sheets" from which we initially transcribed the recorded counts of an individual. We had not routinely abstracted these forms with predominantly personnel information during the initial process of data entry used in our previous studies, and would not have considered these preemployment counts in our previous analyses because they were not linked to a particular job and exposure. The lack of preemployment counts on the remaining 298 St Mary's workers is an unfortunate gap in the available data, which is probably due mostly to the incomplete nature of the combined employment and medical records which we obtained.

Secular Preemployment Trend

To address the issue that secular trends in the blood counts, independ- [illegible] might account for a substantial portion of the previously reported aggregate increases in WBC and RBC counts for the cohort, preemployment WBC and RBC counts were regressed against time for the entire 1940 to 1970 time period and specifically for the 1940 to 1950 time period, where we have previously reported substantial effects.

Blood Count Changes in the First Year of Work

Blood count depressions relative to an unexposed baseline for that worker were sought within the first year of starting work with exposure to benzene. We reasoned that effects of benzene-induced marrow depression on workers' WBC counts would be expected within weeks to months of the onset of exposure and that effects on RBC counts might take longer to manifest because of the circulating RBC's longer lifespan. Confounding by job transfers due to observed low counts was anticipated to potentially diminish any detectable effect of benzene based solely on an analysis from time of onset of exposure. This is dealt with in the subsequent set of analyses.

All workers who actually had a baseline count or had a blood test within 2 months of the start of work were eligible for this analysis, and initially no stratification was done by level of subsequent exposure. The 2-month window is used because only 161 workers have a true preemployment count recorded in our data set. We then computed the number of months (rounded to the nearest month) from onset of exposure to the time of each blood sample during his first year of work. For example, a worker whose first blood test was 2 months from the start of work would not contribute to the mean count at the 0 and 1 month mean counts. When the results of more than one blood sample were recorded in a 1-month period, the mean of all sample results within that month was used. The mean WBC and RBC count across all eligible workers by month was then computed. We restricted this analysis to workers who had five or more blood tests in their first year to

[illegible] first 2 [illegible] employment [illegible] his first Pliofilm job.

This month-by-month comparative analysis was applied exclusively to the 1946 through 1949 time interval. This interval was chosen to maximize the number of eligible subjects (new hires) and minimize the number of years over which data were examined. Large numbers of workers were hired in this period, apparently because of the combined effects of the end of World War II and the rapid expansion of production with a tripling of plant capacity,[15] and we were thus able to identify a relatively large number of workers with baseline counts. Similarly, we chose the 4-year interval because a more narrow interval would not provide sufficient new workers to permit detection of significant trends. An overly broad interval might result in considerable bias as well as heterogeneity of the anticipated effect because late hires would be exposed to lower benzene exposure than would earlier hires if, in fact, exposure was declining in this period, as we have previously suggested.

Regression analysis was used to test for trends in WBC and RBC counts in the first year of work. The entry criteria of five counts or more in the first year and the "time window of enrollment" were varied in a sensitivity analysis to determine their effects on the resulting blood count versus time curves.

Exposure–Blood Count Relationships in the First Year of Work

The primary goal of this extended analysis of the Pliofilm hematologic data was to explore more thoroughly any relationship between exposure and blood count distinct from the relationship between blood counts and time. The aim was to account for effects of secular confounders and job transfers due to effects of previous exposure. Because of uncertainty about inhaled and dermal benzene ex-

be[illegible] [illegible]ntin[illegible] [illegible] [illegible] part[illegible] time. How[illegible] [illegible]sis of employee records [illegible] that almost 75% of the workers [illegible] were hired between 1946 and [illegible] changed specific job classifications (and thus potentially benzene exposure) at least once in the first year. This is a probable explanation of why analyses by specific job classification here and in earlier analyses failed to demonstrate consistent patterns in blood counts (unpublished data). Because of the frequent changes in specific job classification, a new approach was devised.

For each of the time periods from 0 months to 12 months in our previous analyses, the median benzene exposure as estimated by Crump was computed.[10,18] Based on job assignment and year, the median exposure, as estimated by Crump, was computed for all the workers who were sampled at each of the 0 to 12 month periods. The median exposures ranged from a low of 30 ppm (month 0) to a high of 54 ppm (months 4 and 5). The sampled workers were then dichotomized into those whose estimated job/exposure was below the median and those who were above the median for each month postemployment. A two-way analysis of variance (time by exposure category) with time as a repeated measure factor was performed. Blood counts for each level of exposure were also compared at each month using t tests. To demonstrate the robustness of the approach, the analysis was repeated with changes in the two parameters discussed above: the time window and the minimum number of blood tests in the first year required for inclusion. A narrow window of 1948 to 1949 and a wide window of 1946 to 1955 were used. We also varied the minimum number of blood tests required on each worker in the first year of work from 3 up to 11. Identical first-year analyses were also performed using exposure stratifications based on those estimated by Rinsky et al.[15,16]

This same analysis was performed on workers hired between 1955 and 1960 as a comparison to the earlier, probably higher exposure, time pe-

Results

Secular Preemployment Trend

A regression of the 161 preemployment WBC and RBC counts against time over the period 1940 to 1966 showed an almost random scatter. The r^2 values for WBC and RBC versus time are .0168 ($P = .10$) and .0412 ($P = .01$), respectively. When the pre-1950 time period is examined, where the strongest correlations between time and all blood counts was previously demonstrated,[10,11] the number of analyzable counts decreases to 93. The r^2 values are .044 ($P = .04$) and .046 ($P = .04$) for preemployment WBC and RBC versus time, respectively.

Determination of a Depressant Response to Benzene Exposure in the First Year of Work

Figure 1 shows aggregate plots of mean WBC count versus the number of months in the plant during each analyzable worker's first year in the plant. Only subjects hired between 1946 and 1949 with a blood test performed either before the start of work or within the first 2 months of employment are included. Thus, for month 0 (true preemployment) the number of workers is 34, for month 1 it is 57, and for month 2 it is 61. Subsequent months, by definition, all have less than or equal to 61 workers, ranging from 50 to 60 in months 3 to 6, 40 to 50 in months 6 to 10, 34 in month 11, and 25 in month 12. Examination of the plot for WBC count shows declining counts for the first 6 months, followed by a slight rise back toward the baseline. No job title restriction or classification is employed in the analyses.

Regression analysis on the first 4 months of data shows that the decrease in WBC count was statistically significant ($r^2 = .79$, $P = .04$). Including the first 6 months of data results in an r^2 value of .51 ($P = .07$). The lower r^2 value for the 6-month period is likely a result of the higher value at

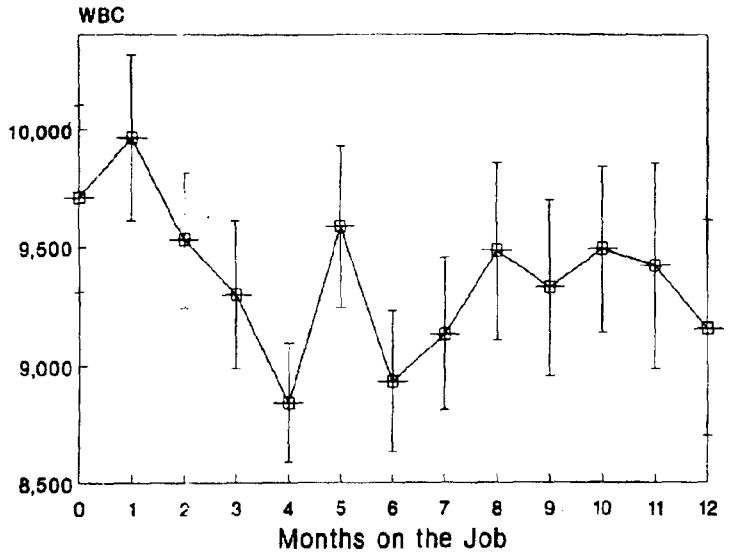


Fig. 1. White blood cell (WBC) count versus months on the job. For workers beginning work from 1946 through 1949 the mean of all WBC values for a given number of months after beginning work is shown. At month 0 (true preemployment), 34 workers were sampled. After 1 month on the job, 57 workers were sampled (23 for the first time); at 3 months $n = 61$. Error bars = ±1 SE.

5 months. The data for months 6 through 11 show a statistically significant increase (r^2 .65, $P = .05$).

Similar analyses for RBC count failed to show any consistent or statistically significant pattern.

Relating Exposure to Blood Count Changes

Although it is interesting to show a decline in WBC count for the first 4 to 6 months of exposure, we sought stronger evidence of a direct exposure–blood count relationship, taking account of differences in estimated exposure between workers. Figure 2, A and B, clearly shows the effects of exposure when it is dichotomized as above or below the median for people sampled in that month. The median estimated exposures ranged from 40 to 54 ppm except for month 0.

In the case of WBC, the high exposure means are consistently below the means of the low exposure group, except for months 0 and 12. A two-way analysis of variance with repeated measures showed that the mean WBC count was highly significantly different as a function of the exposure level ($F = 12.31$, $P = .0005$). The plot of RBC count versus months on the job shows an even more impressive effect. The high exposure group is consistently below the low exposure group for the entire time period. Analysis of variance for RBC count showed a significant exposure effect ($F = 61.03$, $P < .0001$). t tests conducted for each of the months 0 through 12 showed a significant difference for WBC count at months 1 and 10 and for RBC count at months 1 and 4 through 12. The RBC count difference at time zero is not statistically significant ($P > .05$). Because the baseline (month 0) RBC count in the high exposure group was lower than in the low exposure group, we reanalyzed the RBC count by month relationship with all values in the high exposure group adjusted by the baseline difference. The effect of this adjustment was to reduce the overall differences between the high and low exposure groups. The effect of exposure in the two-way analysis of variance was still significant however ($P = .03$). Examination of the adjusted values suggests that the RBC count differences occur in the later months. Dividing the 12 month period in half, 0 to 6 months versus 7 to 12 months, we see no exposure differences in the 0 to 6 month period ($P = .88$) compared with a highly significant difference in the 7 to 12 month period ($P = .004$).

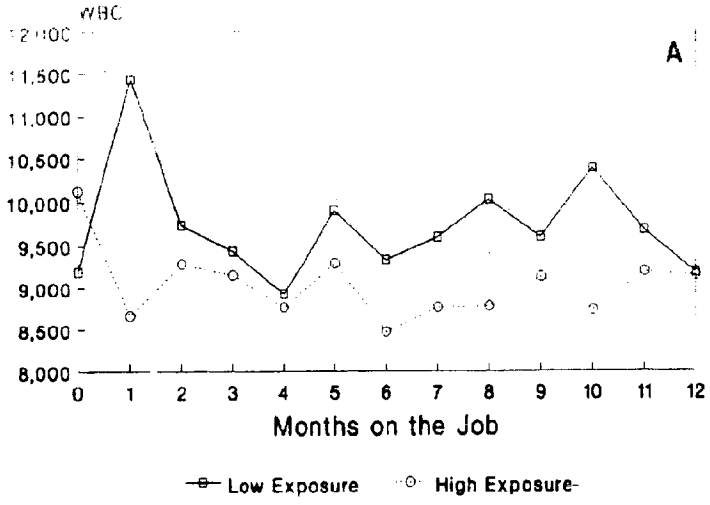
A similar baseline adjustment was not made in the WBC count by month analysis because the high exposure group had a higher WBC count at baseline and an adjustment would have increased an already highly significant difference. We present the more conservative nonadjusted analysis.

By narrowing the time window to include only 1948 and 1949 hires, the exposure effects could no longer be seen. However, this narrow window reduced the number of workers to between 10 and 15 for most months. Choosing a larger window, 1946 to 1955, showed effects similar to those of the 1946 to 1949 window. Varying the requirement for a minimum number of blood tests in the first year of work showed essentially the same exposure effects for both WBC and RBC counts as the five-test minimum discussed above. One further analysis was performed using workers hired between 1955 and 1960. Exposure effects seen in the earlier time windows were not apparent on the WBC and RBC counts versus months on the job plots.

The analyses were rerun using the 1946 to 1949 cohort, substituting exposure estimates made by Rinsky et al[16] in place of the Crump exposure estimates. When this was done, no separation in WBC or RBC count by median exposure category could be detected.

Discussion

These data strongly support the use of hematologic surveillance data to improve understanding of the benzene exposures of the Pliofilm cohort, and should eventually provide improved risk assessments for benzene leukemogenesis based upon this cohort. Yet the use of blood counts such as these are not a complete or ideal tool for the retrospective inference of benzene exposure. Theoretical problems include the insensitivity of the marrow at lower doses and potential



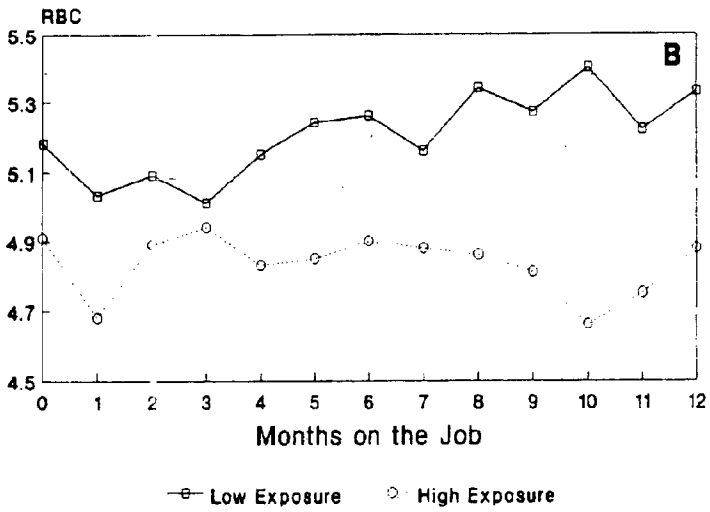


Fig. 2. Plots of mean WBC (A) and RBC (B) for workers beginning work from 1946 to 1949 after a specified number of months at work divided according to whether an individual worker was estimated to be above or below the median exposure (approximately 40 ppm) for that month at the time of sampling. The difference between high and low exposure groups calculated by two-way analysis of variance with repeated measures was highly significant ($P < .0005$) for WBC and RBC ($P < .0001$).

resistance to an effect in selected workers. Recovery of function over time as exposure decreases is also problematic for interpretation. Practical difficulties include the clinical nature of the data collection, the sketchiness of protocol details, uncertainty about laboratory personnel changes in those performing counts, procedural changes, and the admixture of surveillance and clinically indicated counts without labeling differences. Yet on the positive side, blood count depression is a relatively specific effect of benzene exposure in an exposed cohort, especially as this cohort is said to have not had exposure to other hematotoxins.[14] We have previously shown that WBC counts are inversely correlated with estimated benzene concentrations for the entire cohort from 1940 to 1948.[10,11]

The present repeated-measures analysis of variance demonstrated consistent physiological response to benzene exposure within individuals over a defined exposure period, where secular effects are minimal. We sought to analyze workers who were not exposed to high concentrations of benzene before they started work in the Pliofilm plant and came under hematologic surveillance. This may not have always been the case because it is believed that some of the workers starting in the St Mary's Pliofilm operation that we studied may have worked previously in benzene-exposed jobs. To the extent that was true, it would have biased the results of the present analyses toward the null, making it more difficult to show decreased blood counts in the first several months of work, because our baselines would not truly reflect unexposed values and would possibly reflect already pathologically depressed bone marrow. This was likely less of a problem with the large number of truly new workers hired in the postwar expansion than in the pre-1946 workers who were excluded from these analyses.

To verify the observed decrease in WBCs in the first 4 to 6 months of employment, we ran the analyses with different constraints. We varied the number of blood tests we required each worker to have to be included in the analysis from 3 up to 11. The same basic "V" shape emerged, regardless of the setting of this parameter. When more counts were required for a worker's inclusion, the scatter became greater because of the smaller number of workers included. For example, when we required only three counts per worker, there were 81 person-means that were averaged. When we required 9 tests in the year per worker, the 2-month mean was based on 31 workers. The other parameter of interest was the time window of 1946 to 1949. We varied this from a low of 1 year to a high of 10 years. In each case, we could identify a decrease in

the first 4 to 6 months, but not longer.

There are a few potential explanations for the apparent increase in WBCs over months 6 to 11. It could possibly be due to a physiologic adaptation to continued benzene exposure, although there is little biologic basis to support such an adaptation. More likely it could be attributed to some bias in the data, such as sampling bias due to removal from exposure of workers with more severely affected counts. For example, there was a policy that workers with low counts were to be transferred to other areas in the plant where there would be less exposure to benzene or they were given medical leave.[20]

The potential importance of a sampling bias such as this is underscored by the 75%-rate of job change in the first year of hire. Any bias due to job changes for the purpose of reducing benzene exposure would again bias away from the significant blood count depressions we report and toward a rising trend in worker's counts as time passed. Another possible reason for an increase in the later months is that regardless of the date of hire (from 1946 to 1949), there might, on average, be a lower exposure in the last 6 months compared to the first 6 months if the trend toward lower benzene exposure in the entire 1946 to 1949 time period is real. Although such changes did occur from time to time, one would not expect them predictably to be of great magnitude on an ongoing basis for each new hire, and this is not a likely explanation for the effect we have demonstrated.

The approach that makes a median cut of exposure for all workers who contributed to the monthly mean resulted in a successful separation of the WBC and RBC versus months on the job curves. We see this as evidence that those workers in the higher exposure areas had consistently lower counts than did their lower exposed colleagues. The differences at months 1 and 10 were significant for WBC count ($P < .05$), but more important is the consistency of the difference over the extended initial exposure period from 1 month to 11 months.

No consistent trends were observed in the RBC count [illegible] the job curves. Possible explanations lie in the 120-day lifespan of the RBC, creating a much more complex toxicokinetic interaction with benzene exposure, job change, and sampling frames compared with that of the mostly more short-lived WBC. In addition, there is some indication that blood transfusions may have been used to treat some "anemic" workers. This would probably not impact WBC counts, except possibly immediately after a transfusion, but would clearly wreak havoc with a sequential repeated-measures analysis of workers' blood cell counts.

It was somewhat of a surprise to see the dramatic separation in the RBC counts by exposure category because the original plot of RBC counts by months on the job failed to show any consistent trends. A possible explanation for this is that the RBC count remains fairly stable for some months at a specific exposure level, eventually declines, and then remains persistently low in higher exposed workers once they have been moved to a lower exposure environment. This is again consistent with the kinetics of RBC production and senescence, in that red cell life span is 120 days, whereas the life span of granulocytes is only a few days.

There are two likely explanations for the absence of demonstrable effects in the 1955 to 1960 hiring period: 1) there were very few hires between 1955 and 1960 (approximately 10 workers per monthly mean) and 2) because of the reduced range of exposures in these later years due to engineering control, the separation between high and low exposure was not great enough to show a difference. The inability of Rinsky estimates of exposure to discriminate between high and low exposed individuals even in the 1946 to 1949 period is consistent with our previously published results, which demonstrated strong WBC count versus Crump relationships and weak or nonexistent relationships between Rinsky exposures and WBC count.[11] We believe this is likely due to the narrow range of exposure permitted in the Rinsky [illegible] and the [illegible] period classes are more heterogeneous in their membership's actual exposure (misclassification).

Although the correlations between preemployment WBC and RBC counts and time are both statistically significant for 1940 to 1950 ($P < .05$), they are quite small ($r^2 = .044$ and .046, respectively) and do not represent a meaningful upward time trend in the preemployment counts for 1940 to 1950, nor for the entire 1940 to 1975 period. This can be seen when their magnitude is compared with the r^2 values of all WBC and RBC counts versus time (r^2 for WBC count versus time = .88; r^2 for RBC count versus time = .53 for the 1940 to 1948 time period).[10,11]

Conclusions

Using different approaches to retrospective exposure assessment, we have been able to demonstrate repeatedly a relationship between various surrogates of benzene exposure and WBC counts in the workers from the St Mary's Pliofilm cohort. These surrogates include duration of work in the plant, calendar year, and job designation. RBC count effects appear to be more complex when time factors are introduced, but were clearly present for analyses stratified by job-related exposure. We have also clearly demonstrated the small size of any secular trend in preemployment counts.

These results again suggest that the Crump et al. exposure estimates were more realistic than were the Rinsky estimates. They also begin to document that newly hired workers as a whole in this facility experienced clinically detectable bone marrow depression likely due to benzene exposure. These data further suggest that sensitive surveillance systems need to stratify workers based upon exposure to facilitate detection of effects, which may only be significant in those with higher exposures. Many of the limitations of this data set are due to its incomplete nature and poor documentation of the actual data collection protocol. We hope that currently

[illegible] and should [illegible] job's initiation.

Future studies of this cohort should concentrate upon tracking of individual workers from job to job. It is recognized that the small number of data points in the early years of the cohort will always limit analysis of the present data set for temporal changes of benzene effects on blood cell counts.

Acknowledgments

We thank Dr Daniel Wartenberg, Dr George Rhoads, Derrick Petersen, Dr Sandra Mohr, and Dr Bernard Goldstein for advice and assistance. We are grateful to Patricia Hutty for expert assistance with manuscript preparation. These analyses were funded under a contract from the American Petroleum Institute and Dr Kipen also received support from NIEHS Center Grant ES05022.

References

1. Goldstein BD. Hematotoxicity in humans. *J Toxicol Environ Health.* 1977;2 (suppl):69–105.
2. Goldwater LJ. Disturbances in the blood following exposure to benzol. *J Lab Clin Med.* 1941;26:957–973.
3. Greenburg L, Mayers MR, Goldwater L, Smith AR. Benzene (benzol) poisoning in the rotogravure printing industry in New York City. *J Ind Hyg Toxicol.* [illegible] benzene poisoning [illegible] *Br J Ind Med.* 1971;28:296–302.
5. Collins JJ, Connor P, Friedlander BR, Easterday PA, Nair RS, Braun J. A study of the hematologic effects of chronic low-level exposure to benzene. *J Occup Med.* 1991;33:619–626.
6. Tsai SP, Wen CP, Weiss NS, Wong O, McClellan WA, Gibson RL. Retrospective mortality and medical surveillance studies of workers in benzene areas of refineries. *J Occup Med* 1983;25:685–692.
7. Townsend JC, Ott MG, Fishbeck WA. Health exam findings among individuals occupationally exposed to benzene. *J Occup Med.* 1978;20:543–548.
8. Fishbeck WA, Townsend JC, Swank MG. Effect of chronic occupational exposure to measured concentrations of benzene. *J Occup Med.* 1978;20:539–542.
9. Austin H, Delzell E, Cole P. Benzene and leukemia: a review of the literature and a risk assessment. *Am J Epidemiol.* 1988;127:419–439.
10. Kipen HM, Cody RP, Goldstein BD. Hematologic effects of benzene: a thirty-five year longitudinal study of rubber workers. *J Toxicol Ind Health.* 1988; 4:411–430.
11. Kipen HM, Cody RP, Goldstein BD. Use of longitudinal analysis of peripheral blood counts to validate historical reconstructions of benzene exposure. *Environ* [illegible] *Ind Health* 1989;5:1153–1157.
13. Kipen HM, Cody RP, Goldstein BD. Hematologic effects of benzene: a thirty-five year longitudinal study of rubber workers (letter). *J Toxicol Ind Health* 1989;5:1156–1158.
14. Infante PF, Rinsky RA, Wagoner JK, Young RJ. Leukemia in benzene workers. *Lancet.* 1978;ii:76–78.
15. Rinsky RA, Young RJ, Smith AB. Leukemia in benzene workers. *Am J Ind Med.* 1981;2:217–245.
16. Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. Benzene and leukemia: an epidemiologic risk assessment. *N Engl J Med.* 1987;316:1044–1050.
17. Rinsky RA, Smith AB, Hornung R, Filon TG, Young RJ, Okun AH, Landrigan PJ. Benzene and leukemia: an epidemiologic risk assessment. *USDHEW, PHS, CDC.* NIOSH 1987.
18. Crump K, Allen B. Quantitative estimates of risk of leukemia from occupational exposure to benzene. *Occupational Safety and Health Administration 1984;Docket H-059B.*
19. Cody RP, Smith JK. *Applied Statistics and the SAS Programming Language,* third ed. Amsterdam: Elsevier North-Holland; 1991.
20. Wilson RH. Benzene poisoning in industry. *J Lab Clin Med.* 1942;27:1517–1521.

Oh, To Be Rich

"I never dreamed when I married a Rockefeller that I would wind up spending half my time asking people for money." (Sharon Rockefeller on her fund-raising duties as president of a Washington PBS station.)

From Overheard. *Newsweek.* 1993;122:1, p 13.