Letters to the Editor

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Evidence of Excess Cancer Mortality in a Cohort of Workers Exposed to Polychlorinated Biphenyls

To the Editor: To further explore previously reported excesses in cancer-specific mortality in workers who have been occupationally exposed to polychlorinated biphenyls (PCBs), Kimbrough et al[1] reported a retrospective cohort mortality study of 7075 male and female workers exposed to PCBs during the capacitor-manufacturing process at two General Electric (GE) plants in upstate New York. Kimbrough et al concluded that the study results failed to show any association between occupational PCB exposure and cancer-related mortality. We interpret their study findings differently. Although limitations in the study approach (outlined below) tend to dilute any excesses in cancer mortality resulting from PCB exposure, the findings *still* suggest a relationship between PCB exposures and excess cancer in humans.

First, this study demonstrated once again that modern industrial workers are healthier than the general population. Known as the "healthy worker effect" (HWE), this bias results in standardized mortality ratios (SMRs) that are considerably less than expected (eg, SMR < 90) for all mortality and cancer mortality[2–4] when workers are compared with a general population. Consistent with the HWE bias, Kimbrough et al found that all cancer mortality was significantly below that expected in male hourly workers (SMR = 81), male salaried workers (SMR = 69), and female salaried workers (SMR = 75). However, despite the HWE, female hourly workers had elevated SMRs for all cancer mortality (SMR = 110) and for three (intestinal [SMR = 157], rectal [SMR = 169], and melanoma [SMR = 144]) of the six cancers of a priori interest. Melanoma mortality was also elevated for male hourly workers (SMR = 130). Although the elevations in cancer-specific SMRs did not achieve statistical significance, they were consistent with elevations found in other studies of PCB-exposed workers.[4–6] Given the HWE, these elevations are particularly noteworthy.

Second, when looking at cancer mortality rates, it is customary to include a latency period to adjust for the time lag between exposure and clinical evidence of disease (or, in this study, cancer death).[7] However, Kimbrough et al included a latency period only for all cancer mortality and for intestinal cancer mortality among female hourly workers. When female hourly workers with at least 20 years of follow-up were evaluated (ie, with a sufficient latency period), the SMR for all cancers increased from 110 to 117* ($P = 0.058$). The SMR for intestinal cancers increased from 157 to 189, thus becoming statistically significant ($P < 0.05$).

Third, proper assessment of exposure should have accounted for the dates (calendar years) of employment, the intensity of exposure for each type of job, and the specific Aroclor PCB used. For example, in the earlier years of plant operation (1946 to 1954), any exposures would have been to Aroclor 1254, whereas exposures in the 1970s would have been to the less toxic Aroclor 1016.[8,9] Industrial hygiene procedures at the plant probably improved over time as well. Therefore, length of employment alone was an inadequate surrogate of exposure and a likely source of exposure misclassification bias that could have led to an underestimate of effect and distortion of exposure-response relationships.

Kimbrough et al assembled the largest cohort of hourly PCB workers studied to date, including a large number of female workers. However, most of the hourly workers had exposures that were comparable with exposures among the general US population. From the data provided, it appears that approximately one fourth of the person-years contributed by male hourly workers, and approximately 10% of the person-years contributed by female hourly workers, were contributed by workers who had been employed for at least 6 months in high-exposure jobs. Only 112 (3.8%) male hourly workers and 12 (0.5%) female hourly workers were employed exclusively in high-exposure jobs. The majority of the hourly workers never worked in high-exposure jobs. Only a small percentage of hourly workers had evidence of PCB exposure that was appreciably greater than that of the US population. Therefore, relatively small elevations in cancer mortality would be expected for this group, even if PCB cancer potency were alarmingly high.

Fourth, although one of the goals of this study was to evaluate six specific cancers of a priori interest (ie, melanoma, liver, rectal, gastrointestinal tract, brain, and hematopoietic cancers), the study focused almost entirely on all cancer mortality. In planning the study, the researchers should have realized that the size and age distribution of the hourly work-

*Note: There is an error in Table 6 of the study report. The SMR for "all cancers" in female hourly workers with ≥20 years' latency over all lengths of employment should be "117," not "96" as reported.

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TABLE 1
Calculations of Statistical Power to Detect Varying Standardized Mortality Ratios (SMRs) for the Six Cancers of A Priori Interest

Cancer	Expected Number	SMR = 150	SMR = 200	SMR = 300
Male hourly workers				
Melanoma	3.8	12%	35%	80%
Liver	2.5	9%	24%	62%
Rectum	3.4	14%	37%	80%
GI*	14.0	36%	85%	100%
Brain	5.1	15%	44%	89%
Blood	14.1	37%	86%	100%
Female hourly workers				
Melanoma	2.0	8%	22%	55%
Liver	2.2	12%	28%	65%
Rectum	1.6	10%	22%	52%
GI*	12.7	36%	83%	100%
Brain	3.7	11%	32%	78%
Blood	10.5	32%	77%	100%

* GI, Gastrointestinal tract.

force would result in poor statistical power to evaluate the cancers of a priori interest. Table 1 shows the expected number of deaths for each of these cancers for male and female hourly workers and the resulting statistical power for SMRs from 150 to 300, using the study's method for determining statistical significance (ie, the 95% confidence interval). Because of the biases in the study and the low percentage of highly exposed workers, an SMR of 150 might be as high as would be expected for these cancers. As seen in Table 1, for an SMR of 150, the study had less than a one in five chance of obtaining a statistically significant result for four of the six cancers. Given the sample size and the numbers of expected cancers, the study did not have sufficient statistical power (>80%) to detect an SMR of 300 for most of the cancers of interest.

Kimbrough et al examined and reported SMRs for categories of increasing length of employment and years of latency only when ". . . there was an elevated total SMR with two or more observed deaths and for which the lower boundary of the 95% confidence interval (CI) was 90 or above."[1] The impact of this decision can be seen in Table 2. Given

TABLE 2
Number of Observed Deaths and the SMR Required for ≥90 as the Lower Limit of the 95% Confidence Interval

No. of Deaths	SMR
2	744
3	437
4	331
5	278
6	245
7	224
8	209
9	197
10	188
11	180
12	174
13	169
14	165
15	161
16	157
17	154
18	152
19	150

the biases mentioned previously, it is understandable that just one of the six a priori cancers met these requirements. Furthermore, accounting for a latency period should be a prerequisite for calculating any adult cancer SMR. Otherwise, the SMR is biased toward or below 100. For all six cancers of a priori interest, analyses accounting for latency and for length of employment should have been done and presented, allowing the reader to decide whether or not the results were meaningful.

In summary, the Kimbrough et al study suffered from HWE bias, failure to account for latency, exposure misclassification, potentially insufficient dosage differences between exposed and comparison groups, and poor statistical power. Nevertheless, the study did find excesses in three of the six cancers of interest. Future research should include analyses made with internal comparisons (to minimize biases from HWE) of sufficient numbers of highly exposed workers, as well as analyses accounting for cancer latency periods. This might require an additional decade or more of follow-up on this cohort and the addition of exposed workers from other PCB plants (eg, workers at the Massachusetts plant included in Brown[5]), before a definitive statement about the association between PCB exposure and specific cancers can be made.

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To the Editor: We were glad to see the recent article on mortality among workers exposed to polychlorinated biphenyls.[1] At a time when fewer and fewer companies are funding occupational epidemiological studies, we commend the sponsor, General Electric, for this initiative. The completeness of case ascertainment was outstanding. In addition, this report was a model of clear writing and clear display of results.

However, two issues, sample size and exposure, raise significant concern. First, the study population was very small. Over 7000 workers contributed over 200,000 person-years of observation, more than in prior PCB mortality studies. But when attention is restricted to those workers with high exposure, moderate- to long-duration employment, and adequate person-time after a latency period, the numbers are dramatically reduced. For example, only one third of the cohort worked for longer than 5 years. (We note in passing that Table 2, the source of these data, shows 7178 workers in the upper panel and 7075 workers in the lower panel, a disparity the authors do not explain.) Similarly, less than one fourth of the cohort was classified as highly exposed, and the median period of high exposure was less than 2 years. Although data are not presented to support exact calculations, it appears that fewer than 10 cancers of any type, and more typically fewer than three, were expected in any sex-salary stratum with high exposure, more than a year of employment, and more than 20 years of latency. Could this be why the article is conspicuously silent on the issue of statistical power?

The problem of small number could have been addressed. A company as large as GE presumably had other capacitor plants and could have supported a multisite study. Alternatively, an industry-wide study would have been informative, as we have seen in the semiconductor, rubber, petrochemical, automobile, and other industries. Indeed, we wonder why restricting a cancer mortality study to only two plants should not be viewed as a willful effort to avoid a positive finding.

The second major concern lies with exposure assessment. As with many historical cohort studies, the authors created a matrix to characterize each individual's exposure. If the designated "high exposure" jobs did not actually entail high exposure, then misclassification occurred and could have introduced substantial bias toward the null. Were the exposures accurately assessed?

The article makes reference to a readily available way to validate the exposure assessment: serum PCB levels obtained during the 1970s on a sample of several hundred cohort members. Where are these measurements? Did the authors check their exposure assignments against the past serum measurements? If not, why not? If so, why was this comparison not reported?

Another difficulty with exposure in this article is the admixture of various types of PCBs. More carcinogenic forms, such as Aroclor 1254, were used in the early years, and less carcinogenic forms, such as Aroclor 1016, were used later. By combining the two rather than focusing on the early exposures, the authors may have obscured a true effect.

Overall, these concerns significantly limit the conclusions that can be drawn from the study. The authors conclude that their results "would suggest a lack of an association." This conclusion is overstated. These results do offer some evidence that PCBs are not highly potent carcinogens causing relative risks above 10 or 20, a conclusion that was already fairly well established. But they provide little reassurance that PCBs do not double or triple the risk of some cancers after significant exposure.

For this reason, we were especially concerned that the results of the study were not interpreted and presented more carefully. The authors might have noted, in their conclusion, that PCBs are serious health hazards irrespective of carcinogenicity,[2] with effects that include decreased birth weight,[3] neurodevelopmental abnormalities,[4–8] and interference with both estrogen[9] and thyroid[10] hormone function. Accordingly, even negative findings in a cancer study would not reassure us of safety. That omission in the *JOEM* article, in turn, may have contributed to overtly misleading journalistic coverage, such as the *New York Times* headline: "Study Finds Little Risks [sic] From PCB's."[11]

The authors of this study note that our knowledge of PCB health effects is "limited." On the path to a more complete understanding, the current study results represent a great leap sideways.

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