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.

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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The Authors Reply: Thank you for giving us the opportunity to reply to the letters by Bove et al and Frumkin and Oris commenting on our mortality study of PCB-exposed capacitor workers.[1] We disagree with the statement by Bove et al that "... limitations in the study approach tend to dilute any excesses in cancer mortality resulting from PCB exposure. . . . " These assertions are speculative and not supported by the data. Although some degree of misclassification in observational studies is unavoidable, it is usually not possible to determine whether this misclassification is differential or non-differential. Furthermore, non-differential misclassification does not always result in bias toward the null hypothesis. Neither the type nor the effect of the misclassification can be determined by Bove et al. In our article, we do, however, discuss at length the measures taken to limit misclassification, and we feel strongly that we were successful in doing so.

Bove et al assert that the healthy worker effect (HWE) results are an underestimate of the SMRs for all-causes mortality and cancer mortality. This is partially true. The HWE is most pronounced for cardiovascular deaths and thus affects all-causes mortality.[2] It has much less of an effect on cancer deaths.[3]

The presentation by Bove et al of the all-cancers SMRs and selected cancer-specific SMRs without confidence intervals (CIs) gives incomplete information and is misleading. Had the confidence intervals been reported, the lack of significance for these SMRs would have been immediately obvious to the reader. Bove et al selected the female hourly employees' all-cancers SMR of 110 (95% CI, 93 to 129), intestinal cancer (SMR = 157; 95% CI, 96 to 242), rectal cancer (SMR = 169; 95% CI, 46 to 434), melanomas (SMR = 144; 95% CI, 30 to 421), and melanomas in male hourly employees (SMR = 130; 95% CI, 42 to 303). Notably absent from this list of SMRs considered by Bove et al are the male hourly SMRs for intestinal and rectal cancer (SMR = 57; 95% CI, 25 to 112; and SMR = 87; 95% CI, 18 to 255, respectively).

Bove et al suggest that the male all-cancers SMRs of 81 (hourly employees; 95% CI, 68 to 97) and 69 (salaried employees, 95% CI, 52 to 90) are largely due to the HWE. A careful examination of Table 4 in our article suggests that the statistically significantly low all-cancers SMRs in both the hourly and salaried males result primarily from the lower than expected lung cancer SMR (for hourly workers: 42 observed/54.5 expected; SMR = 77; 95% CI, 56 to 104; and for salaried workers: 12 observed/29.6 expected; SMR = 41; 95% CI, 21 to 71).

The statement by Bove et al that these elevations were consistent with elevations found in other studies of PCB-exposed workers is not correct.[4–6] In addition to the three studies cited by Bove et al, there is the Bertazzi cohort and its update by Bertazzi et al[7] and Tironi et al.[8] The results of the Brown[4] and Sinks et al[5] studies are inconsistent with each other. The Loomis et al[6] study of utility workers, not capacitor workers, did report an elevation in melanomas in some subsets of the cohort that were presumed to have had exposure to PCBs while working outdoors. Exposure to sunlight was not adequately accounted for by Loomis et al.[6] Brown and Jones[9] and Brown[4] found an excess of liver and rectal cancers. Neither Sinks et al[5] nor Loomis et al[6] reported such increases. Sinks et al[5] reported a nonsignificant elevation in brain and nervous system cancers. Neither Brown and Jones,[9] Brown,[4] Bertazzi et al,[7] or Tironi et al[8] found an elevation in brain cancer. These inconsistencies were discussed in our article.

Bove et al state that we only included a latency-period analysis for all cancers and for intestinal cancer. This was done primarily because of space limitations. Cumulative exposure and latency tables were computed and evaluated for many other causes of death, including all of the cancers of interest. The interpretation by Bove et al that the intestinal cancer SMR increases to a significant level for women with ≥20 years of latency ignores the importance of examining the trend associated with latency and length of employment. Furthermore, it might be worth noting that for women employed for 10

years or longer with a latency period ≥20 years, the SMR was 100. The individual category–specific SMRs cannot be interpreted as meaningful without examination of the trend across cumulative exposure categories. Although the intestinal cancer SMR for latency ≥20 years was significantly elevated, there was no significant trend indicating an increase in risk with cumulative exposure or latency, as discussed in our article. Furthermore, comparison with the regional population resulted in a much-reduced SMR (SMR = 120; 95% CI, 74 to 186) for intestinal cancer in female hourly workers. The regional comparison is more representative because higher rates of intestinal cancer are observed among the white population of the northeastern part of the United States.

Bove et al raise concerns about our exposure assessment. Several factors need to be recognized when assessing the propriety of our exposure assessment and our use of length of employment as a surrogate of exposure. Workers accumulate PCB body burdens over time, which persist for many years even after their occupational PCB exposure is discontinued. To suggest that PCB body burdens among capacitor workers were comparable to those found in the general population is unjustified and is not supported by previously published data.[10–13] The fact that workers in capacitor plants had significantly higher body burdens than the general population has been demonstrated in other capacitor plants.[14] As reported in our article, average serum PCB levels in the general population between 1976 and 1979 were 5 to 7 parts per billion (ppb; μg/L).[14] Geometric mean serum PCB levels in GE workers in 1979 (2 years after PCBs were no longer used) were 277 ppb (μg/L) reported as Aroclor 1242 and 55 ppb (μg/L) reported as Aroclor 1254. In 1983, 5 years after termination of the use of PCBs, geometric mean serum levels were 116 ppb (μg/L) for Aroclor 1242 and 34 ppb (μg/L) for Aroclor 1254. In 1988, the geometric mean serum PCB levels were 90 ppb (μg/L) quantitated as Aroclor 1242 and 32 ppb (μg/L) quantitated as Aroclor 1254.[15] Workers preferentially retained the more persistent congeners so that the gas chromatographic pattern of their body burden gradually approached that observed in the general population, with primary retention of the more highly chlorinated, poorly metabolized congeners.[12] The half-lives of the major PCB congeners retained in these workers were as follows: for 2,4,4′ trichlorobiphenyl, 1.4 years; for 2,4,4′5 tetrachlorobiphenyl, 3.2 years; for 2,3′,4,4′,5 pentachlorobiphenyl, 5.8 years; and for 2,2′,4,4′,5,5′ hexachlorobiphenyl, 12.4 years.[16] Even though different commercial mixtures of PCBs were used in the capacitor plants, the congeneric composition on a qualitative basis is similar.[17] Production began in 1946 with the highly chlorinated Aroclor 1254, and small amounts of Aroclor 1254 were used in the plant at least through 1971.

The statement that length of employment alone was an inadequate surrogate for exposure and a likely source of exposure misclassification bias leading to an underestimation of the effect and a distortion of the exposure-response relationship is not supported by the toxicokinetics of PCBs, nor is it an accurate representation of the data analyses conducted on our cohort and reported in the article.

Bove et al report that the majority of hourly workers never worked in a high-exposure job, when in fact 1268 of the 2984 male hourly employees (42.4%) did work in a high-exposure job. Only 13.8% of the female hourly employees worked in a high-exposure job, not an uncommon occurrence in an industrial setting. To suggest that the remaining portion of the cohort experienced PCB exposure similar to that of the general population is not an accurate representation of the facts. This is presented in the exposure-assessment section of our article.

Bove et al state in the opening sentence that although the goal of the study was to evaluate six specific cancers, we focused almost entirely on all-cancers mortality. Table 4 in the article presents SMRs and 95% CIs not only for the six cancers of interest but for 32 other causes of death, including 15 additional cancers. The issue of statistical power is raised by Bove et al and two tables were provided. These tables were not properly referenced nor was the methodology used to generate these calculations explained. It is unclear why an SMR of 150 should be considered the "highest expected" for these cancers, when previous publications on smaller cohorts reported statistically significant SMRs well above 150. Our study was an attempt to evaluate these earlier observations in a larger study with a longer follow-up period.

Bove et al question the decision to limit the latency by length of employment calculations to cancers with more than two observed cases and a lower boundary of the 95% CI of 90 or above. This decision was made by the investigators to limit the multiple comparison problem and to provide more meaningful data, rather than to obscure data. Additionally, the lack of presentation of data should not be interpreted as the data not having been analyzed. All six a priori cancers of concern were examined carefully; however, publication space is limited and presenting a table of latency by cumulative exposure for liver cancer, for instance, with two deaths was deemed unwarranted.

In their summary statement, Bove et al dismiss our study findings because of the HWE effect, failure to account for latency, exposure misclassification, potentially insufficient dosage differences between exposed and comparison groups, and poor statistical power, yet they still insist that we did find excess cancer risk for three of the six a priori cancers of interest and give credence to those findings. It is inconceivable to the

investigators of this study how Bove et al, given this litany of problems, were able to differentiate the impact and direction of these biases with such certainty and specificity.

The authors take exception to the tone of the letter by Frumkin and Orris and find statements such as "conspicuously silent" and "willful effort to avoid a positive finding" inflammatory and suggest that such statements do little to advance the understanding of PCBs and cancer risk.

Most of the issues raised by Frumkin and Orris have been addressed earlier. Their suggestion to include more capacitor plants to increase power has merit, however. The General Electric Company had only the two facilities in upstate New York (Hudson Falls and Fort Edward) where capacitors were made using PCBs.

Frumkin and Orris question whether high-exposure jobs actually entailed high exposure and raise concerns about misclassification. The exposure misclassification suggested by Frumkin and Orris is highly improbable, given the distinction between jobs with direct dermal and inhalation exposure and those with only inhalation exposure to PCB air levels in the plant, as explained and referenced in our article. Additionally, the characterization of this bias as substantial is unwarranted and is an overstatement of the potential effect. Assignment of exposure for specific job categories was done before determination of vital status. At both plants, workers were located in the same building, and the same air-ventilating system served the entire building. We verified the physical layout by conducting a walk through the building and by talking to present and former employees. Many workers had different jobs in the different exposure categories (high, undefinable, and low). All workers, including those in low-exposure jobs, had significantly higher exposures than the general population, on the basis of PCB serum levels reported by Lawton et al,[11] Brown et al[15,16] and Brown.[18]

The PCB blood levels (from 194 and 290 workers) mentioned by Frumkin and Orris were of limited value in validating an exposure job matrix for 7075 workers. Although the job histories and the exposure assignment did confirm that workers in high-exposure jobs had high PCB blood levels, these workers were selected either because of their known high-exposure job[11] or they were self-selected.[10] The high-exposure jobs were readily identified by plant personnel and were confirmed by PCB air-level readings and PCB blood levels. Misclassification of jobs into the high-exposure category or misclassifying high-exposure jobs as lower-level exposure jobs was extremely unlikely.

Frumkin and Orris suggested that PCBs are serious health hazards, irrespective of carcinogenicity, with effects that include decreased birth weight, neurodevelopmental effects, and interference with thyroid and estrogen hormone function. It has not been shown that PCBs interfere with estrogen-hormone function in humans. Studies conducted to examine the effects of PCBs in infants and children have been critically reviewed[19–25] or could not be supported.[26] Results from thyroid function tests performed in infants were within the normal range. Furthermore, Koopman-Esseboom et al[27] stated, "The mean dioxin-like PCB toxic equivalent levels and the mean total PCB and dioxin toxic equivalent levels of the neurological normal infants were significantly higher ($p = 0.04$ for both) compared with the levels of the neurologically (mildly or definitely) abnormal infants. There was no relationship between the TT3 (serum total triiodothyronine), TT4 (serum total thyroxine), FT4 (free thyroxine), and TSH (thyroid stimulating hormone) levels in maternal, umbilical, or infant plasma (collected in the second week after birth) and the results of the neonatal neurological examinations. We conclude that overt abnormalities found in the neonatal period are not caused by either direct effects of PCB or dioxin exposure or lowered thyroid hormone levels." According to the National Center for Health Statistics,[28] birth weight is affected by education of the mother, mother's age, birth order, interval between births, gender, inadequate prenatal nutrition, alcohol consumption, smoking, lack of prenatal care, incidence of elective induction, contraceptive utilization, out-of-wedlock births, metropolitan areas (lower), and race. The body size of the parents and maternal illnesses such as diabetes also play a role. These many variables exemplify the difficulties of appropriately designing studies to examine a single factor affecting birth weight. Given these uncertainties and the published criticisms of studies reporting "other health effects of PCBs," it has not been conclusively shown that PCBs cause other "serious" health problems in humans.

We disagree with the final comment by Frumkin and Orris that this study was a great leap sideways on the path to a more complete understanding of the health effects of PCBs. The issue of PCBs and potential health effects has been a significant public health concern for more than 30 years. The lack of consistent findings in the previous cohort studies was assumed to have resulted from small cohort sizes and short follow-up periods. Given the disparate findings in these smaller capacitor cohorts, the appropriate next step was to assemble a larger cohort of PCB-exposed workers and examine them throughout a longer follow-up period. The fact that we were unable to confirm any of the previously reported findings is important and adds to the knowledge about PCBs and health effects. The assumption that a negative study does not provide valuable information imposes significant restrictions on the scientific process and the ability to ade-

quately and objectively assess all data.

Errata: The correct number of female salaried workers with a length of employment of 10 to <15 years in Table 2 is 27; 5.8% is the correct percentage. In Table 6, line 2, last column, total SMR for ≥20 years of latency should be 117. The total number of workers in the upper panel of Table 2 should be 7075.

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Investigation of Elevated Urine Beta-2-Microglobulin in a Cohort of Cadmium Workers

To the Editor: Prior to the issuance of the 1993 Occupational Safety and Health Administration Cadmium Standard, urine testing for beta-2-microglobulin (β_2m) was not frequently performed. Testing for β_2m was an esoteric laboratory test performed only on workers whose cadmium levels had been found to be elevated. The Cadmium Standard mandated that all employees exposed to greater than 2.5 $\mu g/m^3$ cadmium dust or fumes be tested at least annually for urine β_2m, as well as for blood cadmium (CdB) and urine cadmium (CdU). At a nickel-cadmium battery manufacturing facility, approximately 1000 employees, some of whom had been exposed to cadmium and some of whom had not, were evaluated for β_2m levels, most for the first time.

Elevated β_2m was defined as a β_2m level higher than 300 $\mu g/g$ creatinine[1]; expectations were that approximately 10% of workers with cadmium levels higher than 10 $\mu g/L$ blood or 10 $\mu g/g$ creatinine would also show an elevated β_2m level.[2,3] Because 54 employees had such elevated cadmium levels in 1993, it was expected that approximately five or six would also show elevated β_2m levels. It was not known how many employees with other conditions