CORRESPONDENCE

Sex ratio of offspring of men exposed to sodium borates

Editor—Whorton et al report 529 births (250 sons and 279 daughters) sized by men exposed to sodium borates.1 With official data on the comparable non-exposed United States population (adjusted for maternal age, race, parity, and calendar time) these authors estimate an excess of 466-6 births. They took the unusual step of contrasting the observed sex ratio (proportion male) with the numbers of the two sexes expected assuming simultaneously both: a United States live birth sex ratio of 0:512; and the comparable United States fertility rates.

They thus calculate expected values of sons and daughters that are less than both the observed values. So they are able to conclude that the unusual observed sex ratio is not due to a deficit of boys. This, they considered, would allay suspicions that borates represent a reproductive hazard to male fertility.

I should like to present an alternative argument based on their data. It would be more conventional to contrast the observed sex ratio (250 boys, 279 girls) directly with the expected sex ratio of 0:512. This leads to an associated y2 value of 3:3. Bearing in mind the suspicion of reproductive hazard cited by Whorton et al,1 and the evidence that occupational reproductive hazards to men may manifest themselves in low sex ratios of offspring,2 it would seem appropriate to use a one-tailed test. (In this case P < 0.05.) So I would conclude that indeed there are grounds for suspicion that borates affect the male reproductive system. More data should be gathered on the sex ratios of offspring of men exposed to these materials. If these prove to be too low, then more invasive investigation (sporn counts, hormone assays) would be justified.

Lastly, the excess fertility in the exposed men was estimated by adjusting United States national fertility rates for maternal age, parity, race, and time. These men were employed in the Mojave Desert. Would fertility be greater in such areas than in urban areas? If so, the excess fertility may be illusory.

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Author's reply—James's comments on our sex ratio analyses need closer scrutiny on several counts. Firstly, contrary to James's comments, in our sex ratio analysis, we did not assume comparable fertility rates between our study and the United States general population. On the other hand, in his comparison between the observed overall sex ratio in our study and the ratio for the United States, James implicitly made the assumption of comparable fertility rates between our study and that for the United States.

The primary purpose of our study was to determine if there was a deficit or excess of births by sex ratio in the sex ratio itself. As such, a direct comparison of the two sex ratios would have been appropriate only if the underlying fertility rates in our study and in the general population were comparable. As shown through the use of the standardized birth ratio, the fertility rates in our study were significantly higher than those in the general population. From the methodological point of view, the problem of directly comparing sex ratios is similar to that of applying the proportional mortality ratio (PMR) in mortality analysis. It is well known that PMR compares proportions of deaths from specific causes between two groups, and it is known that mortality ratio only if the underlying death rates are comparable in the two groups.1,2 Similarly, a direct comparison of sex ratios determines whether there is a deficit or excess by sex only if the underlying fertility rates are comparable in the two populations being compared.

James's rationale for a one-tailed test assumes an original hypothesis of a lower sex ratio (proportion male) as associated with exposure to sodium borates. Based on previous data on sodium borates, we had no preconceived idea whether the sex ratio (proportion male) should be higher or lower. Thus, James's argument for a one-tailed test was based on a retrospective examination of the data, which would render the conventional P value of 0.05 inappropriate, and the y2 of 3.3 calculated by James would not have been significant.

James implied that male reproductive hazards would most likely result in an altered sex ratio. Among the papers cited in another letter to the editor by James,1 one report by Sjogren et al2-6 includes bronchial cancer cases of mild steel (MS) welders. The lack of systematic bias and the pooled relative risk being 1.94 (95% confidence interval 1.28-2.92). The authors concluded that "it is time to reconsider the IARC (International Agency for Research on Cancer) statement from 1990" and to separate SS welding fumes from other welding fumes".

Here I compare the risks of lung cancer among mild steel and stainless steel welders.

Editor—I have read with great interest the paper by Sjogren et al.1 The authors carried out a meta-analysis of five epidemiological studies—three case-control1-4 and two historical cohort5-6 studies—on the occurrence of lung cancer among stainless steel (SS) welders. The results clearly indicated a relation between SS welding and lung cancer, although the pooled relative risk being 1.94 (95% confidence interval 1.28-2.92). The authors concluded that "it is time to reconsider the IARC (International Agency for Research on Cancer) statement from 1990" and to separate SS welding fumes from other welding fumes".

There are some studies that could link the risk of lung cancer among mild steel (MS) welders with SS welders. Some statistical significant was found in one study which included the meta-analysis of Sjogren et al1 and from other studies not included in this meta-analysis.8-11

The observed odds ratio (OR) among MS welders in the Danish case-control study was 1.65 (95% CI 1.03-2.65), which is similar to that of SS welders, 1.54 (95% CI 0.83-2.84). In the French cohort mortality study the standardized mortality ratio (SMR) for lung cancer was slightly higher for MS welders than for welders predominately exposed to chromium VI—that is, 1.92 (95% CI 1.03-3.02) v 1.03 (95% CI 0.12-3.71).11

Some other studies did not detect high risks of lung cancer among MS welders. Becker et al1 followed up a cohort of SS welders compared with reference group of turners. The welders had a
Correspondence

welders' effects whose welders. Further, SS welders. Additionally, SS welders. Moreover, with an external reference, the lung cancer SMR of SS welders was low (1.1-1.9) 1,2,5. The case-control study by Holl et al in Los Angeles county showed ORs of 0.9 (95% CI 0.5-1.8) for SS welders and 1.3 (95% CI 0.6-2.3) for SS welders predominately exposed to chromium and nickel (manual metal arc welders), whereas the OR was 1.6 (95% CI 0.8-3.1) for MS welders. Adjustments for smoking made little difference. The lung cancer mortality study included 11,092 welders from eight countries.1 This large study provided no consistent difference between MS welders, for which the SMR was 1.78 (95% CI 1.72-2.43), statistically different and predominantly SS welders whose SMR was 1.23 (95% CI 0.75-1.90). The results of this study for cancer incidence provided the same pattern as those for mortality as the standardised incidence ratios (SIRs) of lung cancer were 1.75 (95% CI 1.22-2.42) for MS welders and 1.39 (95% CI 0.74-2.38) for predominately SS welders. In conclusion, it seems to me that, although SS welders are potentially exposed to chromium and nickel compounds, epidemiological studies focused on the risk of lung cancer of SS welders do not provide clear evidence to suggest that SS welders are at a higher risk of lung cancer than MS welders. Therefore, the cause of the excess lung cancers found among MS and SS welders is an unanswered issue. A recent study by Jockel et al supports the hypothesis that some of the excess lung cancer among welders could be due to exposure to asbestos. Further investigations that controlled for smoking, exposure to asbestos, and possible differential healthy worker effects among MS vs SS welders1 are needed.

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Urinary N-acetyl-β-D-glucosaminidase (NAG) and exposure to inorganic lead

Editor—Urinary activity of N-acetyl-β-D-glucosaminidase (NAG) has been reported to be one of the earliest markers to be increased in workers exposed to lead. The underlying mechanism for an increase in NAG activity is yet to be elucidated. It was suggested that the increase in NAG activity may be due to stimulation of exocytosis.1 In a recent publication2 based on workers from a lead smelting plant, it was further suggested that increased NAG activity among workers exposed to lead was due to a concomitant "albeit slight cadmium exposure". Their conclusion was based on the finding that urinary cadmium concentration (CdU) was the only significant variable in explaining the variation in NAG activity through stepwise regression analysis. Furthermore, the correlation coefficient (r) between NAG and CdU, was 0.41 in the non-exposed and 0.35 among exposed workers.2

Our data from exposed workers in a polyvinyl chloride lead stabiliser plant did not support this hypothesis. The increases in NAG, the heat labile isoenzyme (NAG-A), and the heat stable isoenzyme (NAG-B) were all highly associated with the recent change in blood lead (PbB) concentration over the past six months (PbBa). Among several exposure indices derived from serial PbBa concentrations, PbBa was the only significant variable to account for the variation in NAG, NAG-B, and NAG-A. Furthermore, CdU and blood cadmium (CdB) did not correlate well with NAG and its isoenzymes. When they were forced into the regression model, CdU was in fact negatively correlated (table). Activity of NAG is also increased when other xenobiotics affect the proximal tubules.3,4 It is indeed very unlikely that NAG is a specific marker for cadmium. As inorganic lead is known to cause proximal tubular dysfunction, it is therefore not surprising to see an association between lead exposure and NAG.

Among lead smelters, it is possible that there may be significant concomitant exposure to cadmium. This is evident by the fairly wide range of CdB results (0.3-5 µg/l) and the significantly higher CdB and CdU concentrations among the workers exposed to lead. Our cohort of PVC lead stabiliser workers had never been exposed to cadmium. Their geometric mean (range) CdB and CdU were much lower than those of the lead smelters (CdB: 0.56 (0.10-1.92) µg/l; CdU 0.41 (0.12-2.07) µg/l creatinine). We have also previously reported that NAG activity was better correlated with CdB and about 40% of the workers exposed to cadmium with a CdB of less than 3.0 µg/l had increased NAG concentrations.5

It is possible that where there is significant cadmium exposure, cadmium plays a greater part in increasing NAG activity than does lead, and perhaps even masks the contribution of lead. Our data show that lead does increase NAG activity in the absence of cadmium exposure.

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Contribution of PbBa, CdB, and CdU to variation in NAG* 

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Partial regression coefficient (%) (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>PbBa</td>
<td>4.12 (2.22 to 6.01) 0.63</td>
</tr>
<tr>
<td>CdB</td>
<td>0.6 (0.08 to 0.40) 0.10</td>
</tr>
<tr>
<td>CdU</td>
<td>-0.14 (-0.31 to 0.04) 0.22</td>
</tr>
<tr>
<td>NAG-B</td>
<td></td>
</tr>
<tr>
<td>PbBa</td>
<td>11.9 (5.96 to 16.34) 0.66</td>
</tr>
<tr>
<td>CdB</td>
<td>-0.45 (-0.95 to 0.05) 0.38</td>
</tr>
<tr>
<td>CdU</td>
<td>-0.93 (-0.39 to 0.34) 0.02</td>
</tr>
</tbody>
</table>

*Multiple linear regression analysis with log transformed data.

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Assessment of risk of lung cancer among mild steel and stainless steel welders.

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