Errors in TCE Analysis

We read with interest the epidemiologic overview and evaluation of trichloroethylene (TCE) and cancer recently published by Wartenberg et al. (*1*). Unfortunately, there were a number of errors in Table 5 (*1*) concerning risks reported in our study of workers exposed to TCE during the manufacturing of aircraft (*2*). For example, the standardized mortality ratio (SMR) and the 95% confidence interval (CI) presented for multiple myeloma were actually those for Hodgkin's disease. There were also serious errors in the listed SMR and CI for stomach cancer as well as discrepancies in the presentation of CIs for 10 other sites (Table 1). These incorrect values were included in the meta-analyses to make inferences regarding the carcinogenic potential of TCE; thus, they should be revised.

We also found it peculiar that the reported CIs from our study were recalculated. We computed exact CIs, which are methodologically superior to the recalculated ones. The method of recomputation assumed that our upper but not lower confidence limit was correct. These recomputations had the unusual property of exaggerating the lower CI, thus making the results appear more statistically significant (or closer to statistical significance) than they actual were.

Table 1. Discrepancies between TCE and cancer risks as reported by Boice et al. (*2*) and as listed in Table 5 of the recent review by Wartenberg et al. (*1*).

Cancer site	Boice et al. (*2*)	Wartenberg et al. (*1*)
Multiple myeloma		
SMR (no. cases)	0.9 (6)	2.8 (4)
95% CI	(0.3–2.0)	(1.1–7.1)
Stomach		
SMR (no. cases)	1.3 (17)	0.8 (7)
95% CI	(0.8–2.1)	(0.4–1.7)
Cervix		
SMR (no. cases)	0.0 (0)	—
95% CI	(0.0–5.5)	—
Leukemia		
SMR (no. cases)	1.1 (12)	1.0 (12)
95% CI	(0.5–1.8)	(0.6–1.8)
Breast		
95% CI	0.5–2.7	0.6–2.7
Buccal		
95% CI	0.2–1.4	0.3–1.4
Colon		
95% CI	0.7–1.5	0.8–1.5
Esophagus		
95% CI	0.3–1.7	0.4–1.7
Hodgkin's disease		
95% CI	0.8–7.1	1.1–7.1
Kidney		
95% CI	0.4–2.0	0.5–2.0
Larynx		
95% CI	0.3–2.8	0.4–2.8
Rectum		
95% CI	0.6–2.5	0.7–2.5

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2. Boice JD Jr, Marano DE, Fryzek JP, Sadler CJ, McLaughlin JK. Mortality among aircraft manufacturing workers. Occup Environ Med 56:581–597 (1999).

Errors in TCE Analysis: Response

We thank Boice and McLaughlin for their letter commenting on our paper (*1*). They raise three types of issues with respect to our reporting on their study: *a*) differences between our reports of specific SMRs and their original report; *b*) our report of no data for a cancer site for which they report no cases; and *c*) differences between our reported confidence intervals (CIs) for their standardized mortality ratios (SMRs) and the CIs originally reported. We consider each below.

The principal goal in our review was to identify, critique, and summarize the cancer epidemiology of trichloroethylene (TCE)-exposed populations in a more complete and systematic manner than that carried out previously (*2–4*) while making our review and averaging process as transparent as possible. We wanted to enable readers to understand our methodology and to be able to replicate our results or modify our assumptions and make similar calculations using our published tables (*1*,*5*). Therefore, we reported in our tables the data input into our SMR-averaging algorithm rather than copying the exact values published in each original study. We recognized at that time that there were small differences, particularly in the confidence intervals, but felt that the transparency of our approach was of greatest importance.

Our values for multiple myeloma and stomach cancer were incorrect because we had miscopied the SMRs from Boice et al.'s paper (*6*). Using the point estimates presented by Boice et al. (*7*) and recalculating the average SMRs, the average SMRs for the Tier I mortality studies change from 1.9 (95% CI, 1.0–3.7) to 1.0 (95% CI, 0.6–1.9) for multiple myeloma and from 1.1 (95% CI, 0.8–1.6) to 1.3 (95% CI, 0.9–1.7) for stomach cancer. For these two sites, the contribution of the Tier I mortality studies to our overall conclusions is quite minimal. In our review, we suggested that there is weak support for an association between TCE and multiple myeloma, and no evidence for an association between TCE and stomach cancer (*1*). These conclusions remain the same and are still valid in light of the results from the Tier I incidence studies and from the Tier II and Tier III studies. In their letter, Boice and McLaughlin also point out that the SMR for leukemia was 1.05 in contrast to that listed in Table 5 of our paper (*1*) as 1.0. Risks that we present in all tables in our paper are rounded, and the difference between the data reported by Boice et al. (*6*) and our data is due to an unfortunate rounding error. Our calculation of the average SMR for leukemia for the Tier I mortality studies, however, uses the value 1.05. Hence, the average SMR that is in our published paper remains unchanged.

The second issue raised by Boice and McLaughlin is for cervical cancer mortality for which we report no information, whereas Boice et al. (*6*) originally reported 0 observed cases with a 95% CI of 0.0–5.5. This again reflects our desire for transparency. We calculated the average risk by combining the logarithm of the SMRs; because log (0) is undefined, we could not use these data in our calculation. The entry in our table reflects how we handled the data in our calculations rather than how the data were reported originally. This also did not affect our calculations.

The third issue raised by Boice and McLaughlin is about the CIs for several of the SMRs. In particular, they questioned why we recalculated the CIs. Although we recognize that exact CIs are superior to the recalculated ones on statistical grounds, it is not possible to directly determine the underlying variance, a number we needed for our average risk calculations. In most cases, the CIs we calculated differ only slightly from those in the published papers. For example, in their Table 5, Boice et al. (*6*) state that the lower confidence interval for breast cancer is 0.6; in our paper (*1*), we list it as 0.5. The reason that we recalculated the CIs is that to conduct the average risk calculation using the Mantel-Haenszel method, as reported in our paper (*1*), we needed to calculate the variance of the reported relative risk (RR):

$$\overline{RR} = e^{\frac{\Sigma w_i \ln(RR_i)}{\Sigma w_i}}$$

where $w_i = \dfrac{1}{\mathrm{var}[\ln(RR_i)]}$

To do so, we used the reported CI using the following equations:

$$95\%\,CI = e^{\ln(RR_i) \pm 1.96 \sqrt{\mathrm{var}[\ln(RR_i)]}}$$

$$\mathrm{var}\left[\ln(RR_i)\right] = \left[\frac{\ln(upper\,CI) - \ln(RR)}{1.96}\right]^2 = \left[\frac{\ln(RR) - \ln(lower\,CI)}{1.96}\right]^2$$

If the logarithm of the published upper and lower CIs were not symmetric around the ln(RR) (due to rounding errors or alternative calculation algorithms), we needed to choose one for the calculations. Because some of the lower CIs were 0, and the ln(0) is undefined, we used the upper CI. For consistency, we always used the upper CI to calculate the variance. We then used this variance to recalculate the lower CI. We presented our recalculated values rather than the original values because these were input into the statistical averaging program. We believe that this approach is more forthright than reporting the investigators' published lower CI in our tables while using our recalculated lower CI in our average risk calculation. The procedure we used is described in our paper (*1*). We cited Rothman and Boice (*7*) for the above equations.

We apologize for the two typographic errors and hope that our discussion adequately explains why the other numbers did not exactly match the values originally published.

The views in this response are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

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Toward Resolution of the Divergent Effects of Estrogens on the Prostate Gland of CF-1 Mice

In October 2000 an ad hoc panel of experts was convened by the National Toxicology Program and the U.S. Environmental Protection Agency to review conflicting reports of endocrine effects induced by low doses of synthetic estrogens in rodents. Of primary concern were reports by Nagel et al. (*1*) and vom Saal et al. (*2*) of increases in prostatic weight in CF-1 mice exposed *in utero* to comparatively low doses of either bisphenol A (BPA) or diethylstilbestrol (DES), and subsequent reports by Cagen et al. (*3*) and Ashby et al. (*4*) describing the absence of such effects for both chemicals. After the meeting it was realized that the panel had failed to consider the work of Nonneman et al. (*5*) from the vom Saal group. Nonneman et al. (*5*) described the influence of male intrauterine position (IUP) on prostatic weight and suggested that differences in estrogen levels between embryos, according to their IUP, was responsible for the differing prostatic weights observed. That observation led to the evaluation of synthetic estrogens in the CF-1 mouse. Because the results of Nonneman et al. (*5*) indicate that control prostate weights in the CF-1 mouse are more variable than hitherto thought, this variability should be taken into account in evaluating the four sets of mouse prostate data under discussion (*1–4*).

The panel noted, not for the first time, that the CF-1 mouse control prostatic weights reported by Ashby et al. (*4*) (49.1 mg, ~6 months of age) were significantly heavier than those reported by Nagel et al. (*1*) (~42 mg, ~6 months of age), vom Saal et al. (*2*) (~42 mg, ~8 months of age), or Cagen et al. (*3*) (~39 mg, 3.5 months of age). In particular, the prostatic weights reported by Nagel et al. (*1*) for animals exposed to BPA (~55 mg) or reported by vom Saal et al. (*2*) for animals exposed to DES (~55 mg) were similar to the control prostate weights reported by Ashby et al. (*4*). In all of these studies, the IUP of the male pups was not known: either one male pup was selected randomly from the litter (*1,2*) or all male pups were retained without knowledge of IUP (*3,4*). vom Saal suggested to the panel that the prostatic weights of the mice used by Ashby et al. (*4*) may have been increased by some unknown experimental condition leading to a loss of sensitivity to the two estrogens tested (*1,2*). In fact, our animal body weights were higher than those described by Nagel et al. (*1*), but vom Saal et al. (*6*) reported that body weight is not related to prostatic weight in CF-1 mice of this age range (*6*). In contrast, the data described by Nonneman et al. (*5*) may be more relevant to our prostate weights. Nonneman et al. (*5*) recorded prostate weights for CF-1 mice at ~3.5 months of age according to the IUP of the male pups. These weights were as follows: 0M (adjacent to no males) pups, 59.5 ± 3.3 mg (mean ± SE of seven pups); 1M pups (adjacent to one male), not reported; and 2M pups (adjacent to two males), 49.4 ± 3.0 mg (*5*). From these data, the average control prostate weight for CF-1 mice in the vom Saal's laboratory in 1992 must have been > 50 mg, which is greater than any of the control values discussed above (*1–4*). In addition, the variability of control prostate weights in the study by Nagel et al. (*1*) (SE = 1.0) is much lower than would be expected based on the data of Nonneman et al. (*5*) (SE ~3), a difference made more surprising by the fact that knowledge of IUP would have been expected to reduce, rather than increase, the variability in IUP-specific prostatic weights.

The above considerations indicate two things. First, that control prostate weights of ~49 mg reported by Ashby et al.(*4*), although higher than recent values from the laboratory of vom Saal (*1,2,6*), agree with those reported in the only published reference to control CF-1 mouse prostate weights presented according to IUP (*5*). Second, given the dependency of prostate weight on IUP (*5*), it would be of value to statistically analyze the optimum study design for the detection of a 30% increase in prostatic weight, as reported for BPA (*1*). In particular, it would be of value to establish how the use of seven test and seven control pups, each selected randomly from 14 dams without knowledge of IUP, could have achieved such sensitivity. In conclusion, the divergent findings for the prostate gland of CF-1 mice (*1–4*) might be clarified by publishing individual prostate weights from earlier studies (*1,2,5,6*) in combination with an analysis of how IUPs of the pups under study might affect those data.

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Prevalence of Headache among Handheld Cellular Telephone Users

Chia et al. (*1*) conducted a cross-sectional community study in Singapore to determine the prevalence of central nervous system (CNS) symptoms among hand-held cellular telephone (HP) users compared to nonusers. They found that headache was the most prevalent symptom among HP users compared to non-HP users, with an adjusted prevalence rate ratio of 1.31 (95% confidence interval, 1.00–1.70). Their study was partly based on my data in a report of a case series of symptomatic users (*2*). However, they used the classification of "primary headache disorders" provided by the International Headache Society as their case definition. This is at variance with my original data in two ways: *a*) my subjects reported that their symptoms related to mobile phone use were quite different from ordinary headaches, and *b*) their symptoms were unilateral to side of use. These are clinical features that Chia et al. (*1*) did not include in their analysis. The definition of "headache" used by Chia et al. (*1*) would lead to imprecision in case ascertainment and hence a minimal estimate of the risk.

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Prevalence of Headache among Handheld Cellular Telephone Users: Response

We would like to clarify that at no time was our study (*1*) "based on [Hocking's] data in a report of a case series of symptomatic users...." When we were discussing which factors (symptoms) to study among hand-held cellular telephone users, Hocking's paper (*2*) is only one of many to which we referred.

Because ours was a community-based study (*1*), we examined "specific CNS symptoms among handheld cellular telephone users compared to nonusers." Headache is only one of the symptoms we studied. We used the International Headache Society Classification because it is commonly used in publications related to headache; the use of this classification would also enable standardization and comparison with other papers. Because our definition is different from that of Hocking, we certainly cannot analyze "unilateral to side of use" because this information was not determined in our study. We had no intention of confirming or refuting Hocking's report. In fact, we made no reference to Hocking's paper (*2*) in the "Discussion" of our paper. Therefore, we do not see how our definition of headache "would lead to imprecision in case ascertainment and hence a minimal estimate of the risk."

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Corrections and Clarifications

A meeting report by Sameeh A. Mansour [Workshop Egyptox–2000: For Better Environmental Education by the Birth of the New Millennium. Environ Health Perspect 109:197–198 (2001)] was inadvertantly omitted from the table of contents of the February issue of *EHP* (109:A57). We apologize for the omission.