Meta-Analyses of TCE Carcinogenicity

We read with interest the recent report by Wartenberg et al. (1) in which they described an "ad hoc system" and "meta-analysis-type approach" for evaluating the carcinogenicity of trichloroethylene (TCE). In particular, we are concerned that their methods may obscure rather than clarify the relationship between TCE and human cancer.

Briefly, Wartenberg et al. (1) categorized studies on the basis of their design: cohort, case-control, community-based, and case series. Cohort studies were then divided "into three tiers based on the specificity of the exposure information" contained in each. Next, the authors estimated the average relative risk for each tier, which was calculated using a weighted average of the individual measures of effect, where the weights are the inverse of the variance of the individual measures.

That approach, although defensible (2), does not necessarily lead to results that are either biologically or epidemiologically meaningful. To the contrary, it may encourage analysis of groups of studies that would more logically be analyzed separately. Such meta-analyses can either amplify or conceal underlying causal associations.

This can be illustrated by reference to the analysis of kidney cancer incidence rates in the cohort studies (1). There were seven Tier I cohort studies, of which six are large occupational cohort studies Anttila et al. (3), Axelson et al. (4), Blair et al. (5), Boice et al. (6), Morgan et al. (7), and Ritl (8). Four of the Tier I studies included incidence data used to calculate a summary relative risk for renal cancer incidence. Of these four, three were large cohort studies (Anttila et al. (3), Axelson et al. (4), and Blair et al. (5)) that considered renal cancer in 18,182 individuals (12,848 exposed to TCE). The fourth of these studies, Henschler et al. (9), was a small study of only 359 subjects (169 exposed to TCE), which has been the subject of ongoing methodologic controversy and debate because it originated as an investigation of a cancer cluster. For that reason, the International Agency for Research on Cancer (IARC) did not include it when calculating summary relative risks in its assessment of TCE and human cancer (10).

To determine the impact of including the Henschler study (9), we recalculated Wartenberg’s computations, using their inverse variance-weighted technique, with and without the Henschler data. The summary relative risk for renal cancer in the three large cohorts excluding the Henschler study was 0.98 [95% confidence interval (CI), 0.58–1.66]. Including the Henschler data (9), the summary relative risk is 1.7 (95% CI, 1.1–2.7), which agrees with the calculations of Wartenberg et al. (1). Although inclusion of the Henschler study increased the combined study population by only 169 exposed and 359 total subjects (1.32% and 1.97%, respectively), it increased the relative risk by nearly 74% and reversed the conclusions of the analysis.

The impact of the Henschler data (9) stems from its very high incidence rate of renal cancer, about 9-fold higher than that of the other cohorts. It is therefore important whether this population was studied because of a renal cancer cluster in that small TCE-exposed worksite, a finding that assured an elevated incidence rate.

Wartenberg et al. (1) justify inclusion of the Henschler study as follows: “An argument can be made that studies initiated by a cluster report should be excluded...we disagree.” This statement, with which we disagree, has been and will continue to be debated in the scientific literature (11,12). More immediately, the assignment of the Henschler study (9) to Tier I status solely on the basis of the exposure data specificity, without regard to its origin as a cluster investigation, represents a methodologic weakness of the approach of Wartenberg et al. This small cluster investigation overwhelmed the combined findings of several large cohort studies.

Looking at the data, it is obvious that the positive result was produced by the Henschler study (9). A more formal test, such as calculation of a Q statistic to assess homogeneity across studies (2,13,14), demonstrates the substantial heterogeneity between the Henschler cluster evaluation and the three large cohort studies (3–5). The calculated Q statistic for the three large cohort studies, but excluding the Henschler study, is associated with a p-value of 0.47, whereas inclusion of the Henschler study yields a p-value < 0.001, which leads to formal rejection of the statistical hypothesis that the four studies are homogenous. Although debate surrounds the value of such testing as prerequisite to combining relative risks in meta-analyses, this case demonstrates its utility.

In contrast, because Wartenberg et al. (1) ignored the informative value of the exposure data and instead emphasized methodologic specificity, their approach might have obscured an association between TCE and renal cancer. An example of such concern is the growing evidence that renal effects of TCE do not cause nephritis. They also suggest that toxic nephritis is necessary for TCE to cause renal cancer (15,17). It can be reasonably anticipated that TCE-related nephritis occurs only from exposures that exceed some threshold dose and that lower-dose exposures would not be expected to cause nephritis. Accordingly, combining subjects with high and not-so-high TCE exposures might conceal whatever statistical association linked TCE and cancer.

The subjects in the Henschler study (9) were likely exposed to very high levels of TCE for prolonged periods: “concentrations of 500 ppm were regularly achieved and exceeded in this situation” (17). If so, subjects were exposed to levels 10–20 times higher than those reported for subjects in the other cohort studies. Combining the subjects of those various studies would serve to minimize any underlying relationship between TCE and renal cancer, particularly if most of the other cohort subjects were exposed to levels below the threshold dose expected to cause nephritis.

Thus, for different but related reasons, the Wartenberg approach could either enhance a spurious association or obscure a meaningful one. In this case, the former seems to have occurred: inclusion of the Henschler study (9) has probably led to a spurious association. However, the more important and general issue concerns appropriate methods for performing meta-analysis. Meta-analyses that ignore important distinguishing features of individual studies, that emphasize statistical procedures over biologic and epidemiologic issues, and that disregard homogeneity of exposure are unlikely to resolve issues such as the human carcinogenicity of TCE.

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using the same summary methods belies their criticism of concealment or obfuscation.

The principal goal in our review was to identify, critique, and summarize the cancer epidemiology of TCE-exposed populations in a more complete and systematic manner than that carried out previously (2–4). As such, our approach was to provide a broad overview that summarized the major trends and patterns in the data while reserving most study-specific insights and patterns in the data for other venues. Our challenge was to examine and summarize the patterns of results from over 80 epidemiologic publications that we identified. Although we recognize the utility in certain contexts of selecting subjectively only the “best” studies and reporting their results, as is done by IARC (2), we explicitly chose not to do so. Rather, we identified, critiqued, and summarized all studies in a comprehensive fashion.

Faced with a large number of studies, we categorized them by design and then subdivided the cohort studies by the likelihood of TCE exposure and the quality of the exposure assessment. Some may quibble about our particular categorization of the studies, but we believe that our approach is well justified overall and that the analyses were presented clearly and comprehensively. Further, we do not see this venue as the appropriate one to debate the merits and limitations of meta-analysis, in general, nor specifically the opinions of Borak et al. regarding the interpretation of such analyses. This debate has occurred elsewhere (e.g., see references in Pettiti (5)). Our goal in calculating the average risks was to assess the possible role of chance variation in the observed results and to determine whether this body of studies had sufficiently unusual results to warrant further consideration and investigation.

Borak et al. question the inclusion of the controversial Henschler et al. study (6) in our Tier I summary risk calculation. They suggest that the study should have been excluded because it originated as a cluster investigation. They also note that the kidney cancer results from the Tier I studies including the Henschler et al. study (6) are statistically heterogeneous and thus misleading.

The comment raised by Borak et al. regarding the inclusion of the study by Henschler et al. (6) has been raised by others, notably Weiss (3) and McLaughlin and Blot (4), and we explicitly addressed this issue in the discussion of our paper. The notion that data should be excluded from a general review because they were first noted in a cluster seems to misinterpret the very references (9,10) cited by Borak et al. The context of those studies was a discussion of the interpretation of a single cluster study without exposure data and without an a priori idea of what was being investigated other than an overall excess of disease. First, the study by Henschler et al. (6) is not a cluster investigation but a cohort study that was initiated by the observation of excess disease, albeit a cluster. Further, we included it in a comprehensive review of the literature because excess kidney cancer in this workplace with extremely high TCE exposures was a plausible a priori hypothesis based on both animal bioassay and human epidemiologic data that previously had shown increased renal cancer rates from TCE exposure. Further, the results of Henschler et al. (6) were so extreme (5 cases where 0.628 were expected) that the probability of observing such a situation is less than $5 \times 10^{-5}$ under Poisson assumptions. In other words, if there were no association, one would have to search for 500,000 similar workplaces with comparable TCE exposures to find such occurrence due to chance alone. Therefore, these data warranted further consideration, particularly with respect to other studies of TCE exposure and renal cancer. We agree that the study of Henschler et al. (6) is not sufficient on its own to confirm a causative relationship between TCE and renal cancer, as Rothman (7) and Fleming et al. (8) caution with respect to cluster studies. In combination with all the other studies in our review, however, the case for an elevated kidney cancer risk is much stronger.

Second, we are well aware of the issues surrounding heterogeneity in meta-analyses (9–13). We share Borak et al.’s concerns about heterogeneity but disagree with their interpretation. We did provide summary results for each study for the interested reader who could recalculate as they see fit, as Borak et al. did. If we had provided only the average risks, we would have obscured this issue and thus been remiss. The general issue that we were confronted with was how to help guide the reader through 14 tables of data summarizing over 80 articles reporting cancer rates for 23 different anatomical sites. Any summarization of this volume of information will necessarily omit some relevant information. Our point of summarizing these data was to omit what we thought was of lesser importance so that the more casual reader would still understand the main point of the paper without laboring over all of the tables. In fact, we left out even more data because most of the papers report on either effects at several exposure levels or exposures to several chemicals or responses to different subsets of the study population. When available, we did present observations for the most highly exposed subgroup to be consistent with Henschler et al. (6). It was our judgment that the information we included was the most important information for the reader, given the stated goal of our review. Those more interested readers could recalculate various summaries or even go back to the original

TCE Meta-Analyses: Wartenberg et al.’s Response

We appreciate the interest of Borak, Russi, and Puglisi in our summary of the epidemiologic evidence on the possible carcinogenicity of trichloroethylene (TCE) (1). We share their concern for a clear presentation of study results and identifications of methods used in meta-summaries of epidemiologic studies, and labored to do so in our review. The ease with which Borak et al. were able to identify cohort studies that examined renal cancer incidence, reproduce reported results, and recompute estimates on a reduced set of study results

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1. Anttila A, Pukkala E, Salminen M, Hemminki K. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med 37:797–806 (1995).
2. Axelson O, Seldén A, Andersson K, Hogstedt C. Updated meta-analysis of studies on trichloroethylene and cancer risk. J Occup Med 36:556–562 (1994).
3. Blair A, Hartge P, Stewart PA, McAdams M, Lubin J. Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow-up. Occup Environ Med 55:161–171 (1998).
4. Boice JD Jr., Marano DE, Fryzek JP, Sadler CJ, McLaughlin KJ. Mortality among aircraft manufacturing workers. Occup Environ Med 56:581–597 (1999).
5. Morgan RW, Keilh M, Zhao K, Heringer S. Mortality of aerospace workers exposed to trichloroethylene. Epidemiology 9:424–431 (1998).
6. Ritz B, Thomas B, Ulm K. Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethylene. Arch Toxicol 69:291–299 (1995).
7. Rothman KJ. Keynote Presentation: A sobering start for the TCE Meta-Analyses: Wartenberg et al.’s Response

We appreciate the interest of Borak, Russi, and Puglisi in our summary of the epidemiologic evidence on the possible carcinogenicity of trichloroethylene (TCE) (1). We share their concern for a clear presentation of study results and identifications of methods used in meta-summaries of epidemiologic studies, and labored to do so in our review. The ease with which Borak et al. were able to identify cohort studies that examined renal cancer incidence, reproduce reported results, and recompute estimates on a reduced set of study results

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7. Rothman KJ. Keynote Presentation: A sobering start for the
papers for more detailed information and investigation. We accept criticism on this issue but note that we fulfilled our goal and provided a stimulus for scientific debate on the carcinogenicity of TCE.

Despite their comments, Borak et al. seem to place some weight on the elevated kidney cancer risks reported by Henschler et al. (6), because they explain that these tumors may have resulted from high exposure leading to tubular damage and subsequent cancer. We find this hypothesis intriguing but not entirely satisfying since some TCE metabolites, notably those of the glutathione-S-transferase pathway, are highly mutagenic (14,15). Therefore, tubular damage may not be a necessary precursor to TCE-induced renal cancer. Borak et al.’s hypothesis, nonetheless, is worthy of replication in another, highly exposed population. A comparable study, however, may be difficult to undertake because the average exposure levels for populations in the remaining studies included in our analysis were substantially lower than those typically assumed in Henschler et al. study (6). For example, in the studies of Axelson et al. (16) and Anttila et al. (17), the median exposures were around 50 ppm, lower than typically assumed in Henschler’s cohort (7). Furthermore, incidence rather than mortality should be evaluated due to the differences in the rates between the two measures. In the end, Borak et al. apparently agree with our interpretation that exposure to TCE is a risk factor for renal cancer. Unfortunately, we remain at odds with them about our alternative approaches for summarizing rather overwhelming amounts of information.

In short, our analysis more strongly suggests an association between TCE and renal cancer. Renal cancer is a relatively rare disease and our analysis is based on few incident cases. The addition or subtraction of any one study in the analysis can alter the magnitude of the association. The findings of relative risks above 1.0 for incidence in two of the three other cohort studies (16–18) in Tier 1, in addition to elevated risks between TCE exposure and renal cancer in two recent case-control studies (19,20), are supportive of the overall association between elevated renal cancer risk and TCE exposure. Moreover, mode of action hypotheses regarding the genotoxic effects of TCE metabolites and their presence in the kidney add further support for the human observations.

We recognize many limitations of our approach to summarizing the large amount of epidemiologic data on the possible carcinogenicity of TCE. Although other approaches are possible and some have been used in previous reviews of the epidemiologic literature on TCE, they too have their shortcomings. We look forward to further discussion and debate in the scientific community leading to greater consensus about the possible hazards of TCE exposure.

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Particulate Matter Exposure Assessment
Zeger et al. (1) did an excellent job of presenting some of the possible effects of errors in particulate matter (PM) exposure assessment in time-series mortality analyses. However, they (1) state, our assessment of bias assumed that the health effects of personal exposures to particles originating indoors and outdoors are the same.

This assumption seems to ignore the vast toxicology literature, such as the work of Amdurs et al. (2), which establishes that different particles do have different toxicity. There are no traffic and industrial PM emissions originating in a home. House dust and cigarette smoke greatly affect indoor PM concentrations, but barely affect ambient PM measurements. Furthermore, ambient PM may photochemically react with hydroxide radicals, ozone, and nitrogen dioxide and so may contain partially oxidized and nitrated species not present in indoor-generated PM. Inhalation of grams per cubic meter of soil particles during the 1935 dust bowl days (3) and milligrams per cubic meter of tar in tobacco smoke by smokers may produce delayed and chronic mortality effects from pneumonia and cancer, respectively, but no report in the literature states that such PM exposures produce a next-day increase in mortality, which is the basis for the time-series mortality model of Zeger et al. (1).

It has been shown (4), with the same PTEAM data used by Zeger et al. (1), that the exposure to indoor generated PM, $I = x - \alpha z$, is uncorrelated with the magnitude of $z$, where $z$ is the outdoor PM concentration at the subject’s home, $x$ is the subject’s measured total personal PM exposure, and $\alpha$ is the time-weighted average fraction of the outdoor PM to which the subject was exposed. That is, the exposure to PM, from personal and indoor sources of PM, was independent of $z$, which is expected given the fact that $z$ was unknown; thus the people in the subjects’ homes could not consciously influence their decisions to smoke, dust, or cook more or less in relation to the changing value of $z$. This supports Wilson and Suh (5), who argued that the personal exposure measure desired is $\alpha z$, the total personal exposure to particles from outdoor sources, not total personal exposure. If the above analysis is valid, Zeger
et al. (1) agree that “the two types of particles are more appropriately treated as separate pollutants.” I therefore encourage the authors to continue their fine work with that alternative premise because their conclusion of a negative bias, by treating indoor and ambient PM as a single pollutant, may be incorrect.

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Comments on “Determination of Bisphenol A and Related Aromatic Compounds Released from Bis-GMA-Based Composites and Sealants by High Performance Liquid Chromatography”

I was very much disappointed in the paper by Pulgar et al. (1) because their laboratory once again presented unreliable and confusing HPLC data, regardless of my comments (2) on their previous paper (3). They also have provided no scientific response to my criticism (2).

The peak designated as BADGE in Figure 2A and C of their paper (1) is not bisphenol A diglycidyl ether (BADGE) because its retention time reads approximately 6 min from those chromatograms, but it is given as 7.10 min in their Table 1. This is supported further by the gas chromatogram (GC) presented in Figure 3A, which shows no peak for BADGE at 27.9 min. Thus, it is reasonable to assume that BADGE was not contained in Delton.

In addition, the peaks designated as bisphenol A propoxylate (PBPA) and bisphenol A etoxylate (EBPA) in Figure 2C (1) are doubtful because no peaks are noticeable at 27.7 and 23.9 min in the GC presented in Figure 3A and no mass spectra are shown. The presence of bisphenol A diglycidyl ether methacrylate (Bis-GMA) in a polymerized sample of Delton is not clear because Figure 3C shows no molecular ion peak for Bis-GMA, whereas Pulgar et al. (1) identified a GC peak at 22.8 min in Figure 3A as Bis-GMA.

Pulgar et al. (1) also present curious data concerning the elution of bisphenol A (BPA) and bisphenol A dimethacrylate (Bis-DMA) in Tables 6, 8, and 10 and Tables 5 and 9, respectively. BPA eluted more in the polymerized samples than in the nonpolymerized ones at all pHs indicated. This should be reversed because the diffusion of BPA is usually more limited in polymerized samples than in the nonpolymerized ones. The increase in elution of Bis-DMA at pH 9 and pH 12 compared to pH 1 and pH 7 is unlikely because Bis-DMA is hydrolyzed more easily at alkaline conditions than at acidic or neutral conditions.

Therefore, based on these reasons, I suggest that the designation of each peak shown in Figure 2C of Pulgar et al. (1) is not reliable, and therefore all data shown in Tables 3–10 are also doubtful. I also suggest that the HPLC analysis be performed more carefully and thoroughly. Each peak should be carefully examined to establish whether it originates from a single pure compound or from a mixture of different compounds. It is difficult to separate the BPA peak from the those of other compounds contained in Bis-GMA or Bis-GMA-based resins under the HPLC conditions used by Pulgar et al. (1). In their report it appears that commercial Bis-GMA monomer is a pure compound; however, commercially available Bis-GMA is not pure but a mixture of many compounds.

My laboratory (4,5) has established that commercial Bis-GMA is composed of many minor components and four major components: Bis-GMA, 2,2-[4-(2-hydroxy-3-methacryloyloxy-1-propoxy)-4´-(3-hydroxy-2-methacryloyloxy-1-propoxy)]diphenylpropane (Isos-Bis-GMA), 2,2-[4-(2-hydroxy-3-methacryloyloxy-1-propoxy)-4´-(2,3-dihydroxy-1-propoxy)]diphenylpropane (Bis-GMA-H), and 2,2-[4-(2-hydroxy-3-methacryloyloxy-1-propoxy)-4´-(2,3-dimethoxy-1-propoxy)]diphenylpropane (Bis-GMA-M). We analyzed three commercial Bis-GMA monomers and six Bis-GMA-based composite resins including Z-100, Charisma, and Tetric under the following HPLC conditions we used a C18 column (flow of 1.0 ml/min) with acetonitrile/water (50/50) as the solvent, at a temperature of 40°C, a duration of 55 min (isocronic mode), UV detection (at 230 nm), and fluorescence (excitation 275 nm; emission 300 nm) (5). Using this HPLC analysis, we separated the peak of BPA from that of Bis-GMA-H (which has a peak at a retention time close to that of BPA) and other impurities. Moreover, we also confirmed that BPA and Bis-GMA-H are included in the same peak under certain HPLC conditions (4).

Quantification of the BPA content was only possible when a fluorescence detector was used, and it was impossible using a UV detector because of the extremely low BPA content (5). We found 43–130 µg BPA/g Bis-GMA and 1.5–10.2 µg BPA/g unpolymerized composite resin. The contents of Bis-GMA-H were measured at 18–50 µg/g Bis-GMA and 1.1–1.4 µg/g composite resin (5). The elution of Bis-GMA-H from polymerized Z-100 composite was 58 µg/g composite in 37°C distilled water during a 24-hr period (6). This value is within the range of 3–165 µg BPA/g polymerized composite at pH 7 shown by Pulgar et al. (1) in their Tables 5, 7, 8, and 9. This suggests that most of the “BPA” reported by Pulgar et al. was probably Bis-GMA-H from the five Bis-GMA-based resins. Regarding BPA content in this report, Pulgar et al. (7) reported 6.4 µg BPA/g unpolymerized resin for a commercial resin analyzed by GC-mass spectrometry. This value is quite similar to our data. Thus, we suggest that the BPA content in commercial dental resins is usually a maximum of 10 µg/g resin. Moreover, long-term leaching of BPA from a polymerized resin in water has been predicted to be slight and slow (6). Therefore, little or no long-term estrogenic effect due to BPA contained in Bis-GMA-based dental resins can be expected.

Finally, I suggest that Pulgar et al. (1) replace the chemical structures for BADGE and Bis-GMA shown in their Figure 1 with correct ones. In conclusion, I suggest that Pulgar et al. (1) withdraw the confusing data presented in the paper or totally revise their paper.

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We have read the comments made by Imai on our recently published paper (1) and once again disagree with his interpretation of our findings. Unfortunately, we are unable to compare our results (1,2) with those cited by Imai because four of the papers he cited were published in the Dental Materials Journal, which is not available in Europe. Because the British Library was unable to furnish copies of this journal, we assume that these articles are not available to the international scientific community. Perhaps these important papers should be published in more accessible journals.

Notwithstanding, based on the account of the methodologic approach described by Imai in his letter, we believe that we used a superior analytical method: a) we set the wavelength of the UV detector at 280 nm, recommended for aromatic compounds (3,4); and b) we used a gradient that provided a better resolution and a shorter time for running the chromatogram. The methods that we used to detect bisphenols are now the international gold standard (4–7).

We believe that Imai’s reading of our paper is both simplistic and erroneous. He produces interpretations of our figures which go beyond the actual data that they contain. Most of the concerns raised by Imai stem from his overinterpretation of our Figure 2 (1). For example, his comments on the peaks shown in our Figures 2C and 3 (1) imply that all of the information presented in Tables 3–10 should be depicted in a single figure. We chose to present one figure for each experiment. The figures show chromatograms selected from the set of tests that we performed. It would be more fruitful to discuss the results presented in the tables rather than measuring the X-axes and speculating on the basis of illustrations.

Furthermore, we consider the use of retention times for chemical identification, as described in Imai’s letter, to be an inadequate method because these times are relative to the start of the chromatogram and follow a strict sequence. GC/MS should always be the method of choice for the interpretation of these chromatograms. Imai’s charge of some confusion between bisphenol A and Bis-GMA-H can be easily refuted because the analytical conditions that we used clearly differentiated the two chemicals. Some of his other comments are equally speculative and lacking in scientific support. For instance, Bis-GMA is usually broken in GC/MS and is identified by its moieties.

In short, we cannot accept Imai’s interpretation of our results. Above all, we regard as highly speculative his claim for the none-strogenicity of Bis-GMA-based dental resins based on his group’s findings of little bisphenol-A content. Unless he can demonstrate the absence of estrogenicity in these samples, his conclusions are tendentious and lacking in scientific rigor.

Work in progress is revealing the presence of bisphenol A in the saliva of Delton-treated patients several months after exposure. These data, together with growing evidence of estrogenic sealants and bisphenol A in composite resins and saliva (8–12), are increasing our concerns about the safety of Bis-GMA-based resins.

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Collision of Evidence and Assumptions: TMI Déjà View

Evidence of health effects from radiation released during the 1979 accident at the Three Mile Island (TMI) nuclear generating station continues to be of interest, especially following the U.S. Supreme Court’s recent reinstatement of claims of approximately 2,000 plaintiffs. Unfortunately, Talbott et al.’s analysis of mortality of nearby residents (1) does little to increase our understanding of the accident’s health impact.

Talbott et al.’s paper (1) suffers from the same logical mistake that we identified previously (2). Specifically, they undertook a study in which empirical findings cannot lead to rejection of the study’s null hypothesis. Both Talbott et al. (1) and Hatch et al. (3,4), who reported on the Columbia University studies of cancer incidence, began with the assumption that the maximum possible radiation doses from the accident were well below average annual background radiation levels. Even if standard radiation risk estimates are underestimated by an order of magnitude or more, such doses would be associated with very small increases in cancer in a general population with heterogeneous susceptibility (2). Given the measurement constraints of epidemiologic studies, it would not be possible to detect an accident-related increase in cancer at the dose levels assumed by these authors. Thus, when they find increased cancer rates among residents assumed to have received relatively higher radiation doses from the accident, such as the significant linear trend in female breast cancer (1), the authors must conclude that the association is not due to the exposure they are studying. There is no scientific reason to conduct a study in which the null hypothesis cannot be rejected due to a priori assumptions. This logical problem was further discussed in letters to EH P (5–8). Interestingly, Talbott et al. (1) did not cite our paper, which introduced this logical problem (2), or the subsequent letters (5–8).

Talbott et al. (1) did not consider the possibility that some people received radiation doses from the TMI accident that were substantially higher than background. Such a possibility is supported by residents’ reports of acute symptoms following the accident (9,10) and by evidence of elevated chromosomal aberration rates among persons reporting symptoms (11,12). The radiation dose estimates used by Talbott et al. depended on extensive assumptions about
prohibited the investigators from making gators by court order (TMI dosimetry imposed upon other investigators). Dosimetry reminds us of the constraints on relations and defensive epidemiology purification. Gur et al. (13), the authors of the Columbia studies (3,4) discussed exposure measurement error in interpreting their findings.

Gur et al. (13), the authors of the dosimetry report, state that their methodological development was “for educational, public relations and defensive epidemiologic purposes.” This description of the rationale for dosimetry reminded us of the constraints on TMI dosimetry imposed upon other investigators by court order (2,6). That order (14) prohibited the investigators from making upper limit or worst-case estimates of releases of radioactivity or population doses… (unless) such estimates would lead to a mathematical projection of less than 0.01 health effects and specified that a technical analyst… designated by counsel for the Pools [nuclear industry insurers] concur on the nature and scope of the [dosimetry] projects.

We were disappointed in the lack of detail provided by Talbott et al. (1) regarding epidemiologic methods typically used in cohort studies. An advantage of their study compared to the Columbia University study (3,4) is that exposed persons could be followed as they left the area; however, there is no information given regarding methods of vital status follow-up, death certificate retrieval, or determination of loss to follow-up. Talbott et al.’s (1) Table 1 presents information for a “1992 cohort,” including the number of households, implying that a second survey of households might have been done. However, no information is given to explain the 1992 cohort or its relationship to the 1979 cohort.

Because exposed persons were followed, Talbott et al. (1) could also have addressed the problem of tracing birth cohorts through time, a method that could not be employed in the Columbia study (2). Fetal and childhood exposures appear to be particularly effective in producing cancer (15,16); therefore, analyses of cancer mortality among persons exposed at those ages would be of special interest. Talbott et al. (1), however, excluded persons younger than 18 years of age from their dose-response analyses.

The number of persons and cancer deaths included in relative risk regression analyses of dose response were not given (1). These numbers may differ from those presented in Tables 1–4 not only because of the exclusion of persons under 18 years of age but also because of Talbott et al.’s requirement that members of the cohort be born within 1 month of the case in order to be included in the risk set for the case. The authors gave no rationale for using such a narrow restriction, which could limit the size of risk sets, especially at older ages (the median age for the cohort was reported as 29 years), leading to a possible loss of precision because of small risk sets or even loss of cases for which there were no eligible controls.

Studies of relationships between cancer and environmental exposures typically take into account latency periods known to occur between exposure and disease. Failure to consider exposure lag times reduces sensitivity to detect the effects under investigation. Talbott et al. (1) presented no latency analyses.

Although the data collected by Talbott et al. (1) appear to have the potential to advance our understanding of mortality in the TMI area, lack of information about the materials and methods limits our ability to evaluate their report. Furthermore, the statistical issues raised above lead us to question the sensitivity of their analysis to effects under investigation. We hope that more information about this study will be presented in the future, that further analyses will be conducted using methods which increase the study’s sensitivity and precision, and that interpretations will be offered that are not inhibited by the a priori assumption that positive results cannot be interpreted as evidence in support of the hypothesis being investigated.

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Re: “Collision of Evidence and Assumptions: TMI Déjà View”

We appreciate the interest of Wing and Richardson in our recent follow-up of mortality in the Three Mile Island (TMI) cohort (1). We concur with the suggestion that our data have the potential to advance the overall understanding of the health implications of the TMI accident. We also welcome the opportunity to address several of the issues raised and the concerns expressed by Wing and Richardson within the context of the strengths of our recent mortality analysis.

The primary motivating factor for the University of Pittsburgh in conducting the TMI study (1) was to explore the unknown nature of the health effects of low-dose radiation. No other study to date has followed prospectively a large (n = 32,135), free-living, non-occupationally exposed population for an extended period. The only other assessment of low-level exposure was in the Hiroshima atomic bomb survivor studies (2–4), which, by the overall nature of the exposure, was relatively high compared to the more recent TMI incident.

In a reevaluation of an original study by Hatch et al. (5,6) of cancer incidence in the
TMI cohort, Wing et al. (7) suggested that specific factors may have detracted from the ability of previous investigators to detect any association of specific radiotoxic sensitivities with low level radiation exposure at TMI, including: a) the inaccuracy of estimates of the magnitude of radiation exposure during the TMI incident and b) poor classification of relative exposures within the 10-mile study area. The ecologic nature of the Columbia University Study prevented access to individual cancer risk determinants (i.e., tobacco smoking, education, etc.). Further, possible classification associated with assignments of exposure based on residence at the time of diagnosis rather than at the time of the incident (5,6) may have occurred. We believe that the methodology employed in our recent mortality investigation addresses several of these key issues.

The individual dose estimates applied to the TMI population in our study were modeled by Gur et al. (8). Gur et al. used the location of residence in relation to TMI (both distance and direction) and information on movements into and out of the area during the 10 days after the accident in conjunction with estimated time-dependent dose-rate distributions to assign likely and maximum possible doses to members of the 13,000 households residing within a 5-mile radius of the TMI nuclear station. The estimated time-dependent dose-rate distribution used to assign individual dose assessments was similar to that developed by Woodward (9) and is described in detail elsewhere (8). With the inclusion of migration factors, this individualized dose estimate may represent a more sensitive measure of individual exposure than does exposure assignment based on study tracts constructed from census block boundaries and meteorologic considerations. Hach et al. (5,6) noted the potential biases associated with the study tract method, including an inability to control for migration of the population to and from the area and the potential for exposure misclassification, particularly with inward migration. The exposure measures generated by Gur et al. (8) and used in our analyses should at the very least represent a reasonable estimate of individual rather than population-based exposure at the time of the event, and reduce the likelihood of exposure misclassification.

We assessed sociodemographic data and vital status through the TMI Population Registry (10). This registry was a compilation of individual descriptors collected at the time of the special TMI Census in June 1979. Information collected included name, address, age, sex, race, and a brief medical history of cancer diagnoses, thyroid disorders, radiation treatment or therapy, and prior exposure to ionizing radiation on the job. Pregnancies at the time of the accident were noted and smoking history was recorded, as well as the person’s daily travel in and out of the 5-mile radius during the 10-day period. The documentation of the tracing of vital status of these individuals within this population was extremely complete. To maintain the follow-up registry, the Pennsylvania Department of Health (PDcH), with the cooperation of the U.S. Postal Service, devised a system to annually obtain the current addresses of persons in the registry without contacting the registrant directly. Names and addresses of all persons in the registry, aged 16 years or older, are sent to the local post office for address verification and update. The post offices are obliged to respond by supplying all relevant forwarding address information on file. Many post offices also correct spelling errors, indicate deceased addresses, and supply other helpful information. Each year, new current addresses are added to the TMI Population Registry database. Details of the follow-up from 1979 through 1992 are presented in Table 1. The PDcH follow-up yielded only 121 individuals who did not have a verified address and vital status through 1992. This represents 0.5% lost to follow-up, or a 99.5% success rate in tracing individuals in this cohort (11).

After the 1979 incident, the PDcH has updated mortality status annually. The TMI Population Registry data set is matched yearly against the death certificate file maintained by the department’s Health Data Center to identify those TMI residents that have died in Pennsylvania. For TMI residents who have relocated outside of Pennsylvania, the PDcH has an agreement with the National Center for Health Statistics (NCHS) to match the TMI population registry file once every 3 years with the National Death Index (NDI) to identify those who have died outside of Pennsylvania. Data on potential confounders (i.e., sex, race, smoking status, and education) collected at baseline and information on the outcome of interest in the exposed population (i.e., mortality) through 1992 was available for our mortality assessment. Through access of the current NDI national death certificate program, it will be possible to trace all individuals through 1998 and beyond with the same amount of success.

As we suggested in the "Discussion" of our paper (1), mortality, as a function of both incidence and case fatality, may be different from incidence patterns in the TMI cohort. Therefore, it will be important to monitor both cancer incidence and mortality with respect to individualized dose estimates in this population to determine if incidence mirrors the observed mortality experience. However, the mean latency of most radiotoxic solid tumor cancers (lung, breast, and lymphopoetic-hematologic tissue) is 20–30 years (12), and this population is only now experiencing these tumors. In the 1998 follow-up currently in-progress, we intend to assess the significance of this long-term latency and its relationship to cancer incidence and mortality in the TMI population.

Wing and Richardson suggest that the exposures to the population on the day of the accident may have been far greater than previously estimated. In fact, they reference apparent chromosomal effects in this population as potentially attributable to low-level radiation (13,14). A total of 29 blood samples were collected from predominantly older individuals near TMI 15 years after the accident (13,14). There was no local control group and no adjustment for confounding (smoking, occupational exposure) or other environmental insults during this 15-year elapsed period. Hence we can not rule out a spurious cause and effect.

Because we are aware that exposure misclassification error remains a possibility, we agree that it may be reasonable to consider a worst-case scenario regarding exposure, if in

| Year | Population | Lost to follow-up | Deaths | Death certificate | No death certificate |
|------|------------|------------------|--------|------------------|---------------------|
| 1979 | 32,135     | 0                | 166    | 166              | 0                   |
| 1980 | 31,969     | 4                | 336    | 336              | 0                   |
| 1981 | 31,633     | 20               | 322    | 322              | 0                   |
| 1982 | 31,311     | 6                | 310    | 310              | 0                   |
| 1983 | 31,001     | 6                | 312    | 310              | 2                   |
| 1984 | 30,689     | 0                | 301    | 300              | 1                   |
| 1985 | 30,388     | 2                | 303    | 303              | 0                   |
| 1986 | 30,085     | 11               | 263    | 261              | 2                   |
| 1987 | 29,822     | 0                | 278    | 277              | 1                   |
| 1988 | 29,544     | 8                | 263    | 260              | 3                   |
| 1989 | 29,281     | 0                | 274    | 273              | 1                   |
| 1990 | 29,007     | 25               | 288    | 284              | 4                   |
| 1991 | 28,719     | 0                | 263    | 261              | 2                   |
| 1992 | 28,456     | 39               | 266    | 262              | 4                   |

*Lost to follow-up included in population value.*
fact increases in cancer mortality or morbidity are observed in this population over time. With the data analysis thus far, we have noted no increases that would allude to a more serious exposure scenario than we previously suggested. Assuming, however, that exposure was underestimated across all levels of either likely or maximum gamma, we suggest that a linear trend, if not an absolute association, should be evident if all cause or cause-specific mortality was associated with increasing exposure to low-level radiation.

Our finding of a significant trend of higher likely gamma with increasing breast cancer risk is therefore important. We cited two statistical probabilities in the assessment of this association. The global p-value reflected the statistical significance in assessing overall breast cancer risk when comparing risk levels to the lowest category of each risk factor as baseline. The global p-value was not significant (p = 0.17), indicating no overall difference in breast cancer when the reference group for low gamma exposure was compared to all remaining groups. However, the test for linear trend, which assessed whether a statistically significant dose response was evident when comparing groups to the baseline risk category, was in fact statistically significant (p = 0.02). The risk estimates by exposed and nonexposed subjects suggest possible dose response in incrementally dosed groups (1.76, 1.76, and 2.42). However, multiple comparison adjustments were not considered in this study. Multiple comparison problems occur and often yield significance because of the sheer number of tests done on a population. We have continued to follow the trend in breast cancer and likely gamma exposure in the 1995 update. The data indicate that the trend is slightly attenuated and no longer statistically significant. Continued follow-up of this population is critical to reconciling this important issue.

We agree with Wing and Richardson’s comment that using a matching criterion of a 1-month caliper in date of birth may be too precise for such an epidemiologic study. However, we were constrained by hardware and software limitations at the time of the analyses. Because of the size of the total cohort, the risk sets were extremely large, resulting in computational difficulties. The 1-month caliper was used to decrease the risk set size to a more manageable level. This tight match resulted in a loss of only four deaths in the analysis. In comparison to the total deaths, we felt that this was loss was minimal. Fortunately, these software and hardware limitations are no longer an issue, and such a tight match will not be necessary in future updates.

Because childhood cancers are quite different in both presentation and pathology than those manifesting in adults, the mortality and incidence experience of the children of TMI (<18 years of age) is currently being assessed in a separate analysis that includes mortality data through 1996. Because potential confounders (education and smoking) were not available for those <18 years of age at the time of the accident, we restricted our relative risk regression analysis to those ≥18 years of age. Table 2 shows the number of observed deaths for each outcome of interest used in relative risk regression modeling. Also shown is the total number of deaths for the same cause categories that were used in the standardized mortality ratio analyses. As seen in Table 2, 0–4 deaths were omitted when subjects were restricted to those ≥18 years of age. Through 1992, a total of six deaths from neoplasms had occurred in individuals <18 years of age at the time of the accident.

It is reassuring to note that Eastman Kodak (Rochester, NY), in an independent effort, collected and analyzed high-speed photographic film located in the area during the TMI releases (15). None of the film showed any unusual fogging. The minimum exposure level at which fogging occurs is 5 mmR, and no film received an exposure in excess of that amount. At this time, the impact of the radiation exposure from the TMI incident on the mortality of the residents appears minimal. However, due to latency in the development of several radiosensitive malignant neoplasms, we plan to continue our active involvement in the monitoring of health risks in the TMI cohort.

Evelyn O. Talbott

Table 2. Number of observed deaths available for relative risk regression modeling.

|                | Males          |   | Females        |   |
|----------------|----------------|---|----------------|---|
|                | ≥18 years | <18 years | Total |   | ≥18 years | <18 years | Total |
| All heart causes | 814      | 3       | 817    |   | 851      | 2       | 853    |
| All malignancies | 419      | 4       | 423    |   | 382      | 2       | 384    |
| Bronchus, trachea, and lung cancer | 147      | 0       | 147    |   | 56       | 0       | 56     |
| All lymphopoeitic and hematopoietic cancer | 40       | 0       | 43     |   | 47       | 0       | 47     |
| CNS cancer      | 6        | 0       | 6      |   | 11       | 1       | 12     |
| Breast cancer   | NA       | NA      | NA     |   | 78       | 0       | 78     |

Abbreviations: CNS, central nervous system; NA, not available.

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Correction

In the September 2000 issue of EHP, a photograph of both chestnuts and hazelnuts was printed as accompaniment to an article discussing only hazelnuts (“Going Nuts over Pacaltaxel,” EHP 108:397 (2000)). EHP apologizes for any resulting confusion.