of intake were not equivalent to tertiles of exposure level. Tertiles were expected to each contain one-third of the controls. However, the tertiles of controls for live cases in the analyses that were lagged 40 years were biased downward (the first intake tertile included 38% and the third intake tertile included 28%; Web Table 3 of Steinmaus et al. (1) and Web Table 1, available at http://aje.oxfordjournals.org/), whereas the tertiles of controls for deceased subjects in the analyses that were lagged 40 years were biased upward (the first exposure level tertile included 29% and the third exposure level tertile included 37%; Web Table 4 of Steinmaus et al. (1) and Web Table 1).

Further, because the preinterview mortality rate was markedly higher for the lung cancer cases (50 of 92; 54.3%) than for the controls (19 of 288; 6.6%), there were few deceased controls. Most of the cases ($n = 50$) but few of the controls ($n = 19$) had entered the combined analysis after the upward biased controls, whereas the great majority of the controls (269 of 288; 93.4%) followed the downward biased controls. In the combined analysis, the deceased cases were essentially compared with the distribution of the live controls.

One method (Web Appendix) for taking this imbalance into account would be to have the controls enter the combined analyses in the same proportion as do the cases. Because 42 of the 92 cases (45.7%) entered the combined analysis by intake tertile, 45.7% of the 288 controls ($n = 131$) should have entered the combined analysis by intake tertiles. Similarly, because 50 of 92 cases (54.3%) entered by arsenic level tertile, so should have 54.3% of the 288 controls ($n = 157$). The intertertile distributions of each set of the controls should be the same as the group from which they came. In our analyses, the unadjusted odds ratio (third tertile vs. first tertile) for the 40-year lag was 1.63 (95% confidence interval: 0.90, 2.94) (Web Table 1) rather than 1.90 (90% confidence interval: 1.13, 3.13) (Table 2 of Steinmaus et al. (1)); for the 5-year lag, it was 0.95 (95% confidence interval: 0.55, 1.65) (Web Table 2) rather than 1.23 (90% confidence interval: 0.77, 1.97) (Web Table 3 of Steinmaus et al. (1)). Thus, when using appropriately balanced controls, there was no significant association ($P = 0.14$) between lung cancer and arsenic levels below 100 µg/L in drinking water.

The rationale for a 40-year lag was clear in the earlier paper by Steinmaus et al. (2) which included very high (860 µg/L) exposures that had ended 40 years earlier. However, in their more recent paper (1), it is not clear for the low-level (1–60 µg/L) exposures, which remained constant from 1930 through 1994.

Further, the analysis with a 40-year lag excluded the more recent 40 years of arsenic intake, which appears to have been twice as great (third tertile cutpoint >106.4 µg/day) (Web Table 3 of Steinmaus et al. (1)) as that of the 40-year lagged intakes (third tertile cutpoint >63.6 µg/L) (Web Table 3 of Steinmaus et al. (1)). In conclusion, the reported significant association seems to be the consequence of having used unbalanced controls in the analysis.

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THREE AUTHORS REPLY

We agree with the overall concept that we believe Slim and Sewitch (1) are trying to express: Important novel findings like ours should be critically reviewed and, at least initially, interpreted cautiously. Notably, our study was the first with individual-based data on lifetime exposures to identify an association between arsenic concentrations below 100 µg/L in drinking water and increased risks of lung cancer (2). Given this novelty, we believe it is also important to note that our findings met several of the criteria commonly used to evaluate causality (3). For example, we found evidence of dose-response relationships in several of our analyses. We also found very low P values, which suggests that several of our findings are unlikely to be due to chance. We also reported evidence that confounding by smoking, diet, occupation, or other major determinants of lung cancer risk did not cause our results. With regard to the causal criteria of consistency and biologic plausibility, we cited data showing that arsenic reaches our target organ site (the lung) and that it causes

toxicity there. We also cited literature in which it was shown that arsenic is a well-established cause of lung cancer at higher exposure levels and that long latency patterns similar to ours have been found in other studies. In addition, we have no reason to believe the specific issues raised by Slim and Sewitch caused our results. For example, cases were ascertained using the exact same methods in areas with higher and lower levels of exposure; we cited previously presented data that showed that the distribution of our controls in the study area was similar to that in the Chilean census (4); everyone in our 40-year latency analysis was 40 years of age or older; the magnitude of our major findings changed only slightly when proxy subjects were removed (Web Table 3 of our article (2)) and in any case, for arsenic exposure, the proxy interviews only had to identify city or town of residence; and we clearly stated that the subjects were frequency matched (versus 1:1 matched) so that unconditional logistic regression is the appropriate choice.

With regard to our title, our study was about low arsenic exposures and the associations we found with increased cancer risks. Because of this, we believe our title is quite appropriate. As for the "public fear" and "alarm" that our findings might induce: We believe that our findings should raise at least some concern about the possibility that low-level arsenic exposures cause cancer and that this possibility should not simply be ignored. Although we cannot control everyone's reaction to our findings, we believe that most people will take them for what they are and for what our conclusion stated them to be, that is, "new evidence that arsenic water concentrations less than 100 µg/L are associated with increased risks of lung cancer" (2, p. 1082). Overall, we believe it is prudent to consider these findings carefully and not to dismiss them because of spurious methodological issues.

The letter by Lamm et al. (5) contains several misrepresentations. First, they noted that "significant" associations were found only in our combined analysis and not in analyses of only arsenic intake or arsenic concentrations in drinking water. However, this disregards the fact that our arsenic intake analysis had fewer subjects (2). Thus, the odds ratios and not their statistical significance should be compared. Because the odds ratio that we presented for all participants (2.01) was close to that based on only those for whom we had water intake data (1.90; Web Table 3 in our article (2)), it is incorrect to imply that they represent different conclusions. With regard to our analyses of arsenic water concentrations, the results were what we expected, and they support our contention that data on water intake improve exposure assessment and study power.

Lamm et al. also noted an "imbalanced" distribution. However, our category cutpoints were based on all subjects, and as seen in our main analysis (Table 2 in our article (2)), our tertiles were fairly well balanced (although there was some minor unevenness due to overlapping subjects at the cutpoints). The category cutpoints in our analysis of arsenic intake (Web Table 3 in our article) were also based on all subjects (both proxy and living subjects). This was done so that each subject in our main analysis (Table 2 in our article (2)) would be categorized independent of case status, a key element for preventing bias. To do this, we calculated median intakes of drinking water for all living cases and controls

and assigned the case-status–specific median value to each proxy subject. These values were then used to estimate arsenic intakes in proxy subjects, and the estimated intakes in all subjects were then used to set tertile cutoff points. We then used arsenic concentrations in drinking water (again, using tertiles based on all subjects) and not their estimated arsenic intakes to place proxy subjects into exposure tertiles so that they would be categorized based on their best available data. Because our article was a brief report (2), some of the details of these methods were provided in a reference (6).

We could have based arsenic intake tertile cutpoints on only living subjects and based arsenic water concentration tertile cutpoints on only proxy subjects. However, because living subjects were mostly controls and proxy subjects were mostly cases, this categorization would not have been independent of case status. Because cases drank more water and had higher concentrations of arsenic in drinking water than did controls (our Table 1), this would have led to what were essentially lower cutoff points for living subjects (mostly controls) than for proxy subjects (mostly cases). This would have artificially shifted more controls into higher tertiles and more cases into lower tertiles and biased odds ratios towards the null.

The unusual analysis by Lamm et al. ignores water intake data in most controls, the higher water intakes we saw in cases, the fact that people with higher water intakes will generally have greater exposures, and the fact that water intake data improve exposure assessment (5). Their analysis redistributes controls but not cases, does not acknowledge that they still show a dose-response trend, and inexplicably ignores our findings in younger adults with odds ratios going up to 3.41 (90% confidence interval: 1.51, 7.70).

Regarding the last comments of Lamm et al., some subjects moved into the exposed area within the past 40 years (migrants are mentioned). Because of this, our 40 year-lagged analyses are perfectly appropriate for assessing latency. In addition, because of their more recent exposures, migrants had higher exposures using 5-year lags than 40-year lags. In conclusion, although we appreciate the opportunity to discuss these issues, none of the re-interpretations or re-analyses by Lamm et al. impact our findings or conclusions.

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