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Letter to the Editor

Response to Hearne and Lednar

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We would like to respond to the comments that you received from Hearne and Lednar regarding our paper on "Comparing Toxicologic and Epidemiologic Studies: Methylene Chloride—A Case Study."[6]

We disagree with Hearne and Lednar's assertion that our presenting separate risk estimates for each of the exposure groups in the Kodak study is "inappropriate and misleading." They suggest that presenting separate risk estimates may "dilute the precision of the human data." In fact, combining exposure groups in epidemiologic studies may increase the variability in the risk measure along with biasing the risk estimate if a dose–response relationship is present. In this particular instance, where an increased risk was not observed in any of the exposure categories, the results from the combined analysis may in fact be the most informative as suggested by Hearne and Lednar. However, we believe that it is appropriate to present both the results from the individual exposure groups and the combined analysis as we have done in our paper. Incidentally, this criticism is somewhat curious given the fact that Hearne *et al.*[1] also presented individual exposure group and combined analyses in their paper comparing their epidemiologic findings with the animal model-based predictions.

We recognized in our paper the limitations of our healthy worker effect (HWE) adjustment but still believe that this potential source of bias needs to be considered, and this is the only viable solution for this type of data.

We disagree with the conclusion of the "panel of experts" reported by Choi[2] that a HWE is unlikely to be present in cancer studies and, therefore, can be ignored (one of the panel members also did not agree with this position). Steenland and Stayner[3] saw evidence for a HWE for all cancers (SMR = 0.91) in a combined analysis of 10 NIOSH cohort mortality studies, and the extent of the bias appeared to be related to the percentage of inactive person-time in the studies. One member of the panel of experts (Sir Richard Doll) was quoted in the Choi article as suggesting that the HWE was unlikely to effect the risk of cancer "unless there is selection against smokers." As we noted in our paper, the Kodak facility had a policy of not permitting workers to smoke at their workstations. This policy may have resulted in a "selection against smokers" or reduced the risk among smokers and, thereby, produced an unusually strong HWE in this study.

It is difficult to comprehend Hearne and Lednar's argument that our HWE correction was "extreme" because it produced SMRs that were near 1.0. An SMR of 1.0 is precisely what we should expect unless one believes that exposure to methylene chloride prevents cancer, which is hardly a tenable hypothesis.

In our paper we presented results with and without the HWE adjustment. The results from the unadjusted analyses also supported the conclusion of our analyses that the negative results from the Kodak study are not statistically inconsistent with predictions from the animal-based risk assessment model. The example provided by Hearne and Lednar for liver and lung cancer (all exposure groups combined unadjusted for HWE) only reinforces our point. In this example, the human confidence interval was 0.46–1.12, whereas the predicted animal-based confidence interval was 1.00–1.06 (male mouse) and 1.00–1.10 (female mouse). Thus, the confidence interval from the human study fully contains the predicted confidence intervals from the animal-based risk assessment models.

Hearne and Lednar mistakenly suggest that we have chosen to compare upper bound confidence intervals while ignoring the best point estimates of risk. Actually our suggestion was that one needs to consider not only the point estimates but also the variability surrounding these estimates of risk and that confidence intervals are a useful means for making such comparisons. They sug-

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gest an alternative comparison, which is to compare the observed/expected ratio (SMR) to the animal-based confidence interval. The problem with this approach is that it essentially ignores the variability associated with the epidemiologic estimates of risk. Obviously, the SMRs, which were generally less than one, reported in the Kodak study are not consistent with the increase in risks predicted by the animal-based model. However, the question that we were trying to address was whether one could dismiss the animal-based predictions using the epidemiologic results with any degree of confidence. The approach suggested by Hearne and Lednar is inadequate for addressing this issue.

Finally, we do not disagree with Hearne and Lednar's suggestion that ideally it is important to consider the results from all of the epidemiologic studies. We chose the Kodak study for our analysis because it was clearly the best study in terms of having well-characterized exposures, and because this was the study that Hearne *et al.*[1] and Toleffson *et al.*[4] had used to examine this issue. The other studies that are presented in Table I of Hearne and Lednar's letter are clearly supportive of the qualitative conclusion that studies collectively do not provide evidence of an excess cancer risk among methylene chloride exposed workers. It is worth noting that a significant excess of liver/biliary cancer was observed in one of the studies,[5] which is obscured by the combining of lung and liver cancer mortality. However, it is difficult to make any formal comparison of the predictions from the animal-based risk assessment models with these results, because of the lack of quantitative exposure information for these other study populations. Nonetheless, we strongly believe that it is crucial to use all available epidemiologic information in the risk assessment process.

In conclusion, we agree with Hearne and Lednar that the use of epidemiologic data should be strongly encouraged in risk assessment. We also agree that all available human data should be used. We object to the implication that we used human data to justify "toxicology findings derived from non-human species." This reflects a fundamental misunderstanding of our paper. The selection of appropriate data for a risk assessment must be an informed decision: informed by species differences, but also informed by important differences in experimental protocols and study follow-up. Although we disagree with some of their comments, we are pleased that Hearne and Lednar have offered their views and hope that this may generate further discussion and interest in this issue.

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