

(Responses to Reviewers' Comments November 25, 1998)

3. NMRD mortality is notoriously difficult to study with a mortality study because of great uncertainty and variability of disease classification. Emphasize this point more and perhaps some literature comparing death certificate and clinical NMRD diagnosis/classification would help clarify the issue.

We were unable to locate appropriate references for such purposes, and will pursue this at a later date.

4. Healthy worker survivor bias might be discussed. Conceivable that long-term workers represent a "survivor" population in view of the neurotoxic properties of vinyl chloride, at least at high doses. Survivors were less likely to have had intense exposures than workers who left after shorter, more intense exposures. Other aspects of short-term employment that can create biases in the analysis of mortality trends by employment duration include differences in exposure intensity and/or lifestyle characteristics by duration of employment. Some discussion of possible biases would be useful.

Added section to discussion on limitations of exposure assessment and discussed the healthy worker survivor effect. It is not likely that this survivor effect was operating within this cohort, as mortality trends were not markedly different across strata of employment duration. For the known relationship with ASL, however, duration of employment was a strong predictor (i.e., short-term employees did not have as great an excess risk).

From Professor Aronson:

5. To insure the same level of quality in the death search, it could have been done throughout the entire follow-up time, instead of accepting the 1,533 deaths found by previous study contractors. This idea may have been considered, and if so, reasons for not doing this may be perfectly legitimate but should be mentioned.

Because we had to request death certificates, we conducted the death search for everyone in the cohort for whom we did not have a death certificate (had about 400 DC's).

6. Was consideration given to using another occupational cohort as the reference population and in this way avoiding the healthy worker effect?

No. We conducted Cox proportional hazards analyses which utilize an internal comparison, thereby eliminating bias from the healthy worker effect. Cox analyses were conducted for liver and biliary tract cancer, brain cancer and all angiosarcomas, causes

of death for which numbers were adequately large to employ these analytical for these techniques.

From Dr. Collins:

7. Presentation of 1942-82 and 1942-95 groups is confusing. Suggest dropping 1942-1982 and add special section in the addendum about this group. Extended presentation in the main part of document detracts from important messages.

Because of improvements in methods (state-weighted rates), follow-up of cohort members (reduction in the number of study subjects lost to follow-up) and use of NIOSH mortality rates, it was important to re-establish a baseline for the updated analysis through 1995. We think the 1942-1982 section should remain in the body of the report.

8. Findings on STS are difficult to interpret. There may be no unbiased way to compare worker and general population death rates:
1. Different etiologies, but grouping is necessary because STS's are rare.
 2. DC's are a poor source for collecting STS's: half of STS's reported on DC were something else and half didn't appear on DC as the underlying cause.
 3. Changes in diagnosis, classification and coding over time: malignant fibrous histiocytomas were not diagnosed regularly until mid-70's.
 4. 4/12 STS's were angiosarcomas indicating that some or all of these tumors were located in the liver and thus may be misclassified.

We agree that the findings on STS are difficult to interpret. That all of these points are true doesn't negate the excess seen for STS even after removal of four angiosarcomas that are possibly misclassified. The anatomic site of angiosarcomas, however, is not limited to the liver. Furthermore, with 14 soft tissue sarcomas identified (without complete follow-up through 1996) and the addition of five soft tissue sarcomas that were coded to other sites, the number of soft tissue sarcomas in this study is similar to or exceeds the number found in other studies where soft tissue sarcoma was examined (i.e., workers exposed to phenoxy herbicides and chlorophenols contaminated with dioxins).

9. RE: Brain cancer. Benign brain tumors were not mentioned. Were these evaluated and what were the findings? One could conclude that the brain cancer finding was not confirmed in the follow-up because the SMR in the 1942-82 group was 1.6, but only 1.1 (95% CI: 0.6-1.9) in the 1983-1995 group. The argument that the findings could be explained by lower exposures among workers represented most heavily in the update is difficult to make without exposure data.

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Benign tumors were evaluated: the results were reported in Tables 7, 17 and 18 and are discussed for baseline results. We added a small paragraph for the follow-up on benign and unspecified brain neoplasms. In the follow-up, two were observed (2.5 expected). We added that 14 brain cancers were observed compared to 12.2 expected during the follow-up period between 1983 and 1995.

10. p. 19: All DC's obtained in the update were recoded. Authors should present in the text what percentage of the certificates were recoded. Did the recoding of the one liver cancer (p.55) and the 1 brain cancer (p.57) occur after the coding for the current study or were these just a change from Wong's coding of the same information? Since this recoding seems to be "post hoc", I would suggest that the authors note this in the tables where these data appear and discuss in the text how this recoding might bias the estimates of the rates.

All death certificates were recoded prior to the re-analysis of mortality through 1982. After the re-analysis was conducted, the updated analysis through 1995 was conducted. We added in the text what percentage of death certificates were recoded. The recoding of both the liver cancer and brain cancer occurred prior to conducting the analysis.

From Dr. Ramlow:

Dr. Ramlow's only major comment - to add more discussion of the results in the context of the published literature - was addressed in the revision. This was requested specifically with respect to the "discrepancy" between our results and the European study by Simonato, et al. However, Simonato, et al. reported a significant excess of brain cancers among employees in the longest duration of employment category, making the discrepancy less clear. This is also addressed in the text. The three minor comments - to present figures on an arithmetic (vs. log) scale, to prepare a figure for all cancers combined, and to add the analyses indicated in the protocol (multivariable analyses had not been completed at the time of the draft report) - also were addressed in full.