Review of:

"Brain Cancer Occurrence in Vinyl Chloride Exposed Chemical Workers Protocol"

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General comments

This protocol is for a study that will address an important occupational medicine issue, the possible etiologic relation between vinyl chloride and brain cancer. The association has been suggested from some, but not all, previous epidemiologic investigations of exposed occupational cohorts, and therefore remains a controversial issue. The study location will be the same plant where the original cluster of angiosarcoma cases was identified in 1973. A similar methodology as proposed here was used to examine associations of vinyl chloride and other chemicals with angiosarcoma, as summarized in the 1981 publication (J Occup Med 23:353-8.) The proposed study will take advantage of an extensive data base of historical information on disease incidence, work history personnel data, and some exposure monitoring data for vinyl chloride and other chemicals.

The study follows a relatively straightforward and logical approach for exposure assessment, and the case-control analysis should yield some meaningful data about potentially causative associations with specific chemicals. The exposure assessment, which is appropriately acknowledged as an essential determinant of the study's value, relies on a qualitative rating scheme rather than on direct quantification. Insofar as there is unlikely to be exposure measurement data spanning back to 1942 when the plant opened, some compromise is needed to estimate exposures. The Cumulative Exposure Rank Months (CERM) metric used previously in the angiosarcoma study seems to be an unbiased estimator of actual cumulative exposure, although the interpretation of the data will not be translatable into an exposure-response gradient. Confidence in this approach was gained from the analysis of the angiosarcoma data, although it should be realized that this approach may be far less informative, due to exposure misclassification, in a situation

where there is a considerably weaker exposure/disease association than vinyl chloride and angiosarcoma. It may ultimately turn out that ordinal exposure intensity rankings are the necessary underpinnings of the exposure assessment. However, it would clearly be worthwhile to consider quantitation of exposures, at least for vinyl chloride, which is the chemical of greatest prior interest. A qualitative exposure assessment scheme might be suitable for other chemicals (e.g., butadiene) which are of less prior concern. In fact, the analysis is largely dependent on this method which does not yield conventional estimates of relative risk (odds ratios) or dose-response. Standard methods for case-control studies (e.g., Mantel-Haenszel, logistic regression modeling) should certainly be considered, in addition to the descriptive approaches that are presented.

Specific comments

1. Matching cases and controls on year of hire and duration of employment may be overmatching if employment duration relates to cumulative exposure to vinyl chloride. Matching on survival duration should be sufficient.

2. As mentioned earlier, the proposed method of data analysis does not lend itself readily to exposure-response estimation. More convention case-control analytic techniques than the methods described should be considered. Also, there should be some presentation of how multiple exposures will be considered in the analysis.

3. No mention is made of the number of expected brain cancer cases; thus, there are no statistical power calculations shown. It would certainly be useful to present anticipated study power for all brain cancers and possibly for subsets of brain cancers classified by histologic type.

4. On P7 it is mentioned that cancer diagnoses will be "validated" against death certificate information. Death certificates can be unreliable for some diseases, including brain cancer, which would mean that there is no diagnostic "gold standard." Perhaps something other than death certificate data can be used for this purpose.

5. It is not clear how this study will coordinate efforts with the cohort update being performed by Applied Epidemiology, Inc. Is this proposal redundant of that effort, or are there unique aspects of the current proposal?