

Review and Critique of
Tamburro, CH and Shah, HC, "Brain Cancer Occurrence
in Vinyl Chloride Exposed Chemical Workers Protocol"

prepared for
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This review focuses on the biostatistical and epidemiological aspects of the protocol, which are the primary areas of expertise of this reviewer. This review was conducted without access to the eight appendices listed by the authors in the table of contents.

General Comments

Overall Strengths

1. The investigators have access to the University of Louisville's Occupational Surveillance data base of 3,330 workers from the B. F. Goodrich Bells Lane Plant. Once they update the work history and exposure data beyond 1978, this data base will provide, for causes of death with ample numbers of observed events, an epidemiologically valuable resource for assessing the long-term health effects of exposure to one or more of the 22 chemicals that they monitor and for which they have developed retrospective estimates.
2. The cohort data base is theoretically appropriate (relative to types of data, completeness, etc.) for exploring the hypothesized association between vinyl chloride (VC) exposure and brain cancer, but only after a statistically sufficient number of brain cancer deaths are observed.
3. The investigators incorporated a very comprehensive and detailed data quality assurance and control protocol to help ensure the accuracy and completeness of all data associated with the surveillance program.

Overall Weaknesses

1. One of the most glaring deficiencies in the protocol is the absolute omission of any information concerning the expected number of brain cancer deaths. Without this information, it is not possible to evaluate how informative the study will be regarding its ability to detect an important excess (or deficit) in brain cancer mortality and/or to relate brain cancer mortality to vinyl chloride exposure. It is also not possible to evaluate fully the proposed work plan and budget (not included with this reviewer's materials). The investigators propose an elaborate plan for confirming the diagnosis of brain cancer (to the extent of reviewing the histo-pathology records of all deaths due to cancer), but offer the reader no sense of how many brain cancer cases are likely to be found.

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The investigators do report on page 14 that a total of 178 cancers will be examined to confirm that a diagnosis of brain cancer was not missed. Given that roughly 2-3% of all cancers are of the brain and other central nervous system, one would only expect about four or five brain cancer deaths among this cohort. Given this very small number of expected cases it is not reasonable to enter into this investigation with the hopes of learning much about the exposure-response association for VC and brain cancer.

2. The research protocol is neither well organized nor clearly written. The research methods section contains much extraneous information and does not focus clearly and concisely on the stated objectives and aims of the study. For example, the investigators provide a lengthy discussion of available medical illness and disease records, medical history and physical exam data, laboratory studies, and radiological and imaging studies. However, these data have almost no relevance to the proposed study, which is based solely on brain cancer decedents identified from death certificates and confirmed via histo-pathological review.
3. The investigators tout the "analytic approach not widely known in the field of occupational epidemiology" described by Greenberg and Tamburro, and devote a disproportionate amount of protocol space describing the application of the approach to the hepatic angiosarcoma data (as in *J Occup Med* 23:353-358, 1981). While in 1981 or earlier, this may have been a novel analytic approach, more sophisticated, model-based procedures, such as Poisson and Cox regression modeling, have supplanted it for some time.

Unlike the Greenberg-Tamburro approach, the modern procedures provide factor-adjusted estimates of rate ratios or relative risks, which are more appropriate and informative for evaluating possible associations between exposures and health outcomes. The Greenberg-Tamburro approach relies on extensive matching of cases and controls (to the extent of possible overmatching) and provides no summary measures of risk. One must rely on a simple descriptive (or graphical) examination of exposure differences between cases and controls and then make a subjective judgement of the importance of the observed differences. Their method also does not readily enable an assessment of multiple exposures as can be done in the model-based procedures.

Also, while Greenberg-Tamburro argue that the cumulative exposure rank method (CERM) is not considered as an interval scale level summary measure, it is essentially used as such in their approach. Conceivably, the Greenberg-Tamburro approach could still be used as a screen or descriptive assessment of the data as a preliminary step to relative risk regression modelling.

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There are many other questionable aspects of the protocol that are described below in the Specific Comments section.

Overall Evaluation

The primary hypothesis of the study (brain cancer mortality is associated with VC exposure) does not appear to be testable with the proposed research plan given the very small expected number of brain cancer deaths.

Recommendation

It is recommended that this project not be funded based primarily on the very low expected number of brain cancer deaths and secondarily on the generally inadequate research plan and proposal. CMA might consider a revised and analytically improved proposal after additional years of cohort follow-up have taken place and more brain cancer deaths are observed.

Specific Comments

Numerous uncertainties exist in the proposed work plan that the investigators need to address before a revised proposal could be considered. These include:

1. The analysis plan is clearly limited to brain cancer deaths, however, living cases of brain cancer could also be identified via the neurological physical examination and other health records. What, if anything, are the investigators going to do with such cases in terms of testing the main study hypothesis regarding VC exposure?
2. No provisions exist on the protocol for attempting to obtain (with more aggressive techniques, for example) the 40 missing death certificates. Brain cancers could possibly be under ascertained without information on cause of death for all known deaths.
3. No provisions exist for handling the missing or incomplete work histories relative to the exposure assessment and data analysis.
4. No provisions exist for examining the cases and controls relative to multiple chemical exposures. Besides VC, estimates are available for 21 chemicals, and co-exposures to one or more of these agents could act as a potentially confounding or effect modifying factor(s).

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5. The section on "Confounders" (page 7) makes little sense. First, most of the factors listed as potential confounders (viral infections, smoking, alcohol, etc.) are not likely to be important confounders for a VC-brain cancer association because they are not established risk factors for brain cancer. Even if they were important confounders, the proposed analytic approach contains no procedure for explicitly adjusting for their confounding effects.
6. Under Task 1, plans are described for cooperating and coordinating this study with that of Applied Epidemiological, Inc., although the rationale or work plan for this arrangement are neither described nor justified in the protocol.
7. The so-called "Review of the Literature" is simply a listing of related references. An annotated listing or discussion and interpretation of this literature would be more useful to the reader of the proposal. In particular, a fuller presentation and interpretation of the extant literature on the purported VC-brain cancer association would help to support the primary research hypothesis of this proposed study.

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