From:	George Woodall <Woodallg@api.org>
Sent:	Monday, September 24, 2001 4:08 PM (GMT)
To:	Richard Irons (E-mail) <richard.irons@uchsc.edu>; Otto Wong (E-mail) <OttoWong@aol.com>; Robert Schnatter Ph. D. (E-mail) <arschna@fpe.erenj.com>; Thomas Armstrong (E-mail) <twarmst@erenj.com>
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Subject:	FW: reviews
Attach:	Review of API.doc

The rest of the comments will be posted on the web site. Please provide your presentation materials ASAP so I can post them on the web site; several members of the SRP will be tying in via phone and will not otherwise see the materials.
George
-----Original Message-----
From: Robert Herrick [mailto:herrick@hohp.harvard.edu]
Sent: Monday, September 24, 2001 8:31 AM
To: George Woodall
Subject: reviews
Dr Woodall - please find my comments on the three studies attached.
Bob Herrick

REVIEW OF API-SPONSORED BENZENE HEALTH EFFECTS PROTOCOLS

COMMENTS FORM BOB HERRICK

Case-Control Studies Of Acute Non-Lymphocytic Leukemia And Non-Hodgkin's Lymphoma In Shanghai (Principal Investigators:Otto Wong and Fu Hua)

The proposed research is a hospital based case control study of ANLL and NHL in Shanghai. Overall the study approach seems appropriate to the questions the investigator seek to answer. I would raise the following issues for your consideration. Many of the comments made in the case-control review pertain to all three studies, and are not repeated after the first set of comments.

1. There seems to be some inconsistency in the actual levels of benzene exposure that are prevalent today, as well as in the past. Wong and Fu criticize the Dosemechi (NCI) exposure estimates as being too low, however the attached letter from Dr. You-xin Liang notes that the MAC in Chinese workplaces is 12 ppm. Are the majority of Chinese workplaces out of compliance with the exposure limit? This may well be the case, but some documentation of the actual exposure levels that workers have encountered would be helpful in evaluating the proposals. If the exposures actually are close to the Chinese MAC and the Dosemechi estimates, there may be little point in conducting the proposed studies, as that would reduce the likelihood of a meaningful evaluation of the relationship between benzene exposure and ANLL and NHL.
2. The plan to develop individualized exposure profiles is a very good idea. A great strength of the prospective case-control design is that it provides this opportunity, however the discussion of the exposure assessment procedures states than an industrial hygienists will review the occupational histories based upon a list of occupations with potential benzene exposures. This will be the first step in triggering the search for employment records, etc. In order to do a comprehensive exposure assessment it is imperative that this information on employment, job title and job location be obtained for all subjects (cases and controls) not just those on whom the initial determination was that they were benzene – exposed. What becomes of subjects exposed to a potential confounder, but not to benzene? Under the current exposure assessment strategy, it seems that no further information would be obtained for these subjects.
3. The study plan states that information on the work-unit will be obtained for employees in each factory. What will be done for cases and controls who are not employed in a factory that maintains such a system? For example what will be done for a case who worked as a cook or a construction worker?
4. The discussion of the methods that will be used to develop exposure estimates does not mention the time period for which these estimates will be

made. Elsewhere in the protocol package the estimate of a 15 year latency for the outcomes of interest is cited. Will the exposure assessments then go back to 1986, as the recruitment period of incident cases starts in 2001? This is an important issue not only in terms of data analysis but also in study design. As the exposure assessment approach is driven by the available exposure data, this is very likely to be time-dependent. If the exposure window of interest goes back to 1986, that would suggest a very different approach than a larger window going back further in time when production conditions, exposure levels and exposure records may have been very different.

5. The discussion of linkage between exposures and the database of CDPC data makes no mention of the nature of the data contained in the CDPC database. What is known about this data, e.g. was it collected for purposes of determining compliance the Chinese MAC, or to evaluate health hazards and reported symptoms, or to evaluate the effectiveness of engineering controls? The information contained in this data base must be assessed for its representativeness of workplace exposures that were prevalent at the time. It seems unlikely that this data was collected in a representative manner that would be designed for an epidemiologic study.

Protocol I: Analysis of disease progression for aplastic anemia, myelodysplastic syndrome, acute myelogenous leukemia and benzene poisoning in Shanghai, China (Principal Investigators: Richard D. Irons and Hua Fu)

1. The inclusion criteria specify that both severe and mild cases will be included. Considering the exposure assessment, then, is it possible that some of the concurrent sampling conducted to supplement the historical data will be conducted on the cases themselves? This raises the question of what happens to subjects diagnosed with severe vs. mild cases. Would a severe case be likely to be out of work with a disability, while a mild case would return to work? Would the mild case be returned to the same job that may have been associated with the diagnosed disease, or would they be reassigned to a job with lower benzene exposure? If the severe case has not returned to work, would monitoring be done on the person who has replaced that case in the workplace? These questions raise two concerns, one is whether it will really be possible to conduct the exposure assessment in a blinded manner, and second whether the concurrent data that is collected will be representative of the exposures that occurred before the diagnosis was made for the cases. On page 18the investigators state that steps will be taken to deal with situations where blinding has been compromised, but there is no

information what those steps might be. The alternatives presented on page 90 do not fully address this concern.

2. A further question on the mild cases concerns the plan to monitor them with annual CBC to see if their disease progress. Is there a concern here about the ethical considerations of leaving a diagnosed mild case in the exposure environment that may have contributed to initiating the disease? What will these workers be told about their condition and the factors that may have caused it?
3. Overall the three-tiered exposure assessment strategy is sound and appropriate. One question about the initial assignment to an exposure category (Tier 1) is whether the assignment would be based upon current exposure level, whether the subject was ever exposed, or most frequently exposed to a level in a particular range.
4. On page 95 in the discussion of the exposure monitoring statistical plan, the investigators state that they will conduct monitoring of multiple workers to evaluate inter-worker variability. If this sort of comprehensive monitoring effort is mounted, it should be designed to evaluate the within and between worker components of variability. This could provide important information about the use of the job-exposure matrix as a source of information for the individual exposure profiles.

Protocol II: Molecular epidemiology of benzene-exposed workers in Shanghai, China (Principal Investigators: Richard D. Irons and Hua Fu)

1. The protocol states that the population will be stratified into 5 cells based upon benzene exposure. What is the rationale for the selection of these cut-points of exposure? It may be more appropriate to specify the cutpoints after more is known about the distribution of exposures for the population.
2. Concerning the discussion of inclusion criteria, the investigators will select subjects based upon 1 year experience at a station covered by existing exposure monitoring data. Could this introduce a bias in selecting certain types of jobs over others? How have jobs been selected for monitoring? How might this selection process influence the distribution of exposure to potential confounders over the selected jobs?
3. In analysis of exposure, the investigators will select sites with the best-documented exposure records. As in my previous comment, how would this influence the study as to the information available on potential confounding exposures, and the overall representativeness of the study population?