

Draft Ethics Considerations and Status of Resolution

Issue	Resolution	Your Comments and Questions
Scientific Validity of the Study	• Multiple review of protocols by an independent scientific review committee • Approval of protocols by US and Chinese Universities' Institutional Review Boards • Protocol changes to be approved by independent scientific review committee	
Benefits to Participants	• Improved diagnosis of disease • Increased follow-up after treatment • Can we really assure this? Isn't it in the hands of the Chinese? • Improved workplace monitoring • Are we actually "improving" or are we using the CDC data? I did not think that the study was going into the workplace, but that the participants were coming via referral from hospital diagnosis. • Early diagnosis of benzene toxicity and removal from workplace • ONLY if participant goes to the doctor and are diagnosed. • Monetary compensation • Compensation to be based upon level of participation and, to avoid excessive inducement, standard practice in China (and US??) for similar procedures.	•
I think the improved workplace monitoring and early diagnosis are potential long-term benefits to the Chinese (and other) population after the study and not necessarily to the participants themselves		
Appropriateness of Compensation to Participants	• Monetary compensation • Compensation to be based upon level of participation and, to avoid excessive inducement, standard practice in China (and US??) for similar procedures.	
Informed Consent	• Consent forms tailored to type of participation in the study and disease status, e.g., case or control. • Forms to be developed with input of Chinese clinicians and bioethicist. • Forms reviewed by an independent review board.	•
Confidentiality	• Separate password controlled databases for clinical and study-specific research data. Transfer of data between from clinical to study databases requires consent of participant.	•

Culturally Sensitive Questionnaire & History	• Questionnaire to determine occupational history and lifestyle information will be developed with input of local Chinese researchers and Chinese bioethicist. • Questionnaires reviewed by an independent review board.	•
Control of Results	• Independent Scientific Review Committee will review proposed abstracts of presentations and manuscripts for publication. • The investigators will have final control over content and interpretation of published or presented study data	•
Benefits to the General Worker Population Exposed to Benzene	• A committee of the central provisional government believes it can use the molecular epidemiology study to justify a lower benzene occupational exposure standard. • Identification of more sensitive biological indicators of excessive exposure to benzene How would you define excessive? I thought determining exposure/effect was part of the purpose of this study.	•
Other Benefits	• State of the art diagnostic laboratory will remain in Shanghai for future use. • Technology transfer from training of local laboratory technicians • Possible increase in level of hematopoietic disease diagnosis and care after exposure to US study procedures • Technology transfer from high quality industrial hygiene monitoring technology & practices	•
Identification of other unknown benzene effects	• Data immediately reviewed and reported to EPA under TSCA 8(e)	•

The purpose of this document is to outline the answers to the questions most frequently asked regarding these studies.

Glossary of Terms

- AML (Acute Myelogenous Leukemia):** The hematopoietic cancer most commonly associated with exposure to benzene. **Hematopoiesis:** The formation of blood and blood cells, including red & white blood cells and platelets .
- NHL (Non-Hodgkins Lymphoma):** Complex spectrum of malignancies of lymphoid tissues, most often arising in the lymph nodes.
- NCI/CAPM (National Cancer Institute/Chinese Academy of Preventative Medicine) -** The authors of a previous set of studies in China that found NHL associated with benzene exposure, the first study to show such a linkage.
- SMCDC (Shanghai Municipal Centers for Disease Control) -** The Shanghai governmental agency responsible for occupational exposure monitoring and enforcement

Q. For the Case Control Study of NHL, why not just perform a retrospective study; would that not be a quicker and much less expensive way to get the same information?

A. First and foremost, is the lack of complete and verifiable diagnoses from a simple retrospective study. A number of other conditions can mimic NHL, and misdiagnosis is easy in the absence of sophisticated diagnostic procedures. Diagnostic samples are not routinely kept in China and there would be no opportunity to confirm diagnoses for most cases. Secondly, assessment of exposure and confounding risk factors is complicated in a retrospective study. In the case of deceased patients, details of lifestyle and work history must be obtained from relatives or other workers. Taking cases prospectively reduces the distance in time that one needs to go back in order to get needed exposure records.

Q. The diagnostic laboratory is a major expense. Why is it necessary? Why can't we just do a standard case-control study?

A. Non Hodgkin's Lymphoma (NHL) is an aggregate category of ca. 20 distinct lymphocytic diseases. In order to perform an NHL study that conforms with the current diagnostic schema, the subtype of NHL should be known. These subtypes are distinguished by morphological appearance and characterization of cell surface markers by sophisticated immunochemical

techniques. A number of viral infections are known risk factors for some forms of NHL. For example, hepatitis C which is common in China. The presence of the planned laboratory on site in Shanghai assures us of consistent, state-of-the-art diagnostic capabilities under our control without the necessity of the logistic and bureaucratic nightmare entailed in shipping human tissue samples to the US for testing.

We believe that the NCI/CAPM study finding of increased risk of NHL in benzene exposed workers is due to unrecognized confounding factors. We do not want to repeat their mistake.

Q. Why are we including AML in the Case-Control study. AML is also in the Disease Progression study. Isn't this a duplication?

A. Including AML, which we would expect to see associated with benzene exposure, provides a positive control to defend against criticisms that our methodology was somehow not adequate to see associations that do exist. There is some overlap in that the Case-Control study will serve as one source of AML cases in the Disease Progression study.

Q. One of the reasons for pursuing the Molecular Epidemiology study is that the Chinese officials in Shanghai have requested this type of data; why can't they use the existing NCI/CAPM study results?

The NCI/CAPM study was roundly criticized for not providing a good measure of actual exposure; for not accounting for exposures to multiple chemicals; for assuming that all AML, NHL, and other blood-related diseases were caused by exposure to benzene alone; and with poor study design that did not account for confounding factors (e.g, smoking) and other factors. USEPA has taken the position that this study cannot be used to calculate a quantitative cancer risk from benzene exposure. This is precisely the reason this study will be so important.

The Chinese base their occupational standards on measurable effects on people, and not on mathematical modeling of hypothetical risks as is typical in the U.S. and Europe. The NCI/CAPM studies did not provide them with the type of data upon which to base a change in their current standards. Their current standard is based on a decrease in white blood cell counts rather than leukemia. They are interested in the Molecular Epidemiology Study which is intended to provide an objective, measurable indicator of risk.

Q. Why are we taking on the expense of providing laboratory diagnostic services for hematopoietic diseases in Shanghai hospitals during the course of the study?

- A. These services provide crucial benefits to the consortium research in two areas:
- ◆ Research Data – As the central diagnostic laboratory we will assure the quality and consistency of the diagnostic data. This role assures access to blood and bone marrow samples from study participants. Without this role we would have to seek permission to perform a second procedure to obtain these tissues for the research. Patients would be reluctant to undergo such a second procedure, which would

complicate obtaining large numbers of participants.

- ◆ Bioethics – Providing this higher level of diagnostic information to hospital physicians improves the level of patient care which fulfills the ethical requirement that the study benefit participants and the general community in which the research is performed.

Q. If the Chinese are going to be the major beneficiaries of this research, shouldn't they contribute to the project?

- A. Although the Chinese are not providing direct monetary contributions, they will be contributing in-kind support. The laboratory space allocated to the project has been provided by Fudan University. The funds provided by API for the laboratory space have gone toward renovation of that space to make it acceptable for the purposes of this study, but we will not pay any rent for the use of the space during the period of our studies. The considerable resources of the Shanghai Municipal Centers for Disease Control (SMCDC) have been offered freely, including use of their database to identify facilities and individuals to include in the study as well as laboratory support for industrial hygiene monitoring analyses necessary to the study. And most pointedly, the Chinese provide access to the subjects, without whom it would be impossible to conduct such a study.

Q. Why is this being undertaken primarily by the petroleum industry, and why have other industries and/or international companies not been approached to help fund this research?

- A. API has played a lead role in getting this study underway, because the petroleum industry has a major interest in better understanding risks to human health due to benzene exposure. Other industries are being approached to help in this effort, as are international petroleum companies and trade associations. Presentations have been made to CONCAWE, IPIECA, and CEFIC. At least one of our major supporters, BP, is headquartered outside the United States.

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