From:	Bruce Jarnot <jarnotb@api.org>
Sent:	Monday, October 20, 2003 1:51 PM (GMT)
To:	benzconsort-oc@listserve.api.org; benzconsort-tc@listserve.api.org
Cc:	Matt Todd <ToddM@api.org>; benzene-srp@listserve.api.org
Subject:	Shanghai SRP... Memo to the Consortium
Attach:	SRP Memo to Consortium 20 Oct 2003.doc; SRP Memo to Consortium 20 Oct 2003.pdf

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Benzene Health Research Consortium (BHRC) Technical and Oversight Committees -

Attached for your review and consideration is a "Memo to the Consortium" from the Scientific Review Panel (SRP) chair, Dr. Jerry Rice, which documents SRP review of Shanghai Health Study research following the 2003 Asilomar annual conference.

By copy to Matt, please post a pdf copy of the Memo to the SHS website, Panel Info page, in SRP Member Doc's... thanks!

Best Regards - Bruce.

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Shanghai
Health
Study

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Memorandum

To: Technical Oversight Committee and Members of the Consortium

From: Jerry M. Rice, Ph.D., Chair, Scientific Review Panel

Date: October 17, 2003

Subject: Conclusions of the Scientific Research Panel –
Annual Research Meeting, Asilomar, California, August 2003

Executive Summary

- A fully equipped and staffed Central Diagnostic Laboratory has been satisfactorily established. This is an important first milestone for all three (CC, DP & ME) studies.
- The next milestones to be monitored are:
    1. Progress in recruitment of cases and controls for all studies;
    2. Cost-effective implementation of HIV serology for control subjects in the case-control study;
    3. Timely peer-reviewed publication of findings in the scientific literature.
- Additional endpoints have been identified, which the investigators should consider (with external funding if required).
- The SRP and ERP have jointly decided to hold future panel meetings during annual research meetings, and to defer recruitment for 3 SRP vacancies. These actions will significantly reduce the budget required for the two external Panels in future years.

Current status of investigations in view of the formal objectives and goals previously proposed and accepted for funding by sponsors of the Shanghai Health Study

Establishment of the central diagnostic laboratory as a functioning reality, and expanding the number of cooperating institutions to include 23 of the 24 major Shanghai hospitals, are major achievements. It is especially significant that the hospitals that have most recently joined the Study are those that treat the majority of benzene poisoning cases in Shanghai. The enrollment of cases, which has just commenced (July 2003), constitutes a highly significant milestone in this overall research program. The investigators are now in an excellent position to accomplish the specific goals of their respective protocols. As these studies progress, a transition plan for identified cases and an ongoing local role for the clinical laboratory should be considered.

For the NHL component of the case-control study, it is imperative to document exposures of both cases and controls to all risk factors for NHL other than benzene, notably to HIV. For HIV, a questionnaire alone is insufficient. Performing the requisite blood test should not be a technical difficulty for the diagnostic laboratory, but the current case-control protocol does not provide for blood samples from controls, and is not funded to do this. As an action item, Drs. Irons and Wong agreed to confer and propose an approach to obtaining HIV data from control subjects.

Suggestions for further and/or expanded future studies

As the goals of the current studies are progressively reached in future years, the investigators should give consideration to exploring new sources of funding for additional studies that lie outside the work scopes of the current protocols:

1. Establish a Leukemia Tissue Bank

An established leukemia tissue bank, consisting of stored frozen cells and serum, will provide a major international resource for future research. These clinically and biologically well characterized tissues could be made available to future studies of many kinds and thus provide a significant asset to the investigators and their institutions. A mechanism should be developed for other investigators to apply for access to these preserved tissues. The National Cancer Institute Clinical Cooperative Groups have developed and published criteria for reviewing concepts or research proposals from other laboratory investigators for access to their tissue

banks. [See: Schilsky RL, Dressler LM, Bucci D, Monovich L, Jewell S, Suster S, Caligiuri MA, Kantoff PW, Compton C. Cooperative group tissue banks as research resources: the Cancer and Leukemia Group B tissue repositories. Clin Cancer Res. 2002 May; 8(5): 943-8].

2. Include Commonly Evaluated Benzene Biomarkers

The current studies of benzene toxicity and carcinogenicity in many ways will be the most sophisticated ever undertaken, notably in the application of modern diagnostic criteria. It is highly desirable that the results of these studies be directly comparable to results of previous studies. This can best be accomplished by adding commonly evaluated biomarkers of benzene exposure and effect. All three of the study protocols describe dose response, and the study protocol of the Molecular Epidemiology Study describes identification of sensitive biomarkers, as a specific aim. These include specific metabolites of benzene present in urine, and chromosome aberrations assessed in peripheral blood lymphocytes by conventional methods. Enumerations of peripheral blood granulocytes and lymphocytes are already being made by standard hematological assays. The urinary concentrations of S-phenylmercapturic acid (S-PMA) and trans, trans-muconic acid (T,T-MA), which are minor metabolites of benzene, have recently been validated as highly specific biomarkers of recent benzene exposures (Qu et al. HEI Report #11, 2003). Correlations with external exposures, as measured by personal monitors, have been excellent, with linear relationships even between 0.1 to 1.0 ppm. Other benzene metabolites, such as phenol, catechol and hydroquinone do not show such sensitivity or specificity. It is recommended to include at least urinary excretion of S-PMA in studies that investigate acutely exposed workers.

In this same study, conventional chromosome analyses of peripheral blood lymphocyte metaphase spreads also were correlated with benzene exposures. Furthermore, chromosome aberrations and chromatid breaks were correlated also with long term cumulative benzene exposures, as assessed by work histories, etc. FISH analyses of interphase cells (granulocytes and non-stimulated lymphocytes), as well as of metaphase spreads of cultured lymphocytes, showed more variability, suggesting that these newer methods require additional development. Decreases in peripheral blood granulocyte and lymphocyte numbers were also correlated with measured

benzene exposures, even though the white blood cell numbers did not drop below normal levels.

The reason for including these additional biomarkers in this component of the overall study is to assess benzene internal doses by the best-validated methods currently available. This will add validity to the estimates of (current) external benzene exposures being made by worker histories, work area measurements, etc., that are now the only measures of current exposure levels for the subjects in the Molecular Epidemiological Study. As these latter measures are also those being used to quantify benzene exposures retrospectively in the other two components of the overall study, *i.e.* the Disease Progression Study and the Case Control Study, the Molecular Epidemiology Study will serve as an internal validation study of the methods, adding credibility to them and thereby to the exposure assessment in the other two studies.

Conventional chromosome aberration studies using peripheral blood lymphocytes will not be as sensitive or specific for benzene exposures as the urine metabolite concentrations, but good correlations have traditionally been shown between frequencies of chromosome aberrations and chromatid breaks and benzene – as again verified in the Qu study. This biomarker will link the SHS with the many other studies of benzene's human effects that have preceded it. Furthermore, chromosome aberration frequencies are also correlated with long term benzene exposure levels – something that cannot be assessed using the urine metabolites. Finally, chromosome aberrations appear to have predictive value for the subsequent occurrence of cancer, as shown by studies of Hagman and Bonassi over recent decades. (Note: these chromosome studies will not be mechanistic probes; they will be used as biomarkers of exposure to add validity to the methods currently used to assess exposure.)

These biomarker suggestions apply to the Molecular Epidemiology Study only. Urinary metabolites will have no use for measuring the distant past benzene exposures of relevance in the other two studies of the overall SHS, and chromosome changes, although reflecting long-term cumulative exposures, will be difficult to interpret in patients with leukemia and associated diseases.

Administrative support provided by The American Petroleum Institute
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SHANGHAI HEALTH STUDY

Memorandum

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Date: October 17, 2003

Subject: Conclusions of the Scientific Research Panel –
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