From:	George Woodall <Woodallg@api.org>
Sent:	Tuesday, August 14, 2001 7:58 PM (GMT)
To:	'Guilan_li@sohu.com'
Cc:	Patrick Beatty (E-mail) <pwbe@chevron.com>; Shan Tsai (E-mail) <sptsai@shellus.com>
Subject:	Invitation to Participate in a Benzene Health Research Project
Attach:	SRP Overview_.doc

Dr. Li,

A consortium of companies with an interest in the human health effects of benzene exposure has developed a program of three inter-related studies to answer some basic questions related to benzene-induced hematopoietic disease. The consortium is committed to ensuring that the proposed studies meet the highest standards of scientific quality, and are shielded from even the perception of undue influence by the study sponsors. To that end the Consortium has provided for the establishment of an independent Scientific Review Panel (SRP) to oversee the technical aspects of the studies. Your name came highly recommended by Shan Tsai as a potential member for the SRP. The candidates for the SRP that have already accepted include Jerry Rice (IARC), Richard Larson (Univ. of Chicago), and Nancy Mueller (Harvard). The attached document provides an overview of this ambitious study and an outline of the roles and expectations of SRP members.

One of the first tasks of this SRP will be to review the draft protocols for each of the studies. A meeting is currently planned for this purpose in Chicago on September 27. Although I realize that the lead time is very short, if at all possible, we would like to have you involved in the protocol review. If attendance is not possible, written comments would be valuable. Whether or not you are able to review the protocols, your participation in the long-term study oversight process would add greatly to the effort.

The incorporation of an Ethical Review Panel (ERP) to assess the ethical issues in the development of the study protocols and continue to oversee those concerns as the project progresses is also one of the key elements in this project. The ERP will interact with the SRP in ensuring the highest standards of research integrity are applied for the duration of this research project.

You may indicate your willingness to participate via e-mail or feel free to call me if you would like to discuss this project more fully.

Best regards,

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Background and Overview of Proposed Investigation into the Risk of Benzene-Induced Hematopoietic Disease

This document describes a project to investigate the dose response and mechanistic aspects of the hematological effects of benzene exposure primarily in a population of workers in Shanghai, China (PRC) . In addition, the project will attempt to reproduce a reported association between benzene exposure and Non-Hodgkin's Lymphoma (NHL) from an earlier study of a nationwide occupational cohort in China. That study also suggested that average benzene exposures as low as 5 ppm could result in acute myelogenous leukemia (AML) and a spectrum of chromosomal alterations. The project described below will include parallel case control studies of NHL and AML, an investigation of the role of non-neoplastic diseases such as aplastic anemia (AA) and myelodysplastic syndrome (MDS) in a progression to AML, and examination of the dose-response relationship between benzene exposure and selected biomarkers of both exposure and effect.

Data Gaps and Uncertainties

There are a number of areas of uncertainty regarding benzene-induced hematopoietic disease that, if answered, have the potential to result in an increased understanding of benzene-related risks. These are:

1.) The shape of the dose-response relationship between benzene exposure and selected hematological diseases (including the possibility of a true threshold);
2.) Clarification of the role of non-cancer hematological diseases in the etiology of benzene-induced leukemia.
3.) Identification of similarities between leukemia secondary to benzene exposure and the much better understood and studied leukemias secondary to administration of certain chemotherapeutic drugs. This also includes the possibility that one or more immunologic or cytogenetic markers could be identified that would be considered diagnostic of benzene-induced leukemia.
4.) Clarification of the quantitative relationship between benzene exposure and potential indicators of exposure or of effect. This is timely, because there has been considerable discussion and research into the use of "biomarkers" to extend the dose response-curve for benzene-induced leukemia.

Project Description

The proposed project consists of three highly integrated studies:

1.) A population-based case control study to investigate the potential relationship between benzene exposure and both NHL and AML including an attempt to define a quantitative potency for the AML response;
2.) A hospital/clinic-based investigation of the relationship between non-neoplastic diseases of the bone marrow and AML to determine if there is a progression through stages of bone marrow cytotoxicity to an ultimate leukemogenic response. This study would also attempt to define, both a potency and the shape of the dose-response for these "precursor" diseases;
3.) A "molecular epidemiology" study to investigate the quantitative relationships between benzene exposure and potential early indicators of both exposure and effect in a focused population of benzene-exposed shoe manufacturing workers.

Case-Control studies

A collaboration between the US National Cancer Institute and the Chinese Academy of Medicine (the NCI/CAPM study) was published as a cohort study of Chinese workers occupationally exposed to benzene in a number of industries. The NCI/CAPM study reported an association between benzene exposure and Non-Hodgkin's Lymphoma. This association has not been reported previously. The study also has

reported an association between benzene exposure and AML, but interpreted the results to indicate that average exposures around 5 ppm could lead to AML. An association between AML and benzene exposure at these levels has not been reported previously.

This project will initiate a population-based case-control epidemiology study of NHL and AML in the population of Shanghai. The case-control design will allow a focussed examination of the previous report that NHL is associated with benzene exposure. Because NHL is not a single disease but, rather, is a collection of more than a dozen distinct hematopoietic cancers, the proposed consortium study design includes subtyping each individual case. In addition, the viral status of each case will be determined because it is known that active infection with a number of viruses has been causally related to increased risk of NHL. If the quality of the exposure data permit, an estimate of the quantitative potency will be made for any cancer type with a positive association with benzene exposure.

Disease Progression Study

This portion of the project will examine the relationship between AML and non-neoplastic hematopoietic diseases. It has been hypothesized that AML must be preceded by some degree of toxicity to the hematopoietic system. The combination of a relatively stable population (geographically) with both hospital and occupational records of bone marrow related disease has created the possibility of investigating this relationship. The results of annual area monitoring and blood counts for benzene exposed workers are maintained in a computer database by Center for Disease Control and Prevention (CDC). This portion of the project will utilize CDC and hospital records to investigate the relationship between AML and prior hematopoietic disease such as leukopenia, myelodysplastic syndrome (MDS) or aplastic anemia (AA).

Due to the highly controlled nature of benzene exposure in North America and Western Europe, researchers have not had the opportunity to bring modern medical and molecular biology techniques to bear on a single case of AML, MDS or aplastic anemia in which benzene could be considered the probable etiologic factor. This study will attempt to identify individuals with cytopenias, MDS or AML, that can be reliably attributed to benzene exposure, in order to identify cytogenetic and immunologic characteristics of benzene-induced disease. Identification of these relationships will allow a determination of possible similarities between benzene-induced leukemias and other leukemias secondary to chemical exposure (mainly chemotherapy). The Principal Investigator will be Dr. Richard Irons of the University of Colorado with the collaboration and assistance of investigators from the Departments of Hematology and Public Health of Fudan University Medical School.

Molecular Epidemiology Study

One area of benzene research that has received much attention in the last few years is the attempt to identify early biological indicators that predict a later event such as AML or serious forms of bone marrow toxicity such as MDS or AA. Some endpoints which have been measured, such as protein adducts of benzene metabolites, are clearly indicators only of exposure to benzene (although there may be some complicated relationship with biological responses). Some endpoints, such as certain cytogenetic abnormalities, have been claimed to be indicators of future effect, however, at this time no biological predictor of benzene-induced leukemia has been unequivocally identified.

The objective of this series of studies is to investigate the relationship between benzene exposure and various blood dyscrasias and cytogenetic abnormalities in workers primarily in the shoe manufacturing industry in the Shanghai area. The dose-response will be investigated in relation to various types of benzene exposure metrics and will take advantage of a wide range of benzene exposures in this occupational setting, to investigate the shape of the dose-response curve. Specific aims of this facet of the overall project are:

1.) To define benzene dose response patterns for alterations in blood cell counts, bone marrow cytotoxicity and chromosomal alterations;

2.) To define the most relevant exposure indicators for each of the effects in "1";
3.) To assess if the dose response patterns are affected by the presence of other environmental compounds such as toluene or xylene which commonly are co-exposures with benzene;
4.) To assess if the dose response patterns are altered by the presence of reported susceptibility factors in exposed individuals;
5.) To define the relationship between external benzene exposure and selected internal measures of exposure.

Location

The location for the proposed project is Shanghai, China. Shanghai is a major population center with approximately 14 million individuals living in the local area. Shanghai presents the unique situation of a large number of workers with documented exposures to benzene at levels that have not existed in North America or Western Europe since the 1940's or 50's. The regional agency in charge of maintaining occupational health records, the Center for Disease Control and Prevention, has a computerized database of industrial hygiene (IH) monitoring data and blood counts for benzene-exposed workers extending back to the mid 1980's. Those records document that although exposures of less than 10 ppm were the rule, concentrations in the range of 10 – 50 ppm were common and occasional exposure levels in excess of 100 ppm were documented. Shanghai also contains one of the premier medical schools in China associated with Fudan University. The teaching hospital at Fudan as well as 14 other primary and secondary hospitals in the Shanghai area will serve as a source for identifying potential cases for the proposed studies.

The Investigators

The principal co-investigators who are expected to lead the project are:

Epidemiology

Otto Wong, D.Sc. – Applied Health Sciences, San Mateo, CA

Robert Schnatter, Ph.D. – Exxon/Mobil Biomedical Sciences, Annandale, NJ

Hua Fu – Deputy Dean, Fudan University Medical School, School of Public Health, Shanghai, PRC.

Hematology/Molecular Biology

Richard Irons, Ph.D. – University of Colorado Health Sciences Center, Denver, CO

Guowei Lin, M.D. – Director, Center of Clinical Hematology, Hua Shan Hospital, Shanghai, PRC

Industrial Hygiene

Wei Lu – Deputy Director General, Shanghai Municipal Center for Disease Control and Prevention
Shanghai, PRC

Thomas Armstrong, C.I.H. – Exxon/Mobil Biomedical Sciences, Inc., Annandale, NJ

The above list does not limit the possibility that additional investigators may be involved in the future, but these above individuals have been involved in the development of project protocols.

Time Frame and Funding

This project is anticipated to require 5 years to complete, largely due to the prospective nature of the case-control studies. Total funding for all aspects of the project is expected to be approximately $19.7 MM.

Roles and Responsibilities of the Scientific Review Panel for the

Benzene Health Effects Research Program

Objective

In order to ensure the objectivity of the results of this project, a committee of independent experts in disciplines critical to the conduct of this project will be recruited to provide scientific oversight. These disciplines would include epidemiology, hematology, oncology, toxicology, industrial hygiene, statistics and genetics.

Roles and Responsibilities

The responsibilities of the SRP will include approval of any changes to the study protocols, as well as comment on proposed changes in the scope of the research program. In addition, the SRP will review and comment on manuscripts resulting from this study prior to their submittal for publication.

It is anticipated that this group will meet annually with the principal investigators and the Technical Committee to review the research progress. At other times the SRP will convene by teleconference or other means, as necessary, to discharge its duties.

Interaction with other Committees

The SRP will work in close consort with the Independent Ethics Review Panel when reviewing protocols or changes in scope of the project. It is expected that the Chair of the SRP would be an *ex officio* member of the Ethics Review Panel and *vice versa*. The SRP will maintain contact with the Oversight Committee through the Technical Committee and the Chair and vice-Chair of the latter will be non-participating, observers at SRP meetings.

The Oversight Committee will provide the SRP with a reasonable level of support to allow it to discharge its duties. This will include but not be limited to providing the financial resources for administrative support, meeting venues, conference call lines and similar services. These will be agreed upon by both the SRP and the Oversight Committee.