

The Second Annual Meeting of the Shanghai Health Study

Background

The purpose of the Shanghai Health Study is to gain a more refined understanding of the relationship between benzene exposure and potentially associated human health effects. Results of this study will provide useful scientific data for future decisions on health-based air, water and occupational standards for benzene worldwide. While benzene is recognized as a human carcinogen, what is not understood is how benzene exposure may cause certain types of leukemia or other potentially related diseases, the interactions that may occur between benzene and genetic material, and the role biomarkers may play in adding to existing knowledge.

The study is a project of Fudan University Medical Center, the University of Colorado Health Sciences Center, and Applied Health Sciences (an independent U.S. research firm). Other key participants in China include the Shanghai Municipal Center for Disease Prevention and Control and the Shanghai Institute for Public Health and Supervision. The research protocols were subjected to independent reviews by outside experts, including reviews of their consistency with international ethical standards and reviews by an expert scientific panel. The research protocols have been approved by independent review boards at Fudan University, the University of Colorado, and Applied Health Sciences.

This project is being administered by the American Petroleum Institute, and has API Staff assigned to support the activities of each of the committees and independent panels. API is not a sponsor of the project, and does not control the activities of the consortium. API, however, is applying its policies and procedures to the conduct of its administrative duties. The Committees consist of representatives from each of the members of the consortium (Shell, BP, ChevronTexaco, ExxonMobil, and ConocoPhillip). The independent panels consist of experts in the various fields associated with the technical and ethical aspects associated with this project, and serve as a resource to both the researchers and to the consortium committees (in particular, the Technical Committee).

The Meeting

The Second Annual Meeting of the Shanghai Health Study was held August 17-19, 2004 at the Asilomar Conference Center in Monterey, California. The meeting was the second face-to-face gathering all the various groups involving with the study: the Principal Investigators (both Chinese and American research team members), Scientific and Ethical Review Panel members and the project sponsors.

The opening plenary session began with a welcome from Patsy Clegg (Shell), the Chair of the Benzene Health Research Consortium Oversight Committee. Ms. Clegg then introduced the moderator for the plenary session and Chair of the Benzene Health Research Consortium Technical Committee, Dr. Patrick Beatty of ChevronTexaco. Dr.

Beatty laid out the expectations for the day noting that panelists representing the Scientific and Ethics Review Panels would be providing summaries of their work to date and that the Principal Investigators involved in the research would provide an up-to-date look at their progress in Shanghai.

Scientific and Ethnic Review Panel Activities

The first panelist was Dr. Jerry Rice, Chair of the study's Scientific Review Panel (SRP) and Ethnic Review Panel (ERP) and recently retired from the International Agency for Research on Cancer (IARC). Dr. Rice presented the recent SRP and ERP activity. Dr. Rice noted that SRP was charged with reviewing and approving the initial research protocol and continues to review all *significant* proposed protocol changes and issues that might impact the protocol. In addition, he noted that the SRP has reviewed two scientific manuscripts and abstracts related to the study prior to presentation or submission to appropriate journals. In this regard, he explained that the SRP also serves in an Editorial Board-like capacity to provide "quality assurance" and help ensure that papers are more easily publishable. The role of ERP is to ensure that the research conducted under the study meets internationally accepted ethics standards and reflects relevant cultural patterns in Shanghai. In addition to Dr. Xu Zong-Liang (China) and Dr. Juhana Idänpään-Heikkilä of the World Health Organization and Secretary General of CIOMS (Council for International Organizations of Medical Sciences), two new members, Dr. Paul Lombardo (University of Virginia) and Dr. Ellen Clayton (Vanderbilt University) were also present. The ethnic principles of SHS were primarily based on that of the CIOMS guidelines.

An Update on the Study – Reports from the Researchers

Building International Relationship through Shanghai Health Study

One of the study's biggest strengths is in the level of cooperation and collaboration among the academic and health communities and the Chinese government in Shanghai. Professor Fu Hua, Deputy Dean of the Fudan University School of Public Health and one of the Co-Principal Investigators of the Case-Control Study of AML and NHL in Shanghai, provided a detailed overview of the Shanghai Health Study and the interrelationships and support structure that has been developed for the project in Shanghai. Professor Fu provided an extremely informative introduction to the various hospitals, academic institutions and medical societies, and government agencies that currently play a role in the study. Dr. Fu also reported the very successful grand opening ceremony of Shanghai Health Study that was attended by more than 160 participants, including US Consul General, President of Fudan University, directors/coordinators from the hematology/pathology departments in the participating hospitals and officials from the Shanghai CDC and Public Health Supervision service.

QA/QC Approaches in Shanghai Health Study

Dr. Liang (Fudan University) emphasized that the QA/QC policies and procedures are to monitor each study process to ensure facilities, equipment, personnel, methods, practices, records and controls are in compliance with the study protocol. The QA/QC approaches

have been developed, implemented and gradually improved as the development of the SHS project progressed. Standard Operating Procedures (SOPs) have been developed for various processes.

Case Control Study of AML and NHL

Dr. Otto Wong of Applied Health Sciences provided an overview of the design and a status report on the case-control study. As one of the Co-Investigators in the study, Dr. Wong described, in detail, the hospital-based case-control study for AML and NHL. Prospective patient enrollment starting in June of 2003 and will continue in an effort to develop up to 2 individually matched controls for each acute myeloid leukemia (AML) and non-Hodgkin's lymphoma (NHL) case identified in the study. 30 participating hospitals from Shanghai metropolitan areas are included. Dr. Wong described the identification process for study cases and controls, including the interview process and the patient consent procedures. He also provided an overview of the various information sources for data on exposure levels and how the data would be used to inform the exposure assessment in the current study. Based on the current accrual rate, he estimated that by the end of 2006 the study would have (or exceed) 500 cases of AML. He also estimated that between 300 and 350 NHL cases would be ascertained by end of 2006, which is markedly lower than the targeted sample size of 500. Major reasons for the deficit of NHL have been identified, which may improve the case ascertainment by 20%.

Molecular Epidemiology Studies

Dr. Robert Schnatter, the senior scientific advisor for Occupational Health at ExxonMobil Biomedical Sciences, Inc. and a Co-Investigator in the Shanghai Study, described the two-phased (Phase 1, Phase 2a and 2b) molecular epidemiology study and its role in the project. Dr. Schnatter described the first phase as a retrospective study intended to define dose response relationships for past benzene exposure and identify the most sensitive measures of effect for items recorded in routine exams. Dr. Schnatter added that the study will initially focus on shoe workers but will be expanded to include a variety of workplace environments and sites where benzene is used. He described the second phase as exposure response analyses coupled with a study of the effects of current or recent benzene exposure and a measurement of the effects on blood and bone marrow. To date, a total of 114 workers have been recruited to the 2a study from three factories, including a shoe factory and two rubber factories. Phase 2a clinical laboratory screening and physical examinations from 28 workers identified 8 individuals with abnormal hematology values, and 3 of these individuals were recruited to Phase 2b studies. These results confirm that high occupational exposure to benzene still exists in Shanghai, although government efforts to reduce benzene exposure have resulted in fewer factories with existing high exposure concentrations.

Exposure Assessment for Shanghai Studies

Stepping in for his colleague Tom Armstrong, an industrial hygienist at ExxonMobil Biomedical Sciences, Inc. who was unable to attend the meeting, Dr. Schnatter also provided an overview of the exposure assessment processes and procedures to be used in the study. He described the two level process for exposure questionnaires – the first

explores the work history and potential workplace exposures and is provided to all workers who agree to participate; the second is triggered by specific pre-identified occupation/job categories to measure the exposure level in particular industries or occupations. 64 occupations of interest have been identified, e.g., shoe workers, leather workers, painters, mechanics, farmers, mechanists, electricians, assembly workers, health care worker, and textile workers.

The Clinical and Molecular Laboratory – From Concept to Case Accrual

The final speaker for the plenary session was Dr. Richard Irons, Director of the Molecular Toxicology and Environmental Health Sciences program at the University of Colorado Health Science Center and Principal Investigator and Laboratory Director for the Shanghai Health Study. Building on the information from previous presentations, Dr. Irons began by providing an integrated overview of the study and its goals. He described the overarching goal of the study as an effort to “characterize the relationship between benzene exposure and the development of specific hematopoietic diseases.” He provided a detailed outline of the study and the specific disease states that it would address.

Dr. Irons then offered a unique first look at the new state-of-the-art laboratory facility (JCML – Joint Clinical and Molecular Laboratory) that has been built, and is now up and running, at Fudan University. Currently, JCML diagnoses involves routine hematology, bone marrow aspirate analysis, bone marrow and lymph node histopathology, clinical chemistry-liver enzymes, serology, flow cytometric analysis of blood, bone marrow and lymph node preparations, cytogenetics, FISH and molecular genetics. The rate of patient referral has continued to escalate, as of June 30th, 2004, a total of 565 cases (>150 AML, 97 MDS, 58 Aplastic Anemia, 12 Benzene Poisoning, 139 NHL_{WHO}, 108 NHL_{ICD-9}) have been referred to JCML for diagnosis as part of the clinical operation. Based on the current lab caseload, JCML is expected to diagnose 650 new patients by September 1, 2004, which represents one year of full operation. This exceeds the original prediction of 500 cases per year by 30%. As of today, 30 referral hospitals through out Shanghai metropolitan areas participate the study. A hematopathology review of JCML diagnoses was conducted by a board-certified hematopathologist from USA. Overall, a 95% concordance between the previous recorded JCML diagnosis and secondary pathology review. Assuming the present rate of case contact, the following numbers are projected by the end of 2006 (the study end date): 500-600 AML, 250-350 MDS, 200-250 AA, 30-50 BP, and 300-350 NHL. Two abstracts have been submitted for presentation and will be presented later this year. They are: 1) Benzene poisoning in Shanghai, China – preliminary findings (Munich Benzene Conference) and 2) Frequency of MDS in Shanghai, China – using the WHO classification (American Soc of Hematology).

The remainder of the meeting provided time for the various committees and panels associated with the study to meet and to discuss both progress and future actions. Overall, the 2004 Annual Meeting was a success, providing an invaluable opportunity for everyone involved in the study to meet face-to-face and openly exchange information and ideas.