

Progress Report
AML and NHL Case-control Study
Activities through December 2005

Prepared by:
Otto Wong, Sc.D.
Applied Health Sciences, Inc.
181 Second Avenue, Suite 628
San Mateo, CA 94401
USA

Tel: 1 (650) 347-7898 USA
Fax: 1 (650) 344-6887 USA
ottowong@aol.com
ottowong@shmu.edu.cn

July 24, 2006

◆◆◆◆◆◆◆◆

Patient Enrollment

- The number of participating hospitals has increased to 33 (from 29 in 2004). The majority of participating hospitals are municipal hospitals (17), followed closely by district hospitals (13). Of the three remaining hospitals, two are occupational disease hospitals and one is a private hospital.
- As of June 2006, approximately 8300 patients have been interviewed. These patients included both cases and controls in the case-control study of AML and NHL as well as subjects in the disease progression study. Among the cumulative number of 8300 patients, approximately 5700 questionnaires were entered and verified.
- In terms of the case-control study of AML and NHL, the case enrollment rates for both AML and NHL patients during the last 6 months appeared to be quite stable and encouraging. According to the numbers provided by the JCML (Dr. Richard Irons), the cumulative numbers of AML and NHL patients are as follows (as of June 2006):
 - 424 acute myeloid leukemia patients
 - 520 lymphoid cancer (WHO) patients
 - 433 "NHL" patients (part of lymphoid cancer above)

- If the current rates of patient enrollment can be maintained through December 2006, we will likely end up with the following number of cases by the end of the year (end of data collection):
 - 500-550 acute myeloid leukemia cases
 - 550-600 lymphoid cancer (WHO definition) cases
 - 450-500 "NHL" cases (part of lymphoid cancer above)
- In general, compared to previous years, case identification by the Clinical Coordinators at participating hospitals during the last six months has been relatively timely and consistent. This is particularly true for AML patients. Previously, by comparison, the enrollment of NHL patients fluctuated from time to time. Most of the NHL patients come from the Shanghai Tumor Hospital. In 2005 the team at Fudan made periodic reminders to the Clinical Coordinators at the Shanghai Tumor Hospital for timely submission of NHL patients. These periodic reminders seemed to have worked well. Currently, the enrollment of NHL patients seems to be both timely and consistent.

Selection of Controls

- The selection of controls for both AML and NHL patients seemed to be working properly. Matching criteria have been followed closely. During January-June 2006, there were only a few minor isolated problems.
- At a couple of small hospitals with limited number of patients, finding appropriate controls in the right age range, especially when the cases were either very young or very old, remained to be difficult. In 2005, there was some confusion as to whether the age matching requirement was ± 5 or ± 10 years. This point was subsequently clarified: ± 5 years should be attempted first and, if none available, ± 10 years will be accepted. A review of the recently selected controls confirms that this matching criterion is now clearly understood by the Clinical Coordinators at participating hospitals in Shanghai.
- The participation rate among eligible cases or controls has been extremely high. During the last six months, only 3 to 5 patients (mostly controls) per month refused to participate in the study.
- We have been able to select two controls for every case.

- We continue to monitor the distribution of controls by diagnostic category to ensure that there will be no over-representation of any diagnostic category, which in turn may be associated with certain socio-economic class, occupation or lifestyle. The table below shows the distribution of controls by major diagnostic category, which seems to be in agreement with that of the general population of patients in Shanghai.

Diagnostic category	Percent
Cancers	11.26%
Nutritional, metabolic & immune system diseases	12.25%
Neurological system diseases	8.42%
Circulatory system diseases	10.40%
Respiratory system diseases	9.16%
Digestive system diseases	14.48%
Urinary system diseases	13.49%
Musculoskeletal diseases	7.8%
Blood & hematopoietic diseases	0
Mental diseases	0

Please note that, as specified in the protocol, patients with “blood & hematopoietic diseases” or “mental diseases” are not eligible.

Exposure Assessment

- Dr. Richard Irons will present an updated progress report of exposure assessment at the upcoming August 1-2 meeting in Houston. At the moment, the updated information is not available to us to be included in this report.
- For reference, however, we have reproduced some previous exposure assessment information (as of January 2006) below (in blue). The information should still provide a general idea of the range of benzene exposures in our study.
- Based on preliminary exposure assessment, a total of 259 patients were either definitely or potentially exposed to benzene, representing an

overall benzene exposure rate of 7%. The exposure frequency (7%) is slightly lower than that used for power calculation (10%) in the study design.

- The distribution of benzene-exposed patients by major industry is as follows:

Industry	Percent
Painting	32%
Machine maintenance	20%
Rubber	14%
Home remodeling	13%
Shoe making	12%
Printing	9%

- Based on preliminary exposure assessment, some benzene exposure data of study subjects (cases and controls) are presented in the table below:

Earliest exposure	1936
Occupations/industries with highest exposure	rubber plank manufacture, brush & spray painting
Highest maximum exposure	515.7 ppm *
Highest minimum exposure	12.1 ppm *
Highest typical exposure	161.9 ppm *
Longest exposure	40 years

* preliminary estimates

- In addition to the patients identified to have been exposed to benzene, approximately 2800 patients were identified to have been exposed to other substances in a variety of industries. The largest category is farming with potential exposure to agricultural chemicals. Other frequently encountered chemicals are toluene and xylene.
- Plans have been underway to develop exposure profiles for 8 to 10 key industries using data from the 5 or 6 most industrialized districts of

Shanghai. For example, the exposure assessment team has been working in close collaboration with the Yang Pu District IPHS and has been given access to the exposure records maintained at the local IPHS.

- The exposure assessment team continues to develop exposure data/estimates using the "sector analysis" approach. The analysis for two commonly encountered industries (shoe and rubber) has been completed.
- Exposure data from other sources are being collected, including published literature. According to Professor Liang, who heads the literature review task, preliminary exposure data for the following occupations/industries have been completed: shoemakers, painters, paint manufacturers, printers, dyers, and rubber workers. These literature data will supplement the Shanghai Municipal IPHS database and district IPHS data in the development of job-exposure matrix (JEM).
- Benzene exposure data for the shoe industry derived from the Chinese medical literature have been collected and analyzed. A report summarizing benzene exposure data in the shoe industry in China has been prepared and has been accepted for publication in a special issue of *Regulatory Toxicology and Pharmacology* "The Development and Regulation of Occupational Exposure Limits in Asia." The special issue is expected to be published around October 2006. Preliminary data for another two industries, paint manufacturing and painting, have been assembled and will be finalized by August 2006. Preparation of similar reports for these two industries is now underway.

QA/QC

- Pei Xiaodan, who is responsible for QA/QC, has been providing monthly reports on a regular basis. These monthly reports include accuracy checks of the following items: primary and secondary questionnaires, data entry and initial exposure assessment.
- A recent QA/QC of questionnaires taken between September 2005 and June 2006 indicated that 93.7% of primary questionnaires sampled for review were "qualified" (i.e., no problems were found) and 98.4% of secondary questionnaires were "qualified." We have discussed with Chen Xiaobao, who is in charge of interviews, ways to further improve the quality of primary questionnaires.
- The overall data entry error from September 2005 to June 2006 was 2.7%, which is acceptable.

- During my recent trips to Shanghai I conducted three *ad hoc* QA checks of samples of both primary and secondary questionnaires taken in the last six months. I identified only 1 or 2 minor mistakes in these questionnaires (with literally thousands of items/entries) per QA check. These results reinforce/validate the routine QA/QC checks by Pei Xiaodan.

Data Retrieval

- Instead of retrieving the necessary data for the case-control study from the overall Shanghai Health Study database ourselves, an arrangement for data retrieval has been made. We will not have direct access to the finalized data, but we will be provided with the necessary data by Gail Jorgensen of ExxonMobil (under subcontract to the University of Colorado).
- Gail Jorgensen will extract all the necessary case-control study data (questionnaires, diagnoses, family history, medical history, lifestyle, employment and exposure histories) for us. Our analyses will be based on these extracted data.
- To validate the extracted data, we will conduct a sample audit. Using study ID numbers, we will be able to compare the extracted data to the original source documents (such as questionnaires and exposure assessment reports). The results of the data audit will be included in our final report.

Project Management

- Communication with the Fudan team in Shanghai remains a high priority item. In addition to email and telephone calls, I made 3 trips to Shanghai in the first half of 2006.
- At the last annual meeting in Fairfax, Virginia, the following timeline for the case-control study was presented (also attached to our last progress report dated January 23, 2006). The current plan is that case enrollment will be completed by December 2006. Final diagnoses, control selection, interviews and data entry will most likely be completed by the end of the first quarter of 2007. Exposure assessment of newly enrolled patients (cases and controls) will be conducted in the first and second quarters of 2007. Assuming that both diagnostic and exposure data for all patients will be finalized and available by June 2007, we will be performing epidemiologic analyses of the final data in the third quarter of 2007.

- To facilitate data transfer/linkage and to develop plans for statistical analyses, however, we needed relatively large and representative samples of exposure estimates and diagnoses of study subjects by mid-2006 (see table below). These samples would allow us to develop plans for data transfer/linkage and to test-run analysis programs. We received some test datasets from Gail Jorgensen in July 2006. We are currently reviewing the data.

Time	Activities
July 2006	Samples of exposure estimates (from the Exposure Assessment Team) and diagnoses of study subjects (from JCML) provided to AHS.
3Q & 4Q 2006	Case-control study data management and plans for statistical analyses (based on samples provided).
December 2006	End of case enrollment.
1Q & 2Q 2007	Selection of controls. Interviews, final diagnosis and exposure assessment of last group of patients.
June 2007	Final diagnosis and exposure assessment of all patients completed.
2Q & 3Q 2007	Final data editing/auditing. Analysis and report preparation.

To: BenzConsort-OC@listserve.api.org <BenzConsort-OC@listserve.api.org>;
benzconsort-cc@listserve.api.org <benzconsort-cc@listserve.api.org>; BenzConsort-TC@listserve.api.org
<BenzConsort-TC@listserve.api.org>
From: Bruce Jarnot <jarnotb@api.org>
Cc:
Bcc:
Received Date: 2006-07-25 16:29:00 GMT
Subject: Shanghai Health Study... Hotel Reservation *REMINDER* & Houston travel
information

Shanghai Health Study – 2006 Science & Ethics Panel Meeting with Study Investigators

The Woodlands Resort & Conference Center, Woodlands TX 77380

July 31 – August 2, 2006

HAVE YOU MADE A HOTEL RESERVATION?

REMINDER – Please reserve your hotel room today... The Woodlands Resort & Conference Center received only 18 room reservations as of this morning, suggesting that some of you have not yet booked a hotel room. The resort has asked that we release rooms from our reservation block (see below), or pay one night's rental for each unused room:

HOTEL RESERVATIONS

* All attendees need to make individual hotel reservations...

* Reservations can be made on-line:
<https://reservations.ihotelier.com/onescreen.cfm?hotelid=6171&languageid=1>

- o The hotel web site will not automatically recognize the room block, but Woodlands personnel will see this and assign the correct room type and \$159 room rate.
- o Include our group name and reservation code: "Shanghai Health Study - 60B2PV"
- o Include your arrival and departure dates
- o Disregard selections such as "Forest Lake" or "Fairway King" rooms
- o Include your preference for smoking or non-smoking;
- o Include your preference for 1 large bed (King- or Queen-size) or 2 smaller beds (Full-size)

* Alternately, call the Woodlands Resort & Conference Center for reservations at: (281) 367-1100