PROGRESS REPORT
January, 2005

I. ANALYSIS OF DISEASE PROGRESSION FOR APLASTIC ANEMIA, MYELO-DYSPLASTIC SYNDROME, ACUTE MYELOGENOUS LEUKEMIA AND BENZENE POISONING IN SHANGHAI, CHINA

II. MOLECULAR EPIDEMIOLOGY OF BENZENE-EXPOSED WORKERS IN SHANGHAI, CHINA

III. EXPOSURE ASSESSMENT

A MULTICENTER INTERNATIONAL STUDY

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Introduction

I BUDGET SUMMARY *(SECTION OMITTED)*

II JCML OPERATIONS/STUDY PROGRESS

A. Overview

During our first full year of operation we diagnosed a total of 725 cases of hematopoietic and lymphoid diseases. At the time of this writing 687 have been independently confirmed and entered into the database, including 437 myeloid neoplasms, 155 lymphoid neoplasms, 55 AA and 50 nutritional anemias. This represents a 50% increase from our initial projected case contact rate. About an additional 50 cases remain to be confirmed from this first year series. Analysis of first quarter operations for the second year indicates an even greater case-contact rate of 250, bringing total case-contact to well over 1000 between Jun 03 and Dec 04. Consequently, for the second year of operation we are currently projecting diagnoses of between 750-1000 cases. As previously discussed, this increased rate of case contact has greatly increased cash flow requirements for JCML relative to initial projections. On the other hand, if case accrual continues at the same rate, the goals originally projected for study case accrual should be met for all diseases by the end of 2006.

B. Disease Progression

a. As part of the DP study we have described a novel disease developing in a case series of individuals who were previously exposed to high concentrations of benzene (BZ). Patients were recruited based on a medical history of previous BZ hematotoxicity with several having been identified in ME Phase 2a. Subjects employed in the rubber, petrochemical, pharmaceutical, manufacturing or painting industries were referred to JCML with a previous history of BZ poisoning, and exposure to BZ was confirmed by: review of factory industrial hygiene monitoring records, real-time quantitative industrial hygiene analysis, including personal samples (N=325) and breathing zone analyses (N=225), and/or previous evidence of hydrocarbon intoxication and anecdotal descriptions of solvent use and composition. Subjects for which quantitative data was available were estimated to have full shift exposures averaging between 50 ppm and 300 ppm benzene for varying periods of time ranging from 6 to 22 years. Several features of hematopoietic disease in these individuals have not previously been described in cases of benzene toxicity and provide promising avenues for hypothesis-based studies on the pathogenesis benzene-induced hematotoxicity.

b. As part of the DP study, we also examined the prevalence of MDS subtypes in 100 consecutive cases presenting at Shanghai hospitals. The results were published in an abstract in Blood (104:4715. 2004). This study revealed significant regional variations, including a young median age (57 yr), and a relatively high prevalence of refractory cytopenia with multilineage dysplasia (RCMD) (53%) in Shanghai. The overall incidence of clonal cytogenetic abnormalities was 25%. The most frequently encountered lesions were trisomy 8, 20q-, 5q- and 7q-. These

results provide a basis for comparison with BP cases. A manuscript describing these results is in preparation.

c. A comparable AML subtype analysis is underway, reviewing and correlating morphology, phenotype, cytogenetics and molecular characteristics of AML subtypes in Shanghai. Two manuscripts describing this work are in preparation at the present time: one deals with the overall frequency and prevalence of WHO AML subtypes in Shanghai, and the other characterizes the prevalence of myeloid/NK cell subtypes which we evaluating in order to determine their significance with respect to our studies. We have also published an abstract on a case series of aggressive natural killer cell leukemia (ANKL), which is a rare neoplasm of NK cells associated with bone marrow failure and a dismal prognosis. Diagnosis was made using morphologic, immunophenotypic, cytogenetic, fluorescence in situ hybridization (FISH) and molecular data. The differential diagnosis of ANKL is complicated by the lack of clonal markers and morphologic and immunophenotypic heterogeneity, and this disease is often confused for AML.

C. Exposure Assessment

In his progress report dated January 31, Professor Fu Hua provides a detailed outline and discussion of issues related to exposure assessment, which will not be repeated here. Exposure assessment remains our biggest challenge for a number of reasons, and adjustments are currently being implemented. These include: a) recruitment of additional personnel with advanced qualifications. At the present time two new individuals have been recruited including a student and a chemical engineer; b) increased participation of Western study personnel in management and conduct of exposure assessment activities, c) facilitation and encouragement of IPHS involvement by providing a more responsive and knowledgable interface between Fudan and IPHS personnel. This should include a validation and critical review of IPHS database gaps that, ideally, should be suitable for publication; d) Improving guidance and oversight of QA/QC and questionnaire administration procedures, e) shifting emphasis from reliance on historical database and surrogate factory analyses to emphasize timeline, job-exposure matrix evaluations, and f) implementing more real-time model validation. This approach is described in detail in the original study protocol but has not yet been fully implemented.

D. Molecular Epidemiology

Phase I summaries are being prepared from a group of 84 factories that have been selected with historical workplace monitoring data and 1800 workers for whom medical surveillance records are available. At present, a total of 48 factories have been found to match with IPHS records, and 400 medical records have been abstracted. Phase IIa analyses have been performed on 231 workers with relatively high workplace exposures. Recruitment of workers for Phase IIb analyses has proven difficult with only 3 individuals to date formally recruited via this mechanisms. Therefore, we integrated metabolite analyses into Phase IIa, and continue to implement a strategy designed into the original protocol that enables us to recruit BP cases from candidates originally identified in Phase IIa. Through this mechanism we have successfully recruited approximately 20 BP cases into the DP study, simultaneously providing detailed exposure evaluations of these individuals as well as clinical assessment. A manuscript describing our analytical methodology is in preparation.

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Progress Report of Shanghai Health Study

January 31, 2005

Prepared by Research group in Fudan University School of Public Health

Introduction

The Shanghai Health Study (SHS) project represents a comprehensive epidemiologic investigation consisting of three research studies: 1) Disease progression study (DP study) of etiology and pathogenesis of lymphoid and hematopoietic diseases, 2) Case-control study (CC study) of acute myeloid leukemia (AML) and non-Hogkin lymphoma (NHL), and 3) Molecular epidemiology study (ME study) of benzene exposure. Detailed descriptions of these research studies can be found in respective study protocols.

To support these three research studies, the Joint Clinical and Molecular Laboratory (JCML) between the University of Colorado and Fudan University was established in 2002. Clinical diagnoses of all patients with lymphatic and hematopoietic diseases recruited for the CC and DP studies are performed at JCML in collaboration with the Department of Pathology at the Shanghai Tumor Hospital and the Department of Hematology at the Huashan Hospital of the Fudan University. Furthermore, analyses of biochemical molecular biomarkers for the ME phase II study are developed at JCML. The creation and development of JCML took place from October 2001 to June 2003. In July 2003 JCML became fully functional and patients were recruited into the research projects shortly thereafter.

Another major component of the SHS is exposure assessment, which was designed by ExxonMobil Biomedical Sciences, under subcontract to the University of Colorado, and carried out at Fudan. A number of local government agencies are involved in providing support and information to exposure assessment, including the Shanghai Center for Diseases Control and Prevention (CDCP), Shanghai Municipal Institute of Public Health and Supervision (IPHS) and Shanghai District IPHSs. In particular, one of the major data sources is the exposure database maintained at the Shanghai Municipal IPHS.

This report is not designed to account for many of the study successes to date, which are considerable in number. Rather, in this report we will attempt to summarize Fudan's perspectives of the challenges facing the SHS considering the progress to date. We will also discuss Fudan University efforts and suggestions to meet these challenges.

Part I: CC&DP Studies

1. Executive summary

The participating institutions for the CC and DP studies include University of Colorado Health Science Center, Applied Health Sciences, ExxonMobil Biomedical Sciences, Inc., Fudan University School of Public Heath (FUSPH), 31 hospitals from Shanghai, Shanghai Hematology Society, Shanghai Pathology Society, Shanghai Municipal Institute of Public Health and Supervision (IPHS) and Shanghai Municipal Center for Disease Control and Prevention (CDCP).

Up to Dec 14, 2004, a total of 2370 subjects have been interviewed. The exposure status of 1811 subjects was assessed. 84 were classified as benzene exposed; of which 57 were assigned quantitative exposure estimates. Quality assurance (QA) and quality control (QC) checks are being conducted on a regular basis.

Challenges in the CC and DP studies are summarized as follows:

- Lack of adequate involvement of IPHS in exposure assessment
- Overestimated value of IPHS exposure database
- Inadequate technical resources to support the exposure assessment
- Unclearly defined or misunderstood terminologies in questionnaires regarding exposure assessment
- Underestimated the complexity and difficulty of questionnaire interview including the first and second level questionnaires, and factory inspection questionnaire
- JCML database not fully functional
- Insufficient support from clinical coordinators at participating hospitals in following control selection criteria
- Gaps in regular communication between Chinese and US researchers
- Lack of clearly defined roles and responsibilities of some of US researchers

2. PROGRESS

2.1 Questionnaire interview

2.1.1 Number of participating hospitals

A total number of 31 hospitals in Shanghai have engaged in overall SHS that include 16 municipal hospitals, 12 district hospitals, 2 occupational diseases hospitals and 1 teaching hospital affiliated to a Military Medical University.

2.1.2 Number of questionnaires administered

Up to Dec 14, 2004, a total of 2370 questionnaires, including 790 cases and 1580 controls, have been administered since mid June 2003 with an average rate of 132 cases per month.

For the 3 person-staffed questionnaire taking team and approximately 22 working days per month, the average workload is about 2 questionnaires per person per day.

2.2 Data entry and errors check

The double entry approach by two independent persons was introduced for the purpose of minimizing the errors during data entry process and checking the accuracy of data entered. The major procedures for data entry and errors check are as follows:
1) Creating a report comparing the difference between data entered and the original information
2) Checking entered data along with the original questionnaire
3) Revising check report
4) Accessing database and revising data by the data entry personnel
5) Finalizing check report and compiling it with the original questionnaire by the archiving clerk.

1880 (97.2%) of the totaled 1935 pieces of CC/DP questionnaires have successfully passed the double entry check; 55 were failed (2.8%) which were under further checked.. With further improvement of the JCML database and data entry skill, as well as closer cooperation among team workers, the data entry and error check have been more efficient over time. Observed errors have been greatly reduced; and the time spent for producing a check report dropped from 2 minutes to 1/2 minute. All error check reports produced are now printed out for archiving.

2.3 Exposure assessment

The procedure for exposure assessment is based on what US experts have outlined in the protocol with slight modifications.

2.3.*1 Procedures of exposure assessment (from EAT to EA)*

The initial assessment is performed based on the evidence of occupation/job history with potential exposure to benzene obtained from interviewed subjects' questionnaires and literature information. A total number of 1147 literature articles published in the Chinese medical literature related to occupational benzene exposure between 1960 and 2003 were collected and electronically archived by industry and year that covered dozens of industries of relevance. The IPHS database, questionnaire records, literature information and current worksite monitoring data provide a scientific basis for the initial assessment, which will result in a categorized summary identifying "exposure", "non-exposure" and/or "uncertain".

After having completed the initial assessment, the following steps were to have taken place:
1) Questionnaires are doubly checked by the Exposure Assessment Coordinator (EAC), and progressed to data entry if all are considered acceptable;
2) The initially-assessed information such as "benzene exposure", "uncertain benzene

exposure" and "uncertain exposure to other hazards except benzene" is presented at the weekly Exposure Assessment Committee meeting (EACm) for further evaluation and confirmation. The information of confirmed "non-exposure" and "exposure to other hazards" is entered into the JCML database;
3) In collaboration with IPHS, the EAC should further search for supplementary information from the IPHS database, industry records, and other resources available to make a better assessment;
4) Telephone calls by Exposure Assessment Team (EAT) and/or EAC to the subjects for further information, if possible; worksite survey and monitoring for collecting general information and working conditions of the factory to facilitate a quantitative assessment and to provide evidence in selecting a proper surrogate factory;
5) EAC working along with IPHS staff to search for surrogate factory information from the IPHS database.
6) Preparing all materials relevant to exposure assessment including worksite monitoring data from the IPHS database, current survey data, literature information, etc by the EAC
7) Performing both qualitative and quantitative assessments, and/or recommending a work proposal for further assessment by EAC;
8) EAC working along with EAT to implement the assessment proposal, including simulating exposure assessment, current exposure worksite monitoring, surrogate worksite monitoring; and providing literature information in cooperation with IPHSs, where local IPHSs are designated as responsible for providing the worksite;
9) Worksite monitoring and surrogate surveys by EAT;
10) Updating assessment based on the updated information available by EAC; and
11) Data entry and custody.

2.3.2 Key outcomes of exposure assessment

Up to Dec 14,2004, 1811 subjects were assessed to clarify their potential exposures. 1181 (65.21%) of these were identified as "non-exposed" meaning neither exposure to benzene nor to any other occupational hazards; 84 (4.64%) were "exposed to benzene and other chemicals"; 541 (29.88%) were "exposed to other chemicals except benzene"; and 5 (0.28%) were "uncertain" (Table 1.1). Table 1.2 showed sources supporting the quantitative exposure assessment.

Table 1.1 Summary of exposure assessment (up to Dec 14, 2004)

Status of exposure		No. case	%
Exposure	Benzene only	0	0
	Benzene and other chemicals or hazards*	84?	4.64%
	Other chemicals except benzene	541	29.88%
Non-exposure		1181	65.21%
Uncertain/pending		5	0.28%
Total		1811	100%

? Notes: Of these 84 cases regarded as benzene and other chemicals exposed; quantitative assessments for 57 of the 84 cases have been completely accomplished; while the remaining 27 cases are being further quantitatively assessed.

Table 1.2 Proposed evidence-based EA for 84 cases of "Combined exposure to benzene and other chemicals or hazards"

Methods	Quant. assess't Completed	No. No yet completed
IPHS database relevant factory	0	
IPHS database surrogate factory	19	
IPHS database relevant factory + worksite walk through survey	6	2
worksite walk through survey	19	7
Worksite of surrogate factory	5	8
Worksite of surrogate factory + IPHS surrogate database	2	3
Literature + surrogate worksite		5
Literature + expert + worksite	2	
IPHS database relevant factory + surrogate factory	2	
PHS database relevant factory+ surrogate worksite		2
worksite walk through survey + surrogate historical information from other channels outside SHA	1	
Factory historical information + surrogate worksite	1	
No. Bn exposed worker	57	27
Total	84	

2.4 Newly developed DP study

The newly developed phase I study is characterized by the analysis of additional benzene poisoning cases, which constitutes an important component of the DP study although it has not been originally documented in the respective protocol.

To keep pace with the newly developed study, a further searching was initiated in collaboration with Dr. Ni Weimin and the Occupational Physician Committee (OPC), as well as the hospitals responsible for the periodical health surveillance. Under a multi-collaborative approach, we acquired the historical data of health monitoring for 194 cases of benzene poisoning (1964-2003) in late 2003.

We have started abstracting the medical records of hospitalized patients diagnosed as benzene poisoning (BP), to initiate a study in depth of benzene exposure-effect on peripheral hematopoiesis as well as the bone marrow since September 2003. The addition of BP cases is really a new part of the DP study – since it is not only looking at medical records and peripheral blood counts. It is looking at the progression of disease, and is

accessing clinical records and bone marrow smear. As expected, however, this study has also experienced a series of challenges.

2.4.1 *CDCP benzene poisoning database*

It was thought that the acquisition of the historical data of benzene poisoning and its relevant database would have been available in Shanghai CDCP. Unfortunately, the BP database was missing as a result of the separation of IPHS and CDCP.

2.4.2 *Historical data re-collecting from local district CDCPs*

Shanghai Municipal CDCP has promised to work on re-collecting of the historical database on BP. CDCP has asked for the historical benzene poisoning cases from local district CDCPs. However, the re-collected information provided only a basic "demographic data" of the poisoning cases without acknowledging anything about the occupational exposure level, blood counts or bone marrow features.

2.5 Status of QA/QC

2.5.1 Standard Operation Procedure (SOPs)

According to the standard procedure flowchart and SOPs for each study process, QA/QC practical procedures (Version 1) have been established since mid 2004. After several revisions, QA/QC practical procedures (Version 2) have been preliminarily documented. In order to make QA/QC inspection work smoothly, a clearly defined contrast table describing the position title and its corresponding responsibility for each QA/QC coordinator of relevance has also been listed.

2.5.2 QA/QC of CC/DP

As SHS is composed of several studies, the QA/QC approach has thus included a number of inspection processes for the three different studies). In order to make the QA/QC inspection approach concrete and to ensure the entire quality of the study project, QA/QC for each study has been divided into several parts (e.g., the quality of the questionnaire, data entry error, control selection, etc.). For each study component, a QA/QC inspection record, i.e., the summary report is required to be available immediately after each QA/QC inspection has been accomplished. QA/QC inspection for the quality of questionnaire, control selection and the data entry error rate are inspected twice every month. The initial EA and final EA are checked once every month according to QA/QC SOPs.

Two remediation meetings were held on Nov.9th and Nov.10th 2004, respectively for questionnaire quality and data entry errors. Criteria for questionnaire interviewing and filling-in were emphasized and unified. More emphases were placed on how to properly refer subjects to the second level questionnaire, and filling-in its opened-blanks. Scheduled dates for re-inspection on questionnaires and data entry error were also set.

Several improvement reports for questionnaire quality and data entry error after the remediation meeting have been accomplished.

In order to draw attentions from the study session coordinators and project coordinator immediately if any problem is found during the course of a QA/QC inspection, a written QA/QC report is periodically submitted to the session coordinators of each study. Of which, problems and the corrective actions were noted. By now, QA/QC monthly reports summarizing QA/QC approaches of the past three months have been submitted on a regular basis.

3. Challenges and our efforts

3.1 Cooperation and coordination

FUSPH has been facing an unaffordable responsibility shifting that should naturally be borne by other participating institutions of relevance.

3.1.1 Clinical coordinators

To fully inform clinical coordinators with the scope and goals of the study and the responsibilities they should take, dozens of clinical coordinators from all 31 hospitals have been gathered at more than 3 meetings held separately since June 2003 as not all coordinators were be able to present them at the same time. A small number of these coordinators were still absent from all meetings; and some of the coordinators were shifted to other departments that are not participants of the SHS. These changes have brought us much more inconvenience than expected and resulted in profoundly negative impacts, such as: 1) many clinical coordinators did not pay enough attention to fully understand what role they should play, how they should explain the Informed Consent in detail to their patients, that have resulted in some sudden withdrawal from the proposed interview; 2) some clinical coordinators did not properly follow the instruction of control selection, which include matching the closest admission date of control with case, randomizing the distribution of control selecting sources, etc. We have held remediation meetings with some coordinators, and have revised some aspects of control selection criteria thus we believe that control selection is now proceeding sufficiently.

3.1.2 Cooperation with IPHS

We were confronted with similar difficulties while cooperating with IPHS. For example, the original proposal specified that the district IPHSs should have their own work team responsible for worksite monitoring to collect current benzene exposure data for subjects with potential benzene exposure. Unfortunately, neither the municipal nor the district IPHSs have carried out this work so far. FUSPH has to get everything ready in meeting with IPHSs' requirements, which has brought us an unaffordable burden of both time and manpower. In addition, although the leaders of the participant institutions were designated as persons taking primary responsibility for their participation in the SHS, the major

professional and managerial transactions are generally handled by FUSPH side only. For example, EA is recognized as one of the most complicated processes which require an active participation of both municipal and district IPHSs conducive to providing adequate information and helping in timely access worksites of relevance to link the 'case' with 'exposure'. However, the responsibility of professional and managerial transactions has not been regularly shared by the relevant institutions, which sometimes put FUSPH in an extremely overloaded and stressful situation.

(This shifting burden of responsibility is also an issue for the M.E. study – IPHS wanted to lead the factory selection committee, but they did not. This should be mentioned later – in the M.E. part of the report)

3.2 Questionnaires

3.2.1 *Development of questionnaires*

3.2.1.1 *First level questionnaire*

The CC/DP questionnaire is composed of the first level and second level texts which were designed in US but being used in Shanghai, China. To make the questionnaire more practical and feasible, FUSPH researchers worked together with US experts making many modifications in terms of its content and format. These innovating measures generated some updated versions of the questionnaire on 2002/04/01, 2002/06/13, 2002/08/20, 2002/11/19, 2003/01/27, 2003/02/18, etc, based on the initial version of 2001/06. However, some minor gaps still exist between US designed questionnaire and the one commonly used in China. It might be partially derived from cultural difference; but most importantly, it simply reflects the gap between the research desirability and the real practicability. For examples, there are too many "open-ended blanks" in the questionnaire Part 4 "Employment Histories" and Part 5 "Occupational Exposure List" that have been proved too difficult to be completely and accurately answered by interviewees under certain circumstances, such as ill health condition and/or awkward interview environment, since not every hospital was willing to provide a private room for interviews.

3.2.1.2 Second-level questionnaire

The second-level questionnaire was designed relying on a study conducted in the USA, which required that 63 types of occupations/jobs should be referred to the second-level questionnaires. FUSPH researchers translated all the 63 types of occupations/jobs into Chinese but some disputes might still exist due to:

- Conceptual difference in defining and distinguishing occupation and job, work process and job activity;
- Being bored by the redundancies of too many "open-ended blanks" that often make both interviewer and interviewee confused and lose confidence in fully responding them; and
- The information obtained from the second-level has not been substantially useful to

the exposure assessment.

Therefore, most questionnaire administers do not appreciate and do not highly value of using second-level questionnaire. Rather, they would preferably concentrate themselves to achieve the requested goals by interviewing the primary questionnaire as perfectly as they could.

By the end of 2004, it was found that among a total number of 1924 questionnaires, that were accomplished data entry, 459 of them were referred to the second-level questionnaires accounting for 23.86%. The referring rate did not seem to be as high as expected although 43 of the 63 occupations/jobs listed (68.3%) have been referred for further investigation. Of which, farmer (46.2%), textile worker (6.8%), health care worker (5%), mechanical maintenance worker (2.4%), and cook (2.4%) were ranked as the top 5 occupations/jobs being referred.

3.2.2 Questionnaire interview

3.2.2.1 *Pilot tests*

To investigate the feasibility of the questionnaire, we conducted at least three trials of pilot study in hospitals at various levels prior to the formal study started. The three pilot investigations were initially carried out at the affiliated hospitals and gradually expanded to all the 17 participant hospitals on 02/04/23, 02/05/28 and 02/08/02.

3.2.2.*2 Questionnaire interview*

The experience gained from the pilot studies has built a good foundation for the formal study. However, the rapid growth of the number size of hospitals involved, which has been increased from 17 at the beginning to 31 hospitals up now, has increased difficulties. These constraints include: the mobility of clinical coordinators, disorderly work environment, less personal confidentiality protected (most cases were interviewed by bed-side at a multi-patient ward), and patients at ill health condition or elderly age. All theses constraints were so often frustrating questionnaire takers to get all answers in matching with the requirements of “integrity”, “consistency” and “correctness”. However, FUSPH questionnaire administrators have been making every effort in allowing for good quality, even if working conditions are difficult.

3.3 Control Selection

3.3.*1 Criteria for control selection*

The original criteria for control selection of CC study were as follows: 1) Same gender; 2) Age ± 5 years; 3) No disease of the lymph or blood system; 4) Closest admission date; 5) Same hospital; and 6) If the case is an inpatient, controls will be inpatients as well, if the case is an outpatient, controls will be outpatients as well. In addition, the source of the controls should be randomly selected from the “admission registration center” in each of

the hospital involved.

3.3.*2 Challenges in practicing the criteria*

However, the effectiveness of the criteria is very much dependent on how they are followed. Having had some investigations, we found that 1) clinical coordinators could not easily access the "admission registration center" because of its confidentiality; 2) out-patients have always been hasty while they are visiting hospitals, which make them unlikely to be the controls; 3) clinical coordinators are always overloaded and overworked during on their duty that frustrating them to carefully follow control selection criteria; and 4) some of the physicians might not fully understand the importance of the selection criteria.

For example, we spoke to a number of directors from the participating hematology institutions to explore the possibility of control selecting through "admission registration center". 14 of 16 directors did not think it is possible to access the registration system frequently. A meeting was held to further discuss on this issue and got one positive response only saying that they have successfully selected controls through "admission registration center". It implied that the gap between scientific rigor and reality of control selection criteria had become an obstacle preventing CC/DP study to move forward smoothly.

3.3.*3 Efforts in narrowing the gap*

Having had an analysis from our own data and an investigation based on more hospitals beyond the project, we found that: 1) there were no significant differences of both demographic characteristics and life style between outpatients and inpatients if two controls were selected rotating from different departments (Annexed table 1); and 2) it showed no substantial difference of disease distribution between in-patients discharged from hospitals in Shanghai in 2002 and the controls selected in the CC/DP study (Annexed table 2).

3.3.*4 Revision of the criteria*

Based on the analysis and investigation, both US experts and FUSPH researchers decided to make a compromise of modifying some of the criteria to make them more practical without introducing significant bias by adding: 1) If a control cannot be found, relax age to ±10 years; 2) If only one control can be found, we will keep both the case and the one control; and 3) To circumvent the problem of irrelevant people being pretended as "patients" we have limited control selection to inpatient only since early 2004 because anyone can easily become an "outpatient" by going through a simple registration procedure.

(It seems that selecting a patient with the 'closest admission date' is still a problem occasionally, but experts believed that it won't bring significant bias to the study.)

3.4 Communications with US experts

Training courses on different topics with diverse emphases were offered at the early stage that has granted trainees a sound scientific basis of industrial hygiene benefiting to the exposure assessment. However, with the SHS moving forward to a deeper and critical stage, some unsolved problems have become apparent. For example: 1) US experts could not work here as frequent as the project needed, which sometimes leads to a "vacancy" of technical supports; 2) gaps between theory and practice existed due to lack of sufficient practice; 3) unclearly defined role for each US expert at the early stage of the project resulting in team workers confused about to whom they should consult with; and 4) insufficient communication had also brought about barrier and misunderstanding.

3.5 Unstable JCML database

JCML database setting has been a complicated issue, which depends on how well the programmer understands the study design and the data per se, and the frequent communication between project designer and software programmer. However, a big gap existed between the two counterparts for quite a while at the early stage. The process of database setting and refining had been taking too long to meet data entry demands. As a result, the database did not run quite well until later 2003, which had hindered data entry and errors check to a certain extent. Having put in greater efforts, the condition has been dramatically improved, which was witnessed by the efficiency of task performance. For example, by double entry check, the complete match rate for a piece of questionnaire with more than 470 variables has been greatly elevated. However, some more problems still exist in terms of data entry processing and exposure assessment report creating. For example, input content might be accidentally missing in variable item; exposure assessment results could only be linked with one job, etc (see details in 4.6 Further improvement of JCML database).

3.6 Challenges facing exposure assessment

The exposure assessment has been witnessed as one of the most complicated and difficult parts of CC&DP Studies. Unfortunately, we may have underestimated the challenges of the situation and not been taking adequate action in conquering the difficulties although everyone recognizes that would have become a tough issue.

3.6.*1 Overestimating the value of IPHS database*

Imperfect integrity of IPHS database, inadequate factory data records, job mobility of factory workers involved and un-matched exposure data associated occupation were the key elements affecting the study. For example, a total number of 47 factories were identified as the workplaces that were associated with subjects being investigated. However, there were only 13 of them (28%) with data available at the IPHS database; 6 of the 13 were considered partially useful and none were really meeting the requirements of exposure assessment. In addition, as the relevant information has not been timely updated, it has been hardly sorting out convincible evidence from IPHS database to support the proposed "surrogate exposure assessment".

3.6.*2 Lack of adequate involvement of IPHS*

It's commonly recognized that the exposure assessment needs close joint-efforts devoted from both sides of FUSPH and IPHS. However, the contract with IPHS was negotiated between University of Colorado (UC) and IPHS. All the activities of IPHS are in accordance with the above subcontract; and FUSPH has no authority of control over IPHS's performance. Therefore, it has always been challenged by:

- Inadequate information at the IPHS database without effective remediation measure;
- Conflictive role between governmental health inspectors and scientific researchers borne by a limited number of overloaded IPHS staff preventing municipal IPHS to take a lead towards achieving access to district IPHSs;
- Lack of an incentive scheme to motivate active participation of district IPHSs.

All these issues have badly hindered a further progress of exposure assessment.

As being mentioned, exposure assessment will be very time consuming, as it needs a highly multi-institutionally supported and well-coordinated collaboration. The following example presents you a general feature of the entire process for an exposure assessment that took about 8 months to accomplish:

Example:

Case #867, male, a paint warehouse keeper at the locomotive maintaining workshop of Shanghai Railroad Transportation Bureau during 1988-2003.
The hospital-based interview was done on 2003-12-16, which was followed by:

- 2004-4-10: Searching information from IPHS database: EAT obtained some of the exposure data, but failed to locate the exposure site associated with job-type information;
- 2004-4-14: Transmitted IPHS a name list of factories that were supposed to be useful for further assessment;
- 2004-7-23: Made telephone calls to get contact with the subject for further information;
- 2004-7-30: Conducted field surveys;
- 2004-8-3: Received a pile of historical data of worksite monitoring from the Health and Anti-epidemic Station, Shanghai Railroad Transportation Bureau; and
- 2004-8-6: Accomplished the quantitative exposure assessment.

From this typical case, it might imply that: 1) significant information resources are needed to simply make one exposure assessment; and 2) to achieve an information transfer with satisfied response usually take quit a while of time period. For the above case, it took about 3.5 months to get a response with respect to the subject of relevance (from 2004-4-14 to 2004-7-30). The retrospective benzene exposure assessment for historical cases of benzene poisoning might be more difficult versus the phase I study as the cases were distributed into more than 150 factories, which urges a closer and more promising collaboration from both municipal and district IPHSs.

3.6.*3 Inadequate scientific supports to exposure assessment team (EAT/EAC)*

The significant setback with respect with technical support to the exposure assessment issue appeared to be:

1) Different views among researchers

We were not surprised by different views sometime existed with respect with either conceptual or methodological aspects of exposure assessment among researchers. However, problems might thus be derived from insufficient communication and lack of prompt response to the disputes, such as not taking a follow-up study or further discussion on the debatable cases soon after the conflict occurs. For example, how should we categorize the investigated subjects with “low” or “very low" benzene exposure that are very much dependent on the pattern of exposure? For ordinary taxi drivers, the “low” or “very low” benzene exposure due to gasoline could basically be neglected but for mechanical workers who were using benzene-containing gasoline as degreaser, the “low” even “very low” exposure could mean much more than those of taxi drivers. Despite the existence of different opinions among researchers is not uncommon what we have been challenged are how to handle these disputes and to reach an agreement timely conducive to the success of exposure assessment.

2) Limited function of temporary EAC experts

First, the temporary EAC experts serve on a "part time" basis that might not allow them to spend more time and energy to deal with the problems persistently. Second, as the IPHS database has neither provided proper data for the assessment nor the convincible evidence supporting the option of ‘surrogate assessment’ that exaggerates the EA issue becoming even tougher. In that case, the temporary EAC experts would have thus confronted more challenges that are unlikely to be solved by them. Third, the proposed systematic approach of ‘surrogate and/or simulate exposure’ would unable be successfully designed and proceeded without proper historical records and clear definition of the approach that could not be solved by the EAC experts alone either.

4. Suggested solutions

4.1 Human resources

More staff is badly needed. For example, the staff who is responsible for immediate questionnaires check after back from the hospitals to avoid mistake occurring while data entering, and the staff working for EAT and/or ME, etc. Several solutions are suggested as 1) The questionnaire administration coordinator should be released from a heavy workload of making questionnaire copies to the immediate Qs check after being interviewed from the hospitals; 2) 1-2 more team workers might need to be recruited working for EAT and/or ME surveys; and 3) a multi-disciplinary temporary advisors and IPHS staff members might be invited to participate in the EAC meeting either on a regular

basis or under certain circumstances whenever it is necessary.

4.2 Communication and technical support

More timely technical support from US experts and communications between FUSPH researchers and US experts are crucially important to the further progression of the project. The criteria and requirements in meeting with the study Protocol should be clearly stated and defined for each component of the study. A ***Quarterly Summary Report*** focused on work status, QA/QC check and remediation steps taken is suggested to become a routine documented circulation for both sides' researchers to prompt the communication and technical support.

4.3 Second-level questionnaire

Some more errors were found in the second-level questionnaire due to unclearly defined job title or work task in the 63 jobs listed, and/or conceptual difference in understanding the definition for job title or work task between China and US. Most of the questions listed in second level questionnaires cannot be clearly answered by interviewees. Further communication on the value of second-level questionnaire and its proper use should be further clarified towards reaching an agreement between US experts and FUSPH researchers.

4.4 Control selection

Some of control selection criteria still needed to be verified. It seems that the difference of admission date for the cases and controls has not been definitely regulated. Is "the closer admission date, the better?" For example, the difference of the admission date between Case and Control was found to be as long as 61 days (from RenJi hospital), which has been too hard to judge if it is qualified or not during a QA inspection. Some of the criteria need to be further clarified and documented. FUSPH will pursue regular QA/QC approach to monitor how the revised control selection criteria are followed.

4.5 Enhancement of clinical coordinators' involvement

The suggested solutions are:1) pursuing regular QA/QC check on the status of control selection; and 2) enhancing communication between JCML and clinical coordinators via regular meeting and immediate dialogue.

4.6 Further improvement of JCML database

More efforts are necessary to make the database function more stable and friendly for users. The following problems have been reported to database developers and should be solved shortly.

4.6.1 Data entry

- Input content might be missing unexpectedly in variable item 'DI11S At this address since';
- Filled content in the original questionnaires in variable items 'MHD4 and MHH1 "Year Started' and 'Year stopped" ': it was sometimes expressed as 'year', which needs to be converted into 'month';
- Some variable items in the screen questionnaire were provided with both choices of 'Yes' and 'No' simultaneously, which needs to be corrected.

4.6.2 Exposure assessment summary report

- Data couldn't be entered and updated sometimes
- The first entered character always disappears automatically
- Exposure assessment results could be input for one job only, which needs to be corrected by linking different documents with the EA decision.
- Subjects couldn't be linked with his/her factories. Similar corrective procedure needs to be taken.

4.6 Roles of responsibility of US researchers

1) Since there are number of researchers from the States, the role of these researchers should be clearly defined and then FUSPH staff members would know clearly whom they should report to. For examples, FUSPH researchers would like to know who is responsible for making final decision related to each session of these three studies, such as exposure assessment, project management, protocol and/or procedure changing, etc.
2) Greatly appreciate having definitively described roles and responsibilities for each of the US researchers

4.7 A comprehensive re-evaluation of the exposure assessment in terms of expectation and practicality.

It is recognized that SHS is approaching into an important and critical stage, while the exposure assessment becoming a crucial component to the success of the CC and DP studies. Therefore, remediation steps towards prompting exposure assessment are urgently needed, for examples:1) re-evaluating exposure assessment in terms of expectation and practicality; 2) listing necessary information resources and the methodological approach for using the resources 4) human capacity building, enhancing and organizing; and 4) setting a clear work process and time schedule towards solving EA problems on a case by case basis.

Annexed table1 Demographic characteristics of outpatients and inpatients from CC/DP questionnaires accomplished (by Apr 2004)

Variables		Types of patients		Total
		Outpatients	Inpatients	
SEX	Male	78(60.5)	401(55.6)	479(56.4)
	Female	51(39.5)	320(44.4)	371(43.6)
MARTIAL STATUS	DNK	0	5(0.7)	5(0.6)
	DIVORCED	0	7(1.0)	7(0.8)
	MARRIED	111(86.0)	604(83.8)	715(84.1)
	NEVER MARRIED	12(9.3)	76(10.5)	88(10.4)
	WIDOWED	6(4.7)	29(4.0)	35(4.1)
EDUCATION	DNK	1(0.8)	3(0.4)	4(0.5)
	HIGH	37(28.7)	196(27.2)	233(27.4)
	MIDDLE	35(27.1)	228(31.6)	263(30.9)
	NONE	5(3.9)	53(7.4)	58(6.8)
	POSTGRADUATE	3(2.3)	4(0.6)	7(0.8)
	PRIMARY	21(16.3)	111(15.4)	132(15.5)
	UNIVERSITY	27(20.9)	126(17.5)	153(18.0)
SMOKE*	No	72(55.8)	447(62.0)	519(61.1)
	Yes, but not now	16(12.4)	120(16.6)	136(16.0)
	Yes, still smoke	41(31.8)	154(21.4)	195(22.9)
DRINK	DNK	0	5(0.7)	5(0.6)
	No	96(74.4)	544(75.5)	640(75.3)
	Yes	33(25.6)	172(23.9)	205(24.1)
CITY	Shanghai	99(76.7)	586(81.3)	685(80.6)
	Out of Shanghai	30(23.3)	135(18.7)	165(19.4)
AGE(yrs)*	18-	24(18.6)	131(18.2)	155(18.2)
	35-	25(19.4)	88(12.2)	113(13.3)
	45-	32(24.8)	173(24.0)	205(24.1)
	55-	28(21.7)	121(16.8)	149(17.5)
	65-	20(15.5)	208(28.8)	228(26.8)

* P<0.05

Annexed table 2 Disease distribution of inpatients in 68 hospitals (2002, Shanghai) vs. CC/DP controls

Disease	Discharged inpatients in 68 hospitals in SHA		Controls in CC/DP	
	Number	Proportion (%)	Number	Proportion (%)
Infectious disease and verminosis	12952	1.90	0	0
Cancer	74460	10.92	51	11.5

Endocrinopathy, nutrition related disease, metabolic disease, immune disease	15859	2.33	40	9.1
Blood and hematopoietic system related disease	4448	0.65	0	0
Mental disease	941	0.14	0	0
Neurologic system disease and sensory organ related disease	27642	4.05	36	8.2
Cardiovascular disease	100827	14.79	92	20.9
Respiratory disease	93602	13.73	61	13.8
Digestive system disease	105418	15.46	49	11.1
Urinary system disease	40459	5.93	27	6.1
Cyesis, baby delivery and puerperal complications	82255	12.06	0	0
Skin and hypodermis disease	4542	0.67	2	0.45
Musculoskeletal disease, connective tissue disease	16156	2.37	29	6.59
Inherent abnormality	4472	0.66	0	0
Perinatal conditions	3461	0.51		
Signs and symptoms with unknown causes	6040	0.89	17	3.86*
Injuries and poisonings	54607	8.01	0	0
Others	43742	6.41	36	8.2
Total	681883	100.00	440	100.0

* including outpatient controls

Part II: Molecular Epidemiolgy Study

1. Executive summary

The molecular epidemiology (ME) study is designed as a two-phase study, phase I and phase II. The ME project is also a study with multi-collaborative institutions, that include 16 units of Shanghai Institute of Public Health and Supervision (IPHSs) at municipal and district levels, Shanghai Municipal Center for Diseases Control and Prevention (CDCP), and factories of relevance.

The key point of phase I study is to access the historically medical records. Great efforts have been devoted to locating medical records from IPHS and CDCP data system. However, it was witnessed that medical records for phase I study were neither available from IPHS nor CDCP data system. A new Occupational Physician Committee (OPC), which owns a comprehensive network on occupational health surveillance, has taken responsibility for the abstraction of medical records from workers who have been working in factories with benzene exposure. This task has been progressing quite well and should be completed by the end of March 2005.

US side experts were also asking for the medical record abstraction although it was not planned at the beginning stage of SHS. After failing to get medical records for benzene poisoning cases from CDCP and IPHS, OPC doctors abstracted the medical records of 195 historical cases of benzene poisoning in 2004.

Factory selection is the first big challenge for the phase II study. According to US scientists' suggestions, priority was put on higher exposure factories. We had tried searching for the candidate factories along with four information sources, i.e., the IPHS database, historical benzene poisoning cases, CC/DP provided subjects and local IPHS industrial hygiene monitoring data. Unfortunately, above trials did not work well because of the changing status of exposure, IPHS' conflictive role and its improper management system. Some other information sources such as medical records at occupational health hospitals, and other channels of relevance have been showing an optimistic perspective. The second challenge is to get closer contact with both factory managers and workers by further explaining the real nature of the study because they have been so worried about the socioeconomic and health risks that might stem from their participation in the study.

Laboratory analysis of benzene metabolites has been removed from Shanghai CDCP to Fudan since March 2004. With the establishment of the relevant SOPs, the sample analysis has been running quite well.

To facilitate phase II study, new institutions, such as occupational health hospitals other than IPHS, should be closely consulted to promote factory selection. IPHS' adequate involvement in the retrospective exposure assessment should also be emphasized. We believe with these new initiatives, phase II is still a highly feasible study.

2. PROGRESS

2.1 The Phase I study

The phase I study is based on an abstraction form with 2000 annual health-monitoring records (the relevant factories should have record keeping available for workers potentially exposed to benzene for at least five years). At the same time a retrospective exposure assessment should also be conducted. The study requires that the health monitoring data originate from populations with different gender, age and working

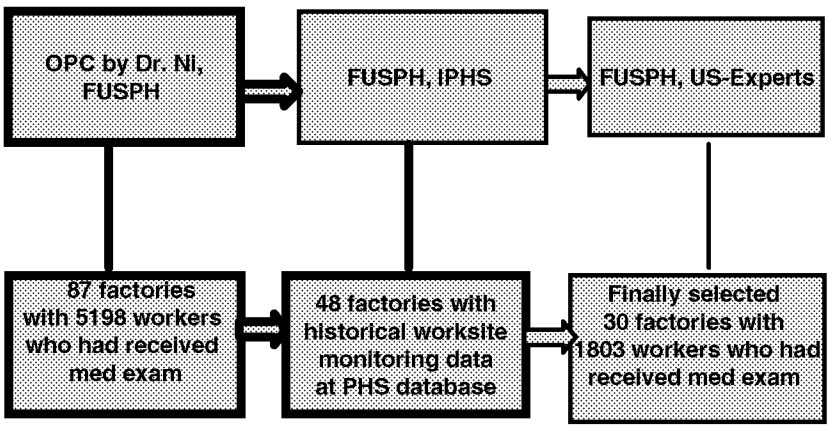
duration, who had been exposed to benzene at a range of exposure levels.

2.1 .1 Collaboration with Occupational Physician Committee (OPC)

Based on the information obtained from a number of large scale hospitals associated with the Occupational Physician Committee (OPC) and hospitals responsible for periodical occupational health surveillance, we have successfully accessed medical surveillance data for 87 factories covering 5198 workers with potential benzene exposure, as well as detailed information regarding factories' title, location and periodical medical examination records. To get further information upon the exposure and effects data, FUSPH has kept in touch with IPHS towards accessing the exposure data for the 87 factories from the database. The historical worksite benzene monitoring data for 48 of the 87 factories (55.2 %) have been accessed from the IPHS database. However, it witnessed us again that Shanghai Municipal IPHS database does not own worksite monitoring data for all benzene related industries in Shanghai. Having had the successful trials via OPC-related paths, in consulting with Dr. Rob Schnatter, we recruited 30 factories with historical worksite monitoring data from a total number of 48 factories covering 1803 workers for further study. The selection criteria for the 30 factories include:1) number of workers receiving regular medical examination over 20 annually; and 2)having IH monitoring data available.

2.1 .2 Basic work procedures of factories selection

The basic work procedures of factories selection are shown in a flow-chart below:



Dr. Ni is now coordinating historical abstraction from the 30 selected factories with 1803 workers who had received the periodical medical exam. This should be accomplished by the end of March 2005. Prior to the initiatives with Dr. Ni, we had also accessed the IPHS

database in retrieving the worksite monitoring data for another 10 factories associated with benzene exposure, and had selected 4 of the 10 factories as candidates for phase I study, and have abstracted medical data at these sites as well. (Table 2-1).

Table 2-1 Summary of the recent progress on phase I study

Sources	No. of selected factory related to benzene exposure	No. workers received med exam	Benzene exposure levels(ppm)
Dr. Ni headed OPC and relevant hospitals	30	1803	0~ 1367
IPHS	4	484	0~ 263

2.2 The Phase? study

2.2.1 Tasks of Phase II study

Phase II study is comprised of Phase IIa and Phase IIb.

- Major tasks of phase IIa study are:

1) Recruit 1000 workers with benzene exposure at various levels
2) Administrator physical examinations, and blood lab analyses (clinical laboratory test + metabolites measurements)
3) Perform industrial hygiene monitoring (area and personal sampling) and chemical analysis

- Major tasks of phase IIb study are:

1) Recruit 200 workers with benzene exposure at various levels (prioritized on workers with higher exposure)
2) Perform blood and bone marrow lab analysis (clinical, polymorphism and metabolism)
3) Perform urine and exhaled breath analysis
4) Perform industrial hygiene monitoring (area and personal sampling) and chemical analysis

2.2.2 Updating of Phase II study

Up to December 2004, we have implemented the phase IIa study at 3 factories where we conducted workplace monitoring and workers' health surveillance that resulted in 905 personal samples by 3M badge sampler and 941 area samples by charcoal tubes; and the routine medical examination and blood sample taking of 231 workers. Besides, 3 workers received health surveillance for Phase IIb studies (Table 2-2, 2-3).

Table 2-2 Summary of Phase IIa study at three work facilities

Factory	Air sampling	No. sampled	Bn levels (mg/m^3)	Mean (mg/m^3)
SHA Rubbery (HQ)	3M badge	273	0- 5217	56.29
	Charcoal tube	379	0- 397	22.64
Xinyuan Rubbery	3M badge	312	0- 258	34.46
	Charcoal tube	177	0- 642	75.5
Golden Cock Cooperate	3M badge	320	0- 1380	147.08
	Charcoal tube	385	0- 1046	93.50

Table 2-3 Summary of workers' health surveillance for Phase IIa & IIb

Factory	No. Phase IIa	No. Phase IIb
SHA Rubbery (HQ)	56	0
Xinhui Rubbery	28	3
Golden Cock Cooperate	147	0

The protocol for exhaled breath was set successfully and 3 workers have been tested. Meanwhile, the metabolites analysis protocol was developed by FUSPH and more than 150 blood samples were analyzed. The first draft on metabolite analysis is under preparation.

3. Challenges and our efforts

3.1 Phase I study

3.1.1 Medical data retrieving from Shanghai CDCP and IPHS data system

Two types of historical data, industrial hygiene (IH) monitoring and annual physical examinations, are necessary for the phase I study. IH data were systematically kept by IPHS. No medical records were available for individual workers in the IPHS database. The key task of phase I is to find workers' medical records from annual physical examinations. Exposure history from medical records will be linked to IPHS IH monitoring data to further retrospectively assess exposed workers.

According to the study design, the data should be provided by IPHS database, and CDCP and its selected industries, which was based on the assumption that the Medical Surveillance Center of Shanghai CDCP could have all the annual health monitoring data in Shanghai available. Unfortunately, it is not the case. In fact, the IPHS database owns merely the worksite monitoring rather than the physical examination data. IPHS may even have no information in respect with how many workers were working for the worksite and whether those who have been exposed to benzene were receiving annual physical examinations. On the contrary, the Medical Surveillance Center of Shanghai CDCP own the information regarding the number size of workers with potential exposure to benzene and their health monitoring results but without knowing anything about exposure levels. In that case, we decided to deal with the problems by using a "two-track policy", i.e., from Medical Surveillance Center of Shanghai CDCP to IPHS to locate the exposure worksite

and its exposure level; and from IPHS database to Medical Surveillance Center of Shanghai CDCP to link the exposure with health effects. However, challenges were found from both methods:

3.1.1.1 *From CDCP to IPHS*

There are 35 hospitals involved in the annual physical examinations for workers with benzene exposure. Of which, the Medical Surveillance Center of Shanghai CDCP is merely one of the 35 hospitals accounting for 2.9% of the total, and being responsible for providing the medical surveillance service for only 11 enterprises in total. The Medical Surveillance Center of Shanghai CDCP has kept the health monitoring data for the recent two years only and the previous historical medical data were retained at each of the 11 factories. Having had retrieved the work environment benzene data for the 11 factories in IPHS database, it was found that only one of the 11 factories with worksite benzene level over 40ppm (or 132 mg/m^3) covering15 workers who had received medical examination with one year data being recorded. As for the remaining 10 factories, they were either "no benzene exposure data at all", or with "extremely low exposure", that showed limited value for a follow–up study.

3.1.1.2 *From IPHS to CDCP*

We identified factories with benzene exposure from IPHS database. However, except for IH monitoring data, neither data for medical examination, nor the number of workers receiving examinations were available. It was also difficult to get access via IPHS to each hospital where medical records were stored. Similarly, it was difficult to access hospital data progressing from IPHS through CDCP to the hospital.

Therefore, it was witnessed that neither IPHS nor the Medical Surveillance Center of Shanghai CDCP database would have provided any supportive evidence to initiate a phase 1 study.

3.1.2 Striving towards success

After being defected by the above trials, FUSPH devoted further efforts towards its success. To prompt the pace of the study, we recommended taking an active action to get a closer cooperation with Dr. Ni Weiming and the organization that he heads, the Shanghai Occupational Physician Committee (OPC). The reasons for the action are: 1) Dr Ni is the Chairman of Shanghai Society of Environmental and Occupational Medicine and the Director of the Department of Occupational Disease of Yangpu District Central Hospital. His headed society has built an extensive network of occupational physicians all around China. The Society has been very influential in the field of occupational medicine and has been keeping close contact and academic exchange with most hospitals responsible for periodical occupational health surveillance. The closer cooperation has profoundly accelerated the process of acquiring all necessary information and/or data from the hospitals which is the key to accessing the matched-exposure information from IPHS database. In addition to the phase I study, the newly activated alliance with Dr. Ni has been

expanded to some other aspects beneficial to the SHS project:

1) Identify newly diagnosed benzene poisoning cases from Shanghai and other areas and recruit these subjects to the DP study;
2) Affirm historical benzene poisoning cases from medical records and abstract these records; and
3) Assist FUSPH to search for appropriate candidate factories for phase II study and coordinate studies in these factories.

3.1.3 Next step to phase I study and the expected difficulties

3.1.3.1 *Major tasks*

- Completing the abstraction of historical medical records of workers exposed to benzene;
- Accomplishing data entry for Phase I study
- Accomplishing the retrospective exposure assessment for phase I workers and the historical cases of benzene poisoning

3.1.3. 2 *Further challenges*

- Little value of the historical data because of the default database in terms of limited sample size, incomplete information regarding when, where, and how the data were collected;
- Worksite monitoring at the 30 factories selected which requires a promising joint-efforts from IPHS that are crucial to the progressive success of Phase I study;
- More information of the "similar factories/worksites" are urgently needed for the "surrogate exposure assessment" as a great number of factories were shut down, transformed or re-combined during the transitional period of economy reform;
- Further literature information searching and reviewing are also essential to the retrospective assessment which demands greater intellectual efforts;

3..2 Phase II study

3..2.1 *Factory selection*

Four information sources were identified for selecting candidate factories at early stages of the ME study. These sources are:
- Shanghai municipal IPHS database;
- Industrial hygiene(IH) monitoring;
- Factories with historical benzene poisoning cases
- Factories with CC/DP subjects exposed to benzene

FUSPH has taken measures to keep pace with the development of the study although the team has experienced many hardships. The following text will describe challenges facing in dealing with each source.

1) IPHS database

Based on our own experience integrated with the literature information generate a list of industries or occupations associated with benzene exposure. According to the listed industries/occupations, we worked with IPHS searching for proper candidate factories with relatively higher benzene exposure from the database. So far, we have visited 31 factories retrieved from the database, and found that the majority of the factories were regarded as "low exposure", and most of them no longer existed, either "shutting down" or being merged into some other big industries. There were no systematically historical monitoring data available; and the oral recall information from senior workers or mangers was usually dramatically different from what the database told. The IPHS staff members were not always kept informed on the changing even relayed that they have "no idea at all" about what had happened there.

2) Local IH monitoring

To check whether announcing a visit was influencing the exposures, 7 factories with average exposure levels ranging from 0- 263PPM were visited without announcing. 2 factories for Phase IIa study in Shanghai were selected predominantly based on IPHS staff's personal information proceeded by "dropping in". The success of that kind of trial was very much depending on how informative and how qualified the IPHS staff was. It is unlikely to be worked as a routine scheme, unless IPHS can make these qualified staff routinely available to us.

3) Historical benzene poisoning cases

In general, we have to have the list of benzene poisoning cases that were reported in the previous year from Shanghai Municipal CDCP; and then forwarded the list to IPHS asking for help in contact with the factories of relevance and making arrangement for the visit and monitoring. We have worked-out for 8 factories and visited there. It was found that 7 of the 8 factories were ranked as "low benzene exposure" ranged from 0- 16.6PPM, which might be due to the data provided have lagged far behind the occurrence of benzene poisoning. The preventive measures had already been taken during the past years; and the work environment had been much improved while we were visiting there. One of the 8 factories, a private-owned plastic manufacturing with 4 employees, remained a relatively "higher exposure level" with an average of 273ppm, but showed no willingness to cooperate with us. Therefore, the path "from case to factory" has not been so successful.

4) CC/DP subjects with benzene exposure

Factory names subjected to potential benzene exposure were forwarded to IPHS for data searching. The ME team visited subjects' factories with potential high exposure to get present exposure level. It was found that in most of the factories, the exposure levels were basically low. For example, among the total number of 22 factories we visited, exposures were of "low exposure" ranging from 2-5 ppm. Fewer factories at higher exposure were

found but they no longer existed.

In summary, the inefficient factory selection could be attributed to:

1) Exposure levels were changed in the factories with poisoning cases

According to the ***Occupational Diseases Prevention and Control Act, P.R. China (ODPCAct)***, which has been put into effect since 2002, the working condition causing poisoning, should be effectively controlled by taking immediate preventive measures without any delay. These factories were no longer considered appropriate for the ME (high exposure) study. .

2) The conflicting priorities of IPHS

IPHS is a governmental agency; its primary task is enforcement rather than research. IPHS staff members couldn't contribute too much of their working hour to keep pace with the project developing.

3) Management system of IPHS

(a) Municipal IPHS works depending on district IPHSs to a certain extent.

Generally speaking, municipal IPHS doesn't work with factories directly. To arrange communication with factories and visit there, municipal IPHS has to ask for help from district IPHSs to get things done because municipal IPHS is primarily responsible for professional guidance and technical support to district IPHSs rather than administrative and inspective authorities. The municipal IPHS has no direct authority to control work performance of its affiliated units. In addition, there is not a good incentive for district IPHSs to participate in the study, nor the QA/QC approach is facilitated in inspecting and promoting work efficiency and quality done by IPHS staff members, which resulted in their work status in an inactive and conflicting manner.

(b) Embarrassing situation of district IPHSs

For ME study, district IPHSs have often been put under an embarrassing situation. On the one hand, we need district IPHSs help in finding out candidate factories with higher exposure; on the other hand, we should sympathize with their embarrassing situation of protecting themselves from being blamed due to "retaining higher exposure" workplace without immediate action taken. Furthermore, IPHSs do not always want to submit all the true data to the municipal IPHS. For example, the higher exposures were mainly reported a few years ago, and the current data usually appear to be much lower than that of previous ones.

3) Communication between FUSPH and district IPHSs

Municipal IPHS is unhappy with FUSPH getting contact with district IPHSs directly.

Sometimes, IPHS staff members own more true data than their municipal counterparts, however, the data can only be delivered through the municipal IPHS because the SHS established contract with the municipal institution instead of the district ones.

3..2.2 *Cooperation from factories*

The reasons for those candidate factories who were not always willing to participate in the ME IIa, particularly IIb studies, are thought to be attributed to:

1) Economic burden

The occurrence of benzene poisoning due to higher benzene exposure at work will be considered a violation of ODPC Act, although the municipal IPHS has promised not to put it on that case if the institute are involved in the SHS. Factories with higher benzene exposure will be treated as the workplaces with higher risk, thus leading to more stringent inspection control. As a result, the factories claimed to put much more capital investment to control the exposure levels that would have brought about an unaffordable economic burden.

2) Political concerns

At the meantime, workers would have appealed for more monetary compensation and other benefits if they knew the abnormal blood counts and other ill health effects from their health surveillance.

All these economically and politically negative impacts on the industries would have created a critical situation of them being faced with a "bank crush" of their enterprises. In addition, workers cannot properly understand how health risks will be found from the bone marrow punching; nobody is really willing to donate his/her bone marrow at any event. Despite all these concerns have been clearly declared in the Informed Consent workers will undoubtedly blame employers based on their cultural and political experience, if anything chaotic did happen. Therefore, the majority of the authorities of the candidate factories are unlikely to be willing to involve in such a conflict and dangerous "game" which might lead to an unaffordable responsibility for the unexpected outcomes.

It usually cannot be helped if the authorities of the factories do not want to involve in the business even for the municipal IPHS per se. In conclusion, there is by no means of sorting it out without the cooperation from both employer and employee sides.

3.2.3 FUSPH's efforts on prompting Phase II study

3. 2.3.1 *Benzene and metabolites analysis*

Shanghai CDCP had an agreement to be responsible for benzene and metabolites analysis; and has been trying to set analysis protocols successfully. However, CDCP failed

to set protocol till early 2004. Then, these tasks have been shifted to FUSPH since March 2004.

3. 2.3.2 Successful exploration in collaboration with OPC

The unsatisfied progress of the Phase II study have prompted FUSPH to consider a more comprehensive and effective way to identifying proper candidate factories for the phase II study. One of the most successful channels is working in collaboration with Dr. Ni, and searching for the proper factories for the phase II study through OPC and its affiliated hospitals, since they are authorized for the diagnosis of occupational disease. We found that this approach has been very beneficial so far.

- Cases of benzene poisoning being diagnosed by above-mentioned hospitals are most likely to be newly occurred ones so that we could track back to the existing factories where they have recently worked to catch recent information and make workplace monitoring at relatively higher exposure worksites.
- Hospitals responsible for diagnosis and treatment of occupational disease are usually most reputable and influential to both employers and employees, which creates a better chance of receiving the cooperation without worrying about punishment from IPHS.

Accordingly, we have so far successfully accessed a total of 9 factories and one of them has been selected as the field site for the Phase II study. Breaking the impasse, we moved straightly forward toward achieving the goals of the Phase II study. In addition to the 9 factories that were found via the occupational disease hospitals, some 69 factories have also been visited. During the period between March 2003 and December 2004, we found a total number of 78 factories that could be considered as candidates for phase II study, with an average "accessing rate" of 3.5 factories per day. 3 factories have agreed to participate in the phase II study, the success rate was much higher than that of doing it based on the theoretical design only (11.1% vs. 2.9%) (Table 2-4)

Table 2-4 Summary of the worksites seeking

Information sources	Types of information	No. factory	Bn level (PPM)	Selected field for Phase II study	Success rate (%)
Theoretical design approaches	SHA CDCP BP information	8	0-273	0	2.9
	CC&DP study scheme	23	0-23.2	0	
	SHA IPHS database	31	0-30.3	0	
	District IPHSs	7	0-263	2	
Occupational diseases hospitals		9	0-432.3	1	11.1
Total		78		3	

3..2.4 Work plan for Phase II study and expected challenges

3..2.4.1 Work plan

- Continuing factory selection primarily via hospitals responsible for occupational disease diagnosis
- Accomplishing data entry of health surveillance for Phase IIa study
- Accomplishing data sorting and entering of industrial hygiene monitoring for Phase II study
- Accomplishing benzene exposure assessment for 231 workers subjected to Phase II study
- Continuing work on regular QA/QC check for Phase IIa study

3..2.4.2 Expected challenges

- For the smaller sample size of 231 cases accomplished there existed a big lag behind the targeted goal of 1000 samples;
- As being stated, there are so many factors negatively affecting the progress of factory selection for Phase II study so that newly developed searching channels and the updated information are really looking forward;
- As more updated biochemical and molecular markers were introduced into Phase II study, US side put prioritized factories and workers with higher benzene exposures over 40ppm that would have still been a big challenge at the foreseeing future;
- A huge amount of industrial hygiene data obtained are waiting for a timely sorting out, analyzing and evaluating, " the longer delayed the more trouble and bias created";
- There has been almost no way of motivating factories to participate in the Phase IIb study, thus frustrating further development of this part study.
- There is a heavy task of industrial hygiene monitoring prior to the bone marrow punching that would undoubtedly exaggerate the difficulty of Phase IIb study. Therefore, an easier and more practical way of selecting the Phase IIb subjects is supposed to be based on the results of hematological analysis and mediated by the clinical physicians of relevance.

4. Suggested solutions

4.1 Factory selection method: Efforts should be focused on additional channels of candidate factories searching, such as CDCP, occupational health hospitals, and other paths out of Shanghai

4.2 Adequate involvement of district IPHSs: This has become crucially important to the success of factory selection and exposure assessment: However, FUSPH is unlike to get access its oversights into IPHS because of no direct contract between SHS and district IPHSs. Closer communication and tighter link between JCML and municipal IPHS/district

IPHSs are urgently needed.

CONCLUSIONS

1. The value of the study

The Shanghai Health Study (SHS) project and its Joint Clinical and Molecular Laboratory (JCML) have provided a good opportunity and proper collaborative path facilitating for conducting a comprehensive epidemiological and clinical investigation with respect to occupational exposure to benzene and its pathogenic effects on lymph and hematopoietic diseases. With the development of the SHS, researchers from both China and US sides have experienced benefits from the collaboration in quit a few fields, for examples:

- Human capacity building: The extensive training activities shared researchers with the state of arts in industrial hygiene, occupational epidemiology and the pathogenesis of lymph and hematopoietic diseases, which have become the sound scientific foundation of capacity building for the work team.
- Teamwork spirit developing: A well-designed work procedure, properly trained investigators, adequately supported human and material resources and well-coordinated collaboration among institutions are essential to SHS success. To achieve the goals of such an influential and complicated research project, the Fudan University School of Public Health has been working closely with US experts and researchers of other institutions involved towards creating a harmonized humanistic atmosphere and promising work environment, which is expected to support the projects successful.
- A far reaching influence for the future scientific research, training and clinical services: The experience that SHS had already gained and would have much more enhanced, as well as the research methodologies, laboratory facilities, and work models that have developed will become a real potential for the scientific research, training and clinical services in China side of relevance in the foreseeing future. It is expected that the Fudan University School of Public Health would have shared more benefits and experiences from the JCML,

2. Significance of collaborating

SHS is characterized by its research difficulty and organizational complexity. For example, it is academically integrating a comprehensive epidemiological investigation with experimental and clinical studies; it is administratively involving governmental health agencies, industries, universities, hospitals and research institutes; and it is internationally, co-sponsoring by two countries, the USA and P.R. China. Therefore, "collaborating" has become the key word of the study and the status of the collaborating become crucially important to the success of the study. We have been benefited from the closer collaboration with all the institutions involved and enjoyed working with all the participants even if we had also verified some of the "difficulties" derived from inadequate collaboration that occurred with the development of the study, that were considered as a kinds of

"growing pains". People would not be growing up without "pains". It implies that we have to continuously put procedures to rectify the problems; and more challenges are expected to come with the project moving forward. We hope a closer and more promising collaboration would made most of the challenges and difficulties not insurmountable. Respecting each other between China side and US side, effective communication and more transparency in decision making procedure of scientific design, management and co-sharing results, would be key factors benefiting the future collaboration.

3. Team work

As mentioned previously, the unique team work spirit of JCML has become a common heritage of the collaboration. Most of the researchers do enjoy working together towards a greater success of the SHS project even if some challenges were often facing. Work coordinating and the QA/QC approach following a virtuous circle of "identification of problems—remediation—re-evaluation—improvement" by the work team's joint-efforts has been developed individually specified to different component of the study project, which will not only ensure the work quality but grant team workers more confidence by maximizing the probability of success for these three important studies.

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Bcc:
Received Date: 2005-05-10 19:27:54 GMT
Subject: SHS-SRP/ERP... Draft Minutes from 09 May Call / Reminder for 17 May Review

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SHS Ethics & Science Review Panels -

Please take a few minutes to review the attached draft minutes from our recent ERP / SRP conference call, and Reply with comments or feedback by Friday, May 20th.

For those who were unable to join Monday's discussion, we will use these minutes as the basis for our Review call on Tuesday 17 May at 10:00am EDT:

May 17 Review - Agenda Items:

- August 2004 Asilomar Research Meeting SRP/ERP Summary Report - no response = approved (?)
- Follow-up On Exposure Issues:
- October conference call/Munich Benzene meeting
- Exxon/Mobil contributions to on-site staffing/advisory activities:
- Chinese Speaker
- Gary Krieger
- Progress Reports (Fudan, Wong, Irons)
- Annual Meeting 2005
- Shift in venue from Shanghai to Virginia (site visit by up to 3 Panel members instead)
- Invitation to suggest agenda elements and timing
- Pre-publication Review of MSS by SRP
- Irons paper
- Note on status of proceedings of Munich symposium (no paper from Irons)
- Other Informational Items

Review - date / start time: Tuesday, 17 May 2005

7:00am PDT Pacific Daylight Time
10:00am EDT Eastern Daylight Time
4:00pm CEST Central European Summer Time
10:00pm Shanghai China Time

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With best regards - Bruce.

Attachments:

09May05 draft SRP-ERP ConfCall Minutes.doc