PROGRESS REPORT

January 2007

Shanghai Health Study

Richard D. Irons*

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

II. EXPOSURE ASSESSMENT AND DATA ANALYSIS

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

*With input and major contributions from numerous Project Staff.

I. JCML

A. Case Contact

Between August 8, 2003 and December 31, 2006, the laboratory processed 3008 new cases. Figure 1 illustrates the rate of case contact per month between June 2005 and December 2006.

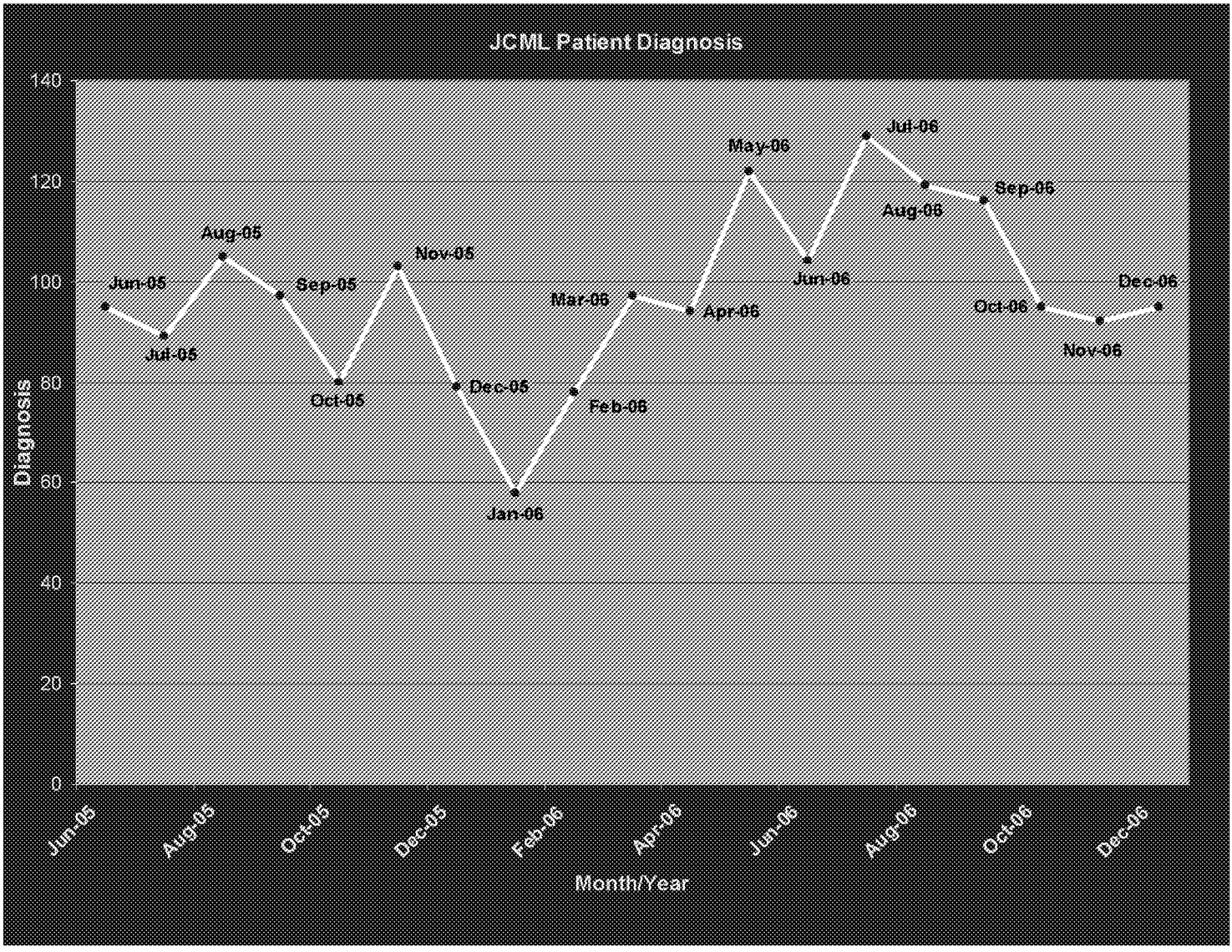

Figure 1. History of JCML Caseload by Month since June 2005

B. Review of Classification and Diagnostic Criteria

The diagnostic standard used by the laboratory to diagnose patients is the World Health Organization (WHO) classification published in 2001, which is based on state-of-the-art technology and requires analysis of histopathologic, immunophenotypic and genetic features. Importantly, WHO is also an epidemiologic classification scheme and will be the scheme used to define and classify all cases in this project.

The International Classification of Disease, Ninth Edition, (ICD-9) is an older, different classification scheme first published in 1977 that was used for most epidemiology studies conducted between 1977-2001. ICD-9 is only a classification scheme and does not provide criteria for disease diagnosis. Studies using the ICD-9 classification system are based on diagnoses that 1) were obtained using histopathologic criteria alone, and 2) vary from study to study, period of time and place. As a result, direct conversion of the ICD-9 classification to WHO is not feasible.

At the beginning of this project, numerical goals for case accrual were selected in order to be comparable in size to previous study results that used the ICD-9 classification. However, all diagnoses and classification criteria used in this study employ the full set of diagnostic and technical tools required for WHO. Estimates of ICD-9 numbers presented in progress reports represent a cursory look back by study pathologists at the older classification criteria and are intended solely for use in assessing study progress on a numerical basis compared to previous studies. Estimated number of cases based on the ICD-9 criteria realized in December 2006 versus those predicted in June 2006, are presented in Table 1 for assessing study progress and do not represent a study result. Some other selected outcomes based on the WHO classification are presented in Table 2, but do not represent a comprehensive list of study results (cases listed in Table 1 are not duplicated in Table 2).

Table 1. Current versus Projected Case Goals Based on ICD-9 criteria (See text above).

Classification	Study Goals	Projected Case Accrual* (12/31/06)	Actual Case Accrual (12/31/06)
AML	500	424	423
NHL	500	433	214**
MDS	350	480	519
AA	250	137	131
BID***	50	36	54

*Projected as of 6/30/06

**Number of NHL's with confirmed documentation. (Total number of NHL's diagnosed: 410).

***Benzene-induced dysplasia, Irons et al (2006) Leukemia Research 30: 769-775.

C. Follow-up

Patients initially diagnosed in the disease progression study are contacted at 6-month intervals and asked to return for follow-up evaluation. As of the end of December 2006, a total of 239 follow up cases have been evaluated by the laboratory. This represents an increase of 80 follow up cases since September 2006, indicating an increased rate of follow-up accrual as we approach the end of the project. However, follow-up accrual remains short of the goal of 635 projected in the original proposal.

Table 2. Case Accrual for Other Selected Outcomes.

Additional Cases	Case Accrual (12/31/06)
AML (WHO)	207
Other Lymphoid Neoplasms (WHO)	213*
Cytopenias	117
CML	83
Nutritional Deficiencies	242

* Number of other lymphoid neoplasms with confirmed documentation. (Total number of other lymphoid neoplasms diagnosed: 230).

D. Quality Assurance/Quality Control

1. IC/EA documentation

In late August 2006, a discrepancy was discovered between the number of accrued cases and the number of exposure questionnaires received. By October it was determined that this coincided with the inability to document informed consents for a subset of 416 case subjects referred by one of the major participating hospitals. Informed consent was routinely obtained from patients presenting at the hospital for collection of diagnostic material. However, we were unable to confirm that written informed consents were obtained specifically for our study. In November a series of meetings were held between SOPH, JCML personnel and hospital staff to identify the problem and formulate a plan for correction and remediation. Despite general agreement on a plan, nothing of substance was achieved during December. Subsequently, a contract was executed directly between the Institutes of Biomedical Sciences /Fudan University and the hospital to implement a corrective plan of action and to prevent future occurrences. To date, hospital clinical staff have contacted a total of 115 cases for which IC could not be documented. Informed consents have been signed, questionnaires have been administered and new controls assigned by 33 of these cases. An additional 34 subjects have been contacted and appointments are pending, and 11 patients have declined further participation. Efforts continue to contact and recruit additional cases with outstanding documentation (See Tables 1 & 2).

2. In-house IC validation

During the last quarter JCML has embarked on a separate in-house physical validation of informed consents for all study subjects. To date, documentation has been confirmed for cases and controls presenting between August 8, 2003 and February 28, 2006. Excluding the outstanding cases discussed above, 5 out of 2059 case files failed validation. Validation of documentation for the remaining 2006 case files is in progress and has been implemented as a routine procedure for the duration of the study.

3. Validation of study diagnoses

A QA program for confirmation of clinical diagnosis and nosologic assignment of disease classification (i.e. Study Diagnosis) has been ongoing since the beginning of the study (August 2003) and is independent of diagnostic review. As of December 2006, 2823 out of 3008 cases have been diagnosed and WHO case assignment independently confirmed. This step is linked to 1) verification of database entry and 2) the development and validation of query strategies that link study diagnoses to individual clinical and research laboratory data sets. This QA process is a prerequisite for populating the tables that form the basis for export of study data for analysis. To date, the logic for 12 query strategies involving up to 3000 entry fields per case has been validated.

II. Exposure Assessment

A. Sector Analyses and Literature Review

A meeting of the IH steering group with Drs. Cherrie and Herrick was held in October 2006 with bi-monthly telephone conferences scheduled beginning in December. To date, the initial focus has centered on CC/DP study processes, with the first meeting involving a detailed review of the shoe sector and the development of plans for optimizing data use. The group decided to obtain additional information available in the Chinese and Western literature on solvent and glue composition. The Western literature review focuses on pre-1960's data, especially for earlier years, before rigorous control of benzene exposure in Europe and North America. This is applicable to many aspects of pre-1990's Chinese operations. A report on Chinese glues and adhesives is scheduled for completion at the end of March and will include information on glue compositions for a broad range of industries in addition to the shoe sector.

Additional industry sector reports for commonly seen industry and task combinations are in preparation to provide exposure-related details for the CC/DP study. Reports on paint making and paint use are nearly complete, while additional reports on shoe making/leather goods manufacturing, and printing are scheduled. ME factory inspections, surveys and analyses of the rubber industry provide a wealth of information for IH analysis in the CC/DP study.

B. Exposure Simulations

Simulations for painting and small part degreasing have been completed. These employed traditional work methods, and materials similar to those used before recent reductions in benzene use. These studies included determining the ventilation rates, material composition and materials use rates that are key variables in modeling exposure for scenarios where relevant exposure data are not available from field investigations or the literature. Results of these simulations provide direct data for commonly seen tasks in CC/DP subject work histories.

C. Questionnaire Administration and Analysis

The CC/DP exposure assessment process, which has been described in previous reports, is again outlined in Figure 2. Individual subject EA is a dynamic and iterative process with cases undergoing continuing review. Therefore, statistics that describe progress for individual subject EA represent a "snapshot" in time and are not cumulative, i.e. the status of each case is subject to change. Consequently, EA progress cannot be directly reconciled with diagnostic case accrual (which is cumulative). To date, 7200 EA questionnaires have been collected, 6802 entered into the database, 6628 have been validated and 6462 have had preliminary EA completed. The difference between total cases + controls (~9000) and EA collected generally reflects EA questionnaires in process, some excluded cases, and shortfalls in documentation previously described.

D. Translations

From August 2003 until June 2006, a total of 3235 questionnaire files out of approximately 6500 were translated by the SOPH. In July 2006, JCML assumed responsibility for translations, and over the last 6 months a total of 2300 translations have been performed resulting in 2000 currently outstanding files. Assuming a case plus control accrual rate of 2400-3000 in 2007, we are on track to complete translations coincident with completion of EA.

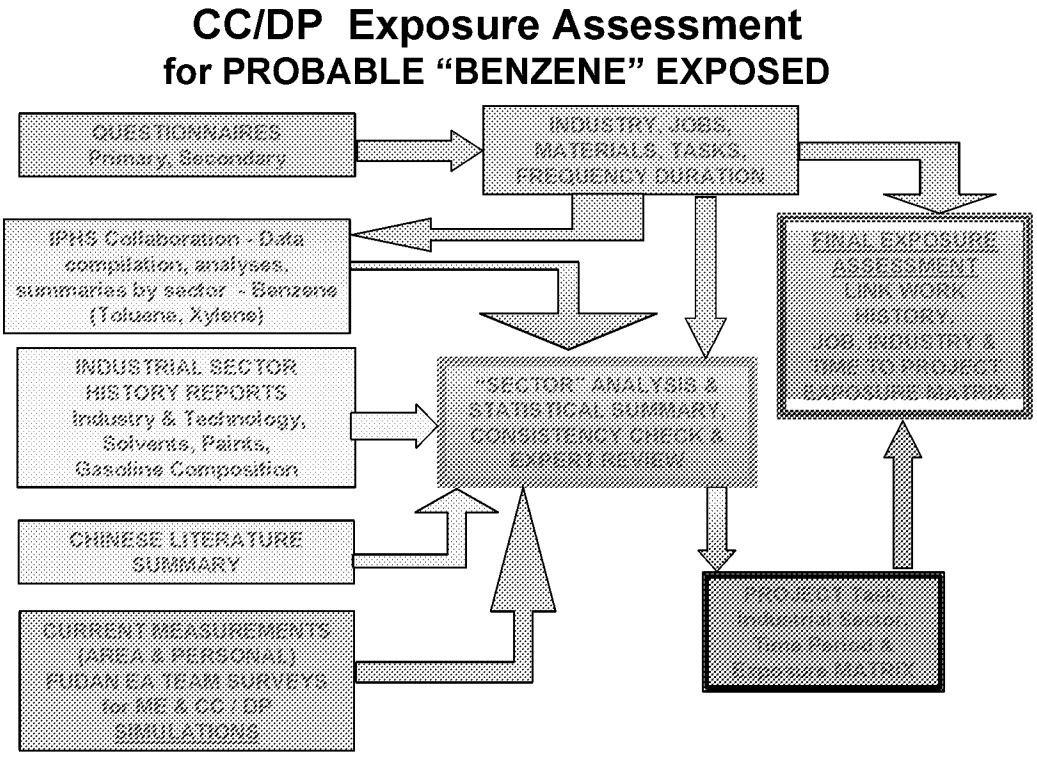

Figure 2. CC/DP Exposure Assessment for Probable "Benzene" Exposed.

III. ME

A. Phase I

In light of other activities, no progress on Phase 1 has been made since the August 2006 report. However, a review of Phase I data is slated for early March. This will include analysis of existing exposure data on potential Phase 1 factories and categorization of each factory as follows: (a) exposure data inadequate and cannot be remediated in a reasonable time, (b) exposure data inadequate and remediation plan developed, (c) exposure data adequate for analysis.

B. Phase II

To date, 890 individual subjects have been recruited to the Phase II study from 5 factories representing the rubber, pharmaceutical, asbestos/rubber composites and shoe manufacturing industries. A subset of these workers have been evaluated up to three times under different working conditions in order to obtain an accurate profile of their exposure. During 2006, a total of 583 urinary and blood metabolite samples were collected spanning exposure ranges from <1 ppm to >40 ppm. Blood CBC, benzene metabolites, polymorphism and exposure datasets are being organized and preliminary analysis is in progress. In order to round out and complete the exposure range, additional factory sampling and subject recruitment will be conducted this spring.

To: Clegg, Patsy M SCC-DCS/22 <patsy.clegg@shell.com>
From: Snyder, Phil J SCC-DCS/2
</O=SHELL/OU=MSXSCC/CN=RECIPIENTS/CN=PS193987>
Cc:
Bcc:
Received Date: 2007-03-07 13:59:16 GMT
Subject: RE: Report of Expenditures

Time to confront Irons with his note yesterday where he says he has no money. I will be in Asia in April. Any thoughts how I would swing by the operation in Shanghai?

Phil Snyder
Global Manager Downstream Product Stewardship
Shell Chemical LP
One Shell Plaza, P.O. Box 2463, Houston, TX 77252-2463

Tel: +1 713 241 7826 Fax: +1 713 - 241 2494 Other Tel: +1 832-721-6493
Email: Phil.Snyder@Shell.com
Internet: http://www.shell.com/chemicals

-----Original Message-----
From: Clegg, Patsy M SCC-DCS/22
Sent: Wednesday, March 07, 2007 5:59 AM
To: Snyder, Phil J SCC-DCS/2
Subject: FW: Report of Expenditures

Financial info re U of C final payment on current grant.

Will be back in office on Thursday.

Patsy
-----Original Message-----
From: Russell White [mailto:whiter@api.org]
Sent: Tuesday, March 06, 2007 3:16 PM
To: BenzConsort-OC@listserve.api.org; BenzConsort-TC@listserve.api.org
Subject: FW: Report of Expenditures

All,

At the end of 2006 the University of Colorado reports that Dr. Irons had about $850,000 at his disposal (see attachment). The final grant payment of about $570,000 was processed by API today for payment this week to the University.

At the end of 2006 Dr. Irons had about $112,000 for Field Expenses at his disposal. The final contract payment of about $104,000 was processed by API today for payment this week.

From: Ann.Louden@UCHSC.edu [mailto:Ann.Louden@UCHSC.edu]
Sent: Thursday, March 01, 2007 5:12 PM
To: Bruce Jarnot; Russell White
Subject: Report of Expenditures

Good afternoon Bruce and Russ,

My apologies for the delay but I just received the official Grants & Contracts report of expenditures this morning. Let me know if you have any questions or problems with the file.

Best wishes,

Ann Louden
University of Colorado at Denver & Health Sciences Center
4200 E. 9th Avenue/C238
Denver, CO 80262

(303) 315-7170 phone

(303) 315-7223 fax

To: Clegg, Patsy M SCC-DCS/22 <patsy.clegg@shell.com>;
brian.e.doll@exxonmobil.com <brian.e.doll@exxonmobil.com>
From: Russell White <whiter@api.org>
Cc: Robin Tillery <tilleryr@api.org>
Bcc:
Received Date: 2007-03-14 14:22:04 GMT
Subject: 4Q Shanghai Health Study budgetsheet

We will have paper copies and a computer LCD screen to look at the budget tomorrow. It now includes the UofColorado EOY numbers.

When you come to API, sign-in in the lobby. The guard will get you on the elevator to the 12th floor. The receptionist will give you a visitors badge and call Robin or myself to pick you up.

>

Russell White
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Washington, DC 20005-4070

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Fax: 202-682-8270

Attachments:

BHRC Program Expenses 4Q06 rpt - DRAFT.xls