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Subject:	Shanghai Health Study - progress report
Attach:	SHS PR Jan2008.pdf

Attached is the most recent 6-month progress report from Cinpathogen/Univerisity of Colorado.

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PROGRESS REPORT

January 2008

Shanghai Health Study

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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 contributions to ME and EA from T.W. Armstrong, S.M. Bowes, A.R. Schnatter, P.J. Kerzic and Y. Zhou

I. JCML: Disease Progression (DP)

Case Contact

Between August 8, 2003 and December 31, 2007, the laboratory processed 3834 new cases. Figure 1 illustrates the rate of case contact per month between December 2005 and December 2007. The decreased rate of case contact in the June 07-December 07 time frame relative to past years was due to cessation of all case accrual except for NHL.

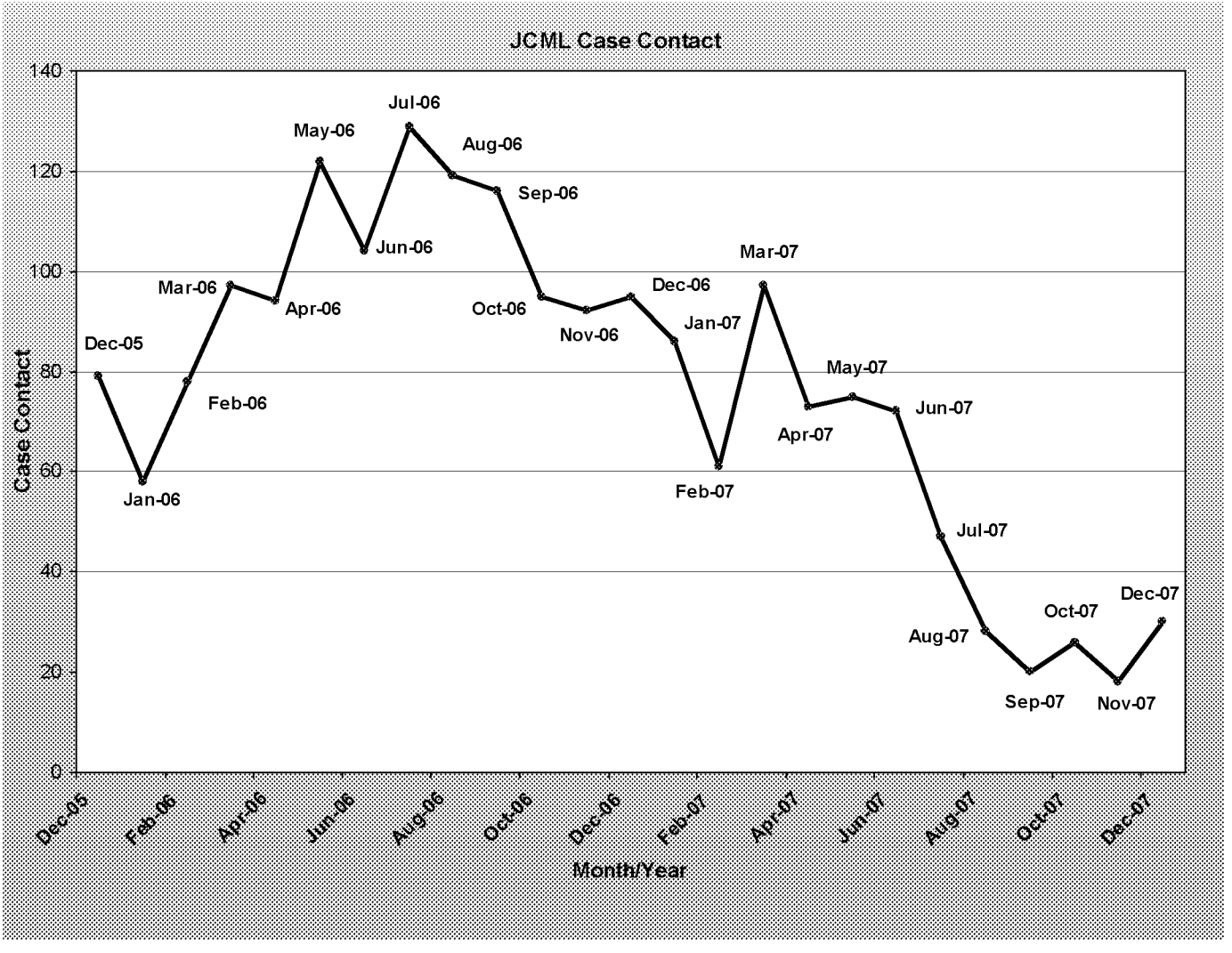

Figure 1. History of JCML Monthly Case Contact as of December 2005

Case Accrual based on WHO Criteria

For AML, 739 cases have been diagnosed according to WHO criteria and have documented informed consents. Of those 739 AML cases, 717 questionnaires have been validated and 630 have reached the preliminary exposure-assessment-completed status. Controls have been

selected, informed consent documented and questionnaires validated for at least 720 of the AML cases. As of December 31, 2007, at least 666 AML cases have assigned controls with preliminary exposure assessment completed.

For lymphoid neoplasms, 596 cases have been diagnosed according to WHO criteria and have documented informed consent. A total of 550 questionnaires have been validated and 493 of these have reached exposure-assessment-completed status. Controls have been assigned, informed consent documented and questionnaires validated for at least 551 of these cases, and preliminary exposure assessment completed on controls for approximately 502 cases.

Recruitment of cases of lymphoid neoplasms at the Tumor Hospital has continued together with efforts to contact cases with outstanding documentation. These efforts are scheduled to continue through January 2008. Final case accrual study numbers will be available after April following pathology peer review of study diagnoses.

Table 1. Current Number of Study Cases Diagnosed as of December 31, 2007.

Classification	Case Accrual (12/31/07)
AML	739
Lymphoid Neoplasms	596
MDS	613
AA	141
BID*	58

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

Follow-up

Patients initially diagnosed in the disease progression study were contacted at 6-month intervals between August 2003 and June 2007 and asked to return for follow-up evaluation. A total of 266 cases were collected.

In order to diagnose cases that are relevant to the case control study, other disease outcomes have been accrued as part of DP. These include, but are not limited to, the selected outcomes listed in Table 2.

Table 2. Case Accrual for Other Selected Outcomes.

Additional Outcomes	Case Accrual (12/31/07)
Cytopenias	140
CML	90
Nutritional Deficiencies	309

Publications

Our paper, "The TNF-α 238A polymorphism is associated with susceptibility to persistent bone marrow dysplasia following chronic exposure to benzene," was published in *Leukemia Res.* 31 (2007) 1479-1485. A manuscript on the biology and prevalence of Precursor B lymphoblastic leukemia is in the final stages of preparation and will be submitted for SRP review when completed. In addition, clinical case reviews have been completed by JCML for lymphoid neoplasms independent of the SHS, from which two manuscripts have been generated: one dealing with the prevalence of NHL subtypes and another with the prevalence and biology of CLL/SLL in Shanghai, China.

II. Exposure Assessment

Sector Analyses and Literature Review

Several productive conference calls and an in-person meeting of the IH steering group with Drs. Cherrie and Herrick have been held since the last progress report. The investigators and EA Team provided detailed information to facilitate the involvement of the SRP in doing the first-stage QA evaluation of the Exposure Assessment program. A meeting in the first quarter of 2008 is scheduled with Drs. Cherrie and Wong in Shanghai (prior to the annual meeting February 2008) to review the consistency of the exposure assessments for several industry sectors/job categories (shoes, rubber, general mechanical repair, printing) for the CC/DP studies.

Commonly seen industry and task combinations have been organized according to similar work/materials, summarized, and discussed previously with Drs. Herrick and Cherry. This is an evolution of the jobs/industry categories identified earlier that have been guiding the assembly of information for the CC/DP study matrix. These categories provide the groupings for the internal consistency checks underway for the benzene exposed subjects in the CC/DP studies. Preliminary consistency reviews of shoe, rubber, printing, and general mechanical repair have been completed. The preliminary consistency reviews confirmed and strengthened the EA results and documentation produced by the Shanghai exposure assessment team and process. These will also be covered in the February review with Drs. Cherrie and Wong.

Sector Reports

A manuscript on the paint making and paint using segments has been completed as a project report and was submitted for publication. Two reviews of the Chinese literature with benzene exposure data (general for multiple industries and for shoe manufacturing) have been published. Additional project reports on printing and glues/adhesives are now available in English drafts. The review of solvent and glue composition and trends over time proved intractable due to information access challenges.

A summary of the Western literature on historic exposures in industries relevant to China (report described in a prior progress report) remains part of the overall EA strategy. A recently completed review of the OSHA Docket on benzene has provided additional data to incorporate into this Western literature report.

Sampling and Analytical Methods Comparison

The project to compare historical and modern sampling methods has been delayed. This project would evaluate the influence that changes in sampling and analytical methods have had on historical benzene exposure data over time. The goals of the comparison study include determining real world limits of quantification and defining any biases due to sampling or analytical practices. The protocol for the study was completed in 2007 and laboratory work is planned for the first half of 2008.

Exposure Simulations

Data analysis and report preparation continues for the interior redecoration painting and small part degreasing simulations summarized in the previous progress report. The analyses needed for the CC/DP exposure assessment have been completed.

Questionnaire Administration and Analysis

The CC/DP exposure assessment process, which has been described in previous reports, is outlined in Figure 2. To date, 8,580 EA questionnaires have been collected, 8,388 entered and validated (98%). Preliminary EA is completed for 8,347 (97%). The difference between the total number validated and EA reviewed generally reflects EA questionnaires in process, some excluded cases, and shortfalls in documentation previously described.

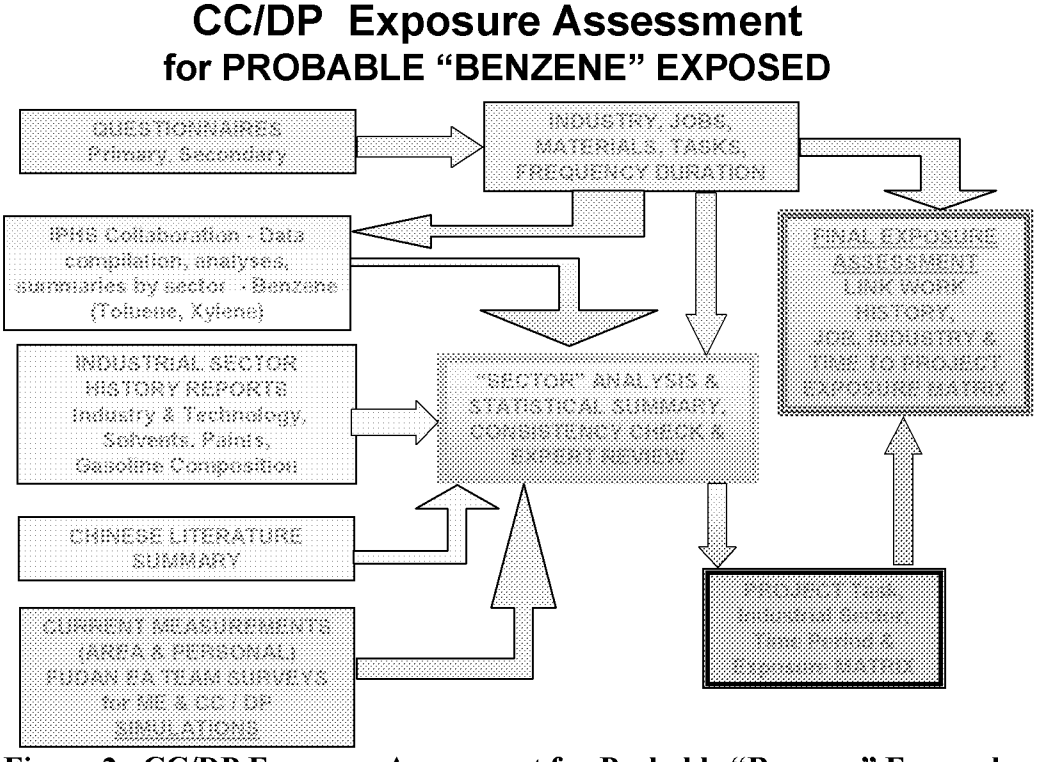

Figure 2. CC/DP Exposure Assessment for Probable "Benzene" Exposed.

Preliminary Analyses of Benzene Exposures

Table 3 provides an update on the current percentages in the identified industry/job sectors and a summary of the preliminary exposure ranges. These are subject to change following the consistency checks and final matrix applications.

Table 3. Benzene Exposure Analysis on Preliminary Assessments

Industry/Job Category	Benzene Exposed Subjects	Number in Range (in mg/m^3)			
		<1	1 to <10	10 to <100	>100
Painting	22%	32	47	74	14
Machine repair	17%	57	32	5	5
Printing	10%	21	18	7	3
Making shoes/leather products	10%	8	21	26	6
Organic chemical industry	5%	19	12	2	2
Rubber industry	5%	2	3	1	26
Other (includes # for all below)	31% (without split below) 13% (with split)	63	18	7	5
Home renovation	8%	-	-	-	-
Science and technology workers	5%	-	-	-	-
Professional driver	4%	-	-	-	-
Gas station workers	1%	-	-	-	-

Preliminary Analyses "Exposed to Other"

Based on data assembled in November 2007, there are approximately 14,400 total jobs assessed. Roughly, 3000 of these jobs had assessments for exposures to study substances of concern other than benzene. The "Top 20" with the count of assigned jobs follows in Table 4. Some of these categories also include workers who had benzene exposure. Review of these assessments is underway as is a statistical sample review of those rated as "not exposed" to any study exposure agent.

Table 4. Industry Categories with Exposures to Substances Other than Benzene (Top 20 by job count)

Industry Category	Count of exposed jobs
General agriculture	1115
General Machine mfg.	370
Public health, hospital workers	217
Electrical & electronic mfg.	211
Transportation	186
Metal products mfg.	160
Metal milling industry	140
Textile industry	110
Construction industry	105
Stationary, arts and printing	92
Rubber & plastic mfg.	79
Chemical industry	73
Precision machine mfg.	73
Military	70
Public work & social service	69
Warehousing	60
Non-metallic minerals production	55
Leather and fur products mfg	48
Misc. manufacturing and repair	29
Education, culture and arts	27

Translations

The descriptive information from the questionnaires on the nature of the tasks done and conditions have been largely translated. Progress continues on track with a total of 19,749 out of 24,183 work history entries having been updated during the last 6 months. (Note that these do not easily reconcile with number of accrued subjects, since a worker with a single job-exposure scenario = 1 work history entry; and a worker with 2 job-exposure scenarios = 2 work history entries, etc.). In addition, *ad hoc* translations of Exposure Assessment Committee documentation continues and provides support for the consistency checks.

III. Molecular Epidemiology (ME)

As mentioned in the last report, the fieldwork is complete for the ME study. Five factories with exposure have been visited and data are being validated. Ongoing activities include:

- assembling the exposure data into an Access database

- validating and refining the construction of similar exposure groups for the factories
- extracting necessary fields from the JCML data base (i.e. demographic and blood data)
- translating key fields from Chinese to English
- defining subjects meeting exclusion criteria due to pre-existing blood diseases, treatment with cytotoxic agents or infection-induced proliferative action, and invalid or uncertain data in key fields
- performing preliminary QA/QC, data scrubbing, data-consistency checks and resolution activities

To date, over 900 individual subjects have been recruited to the Phase II study from five different factories representing the rubber, pharmaceutical, asbestos/rubber composites and shoe manufacturing industries. A sixth factory, which had no documented exposure but which was part of the pilot feasibility test, is being evaluated as a possible control factory for some analyses.

We have collected information on:

- exposure concentrations
- urine (and blood) metabolites
- blood counts
- demographic information
- lifestyle variables (including smoking and drinking patterns)
- medical history
- work history

This information has been merged into one Access database. Numerous edits and consistency checks have been performed to validate the data. In some cases, this involved going back to the paper record, translating Chinese entries, and occasionally, going back to the factory for the needed information. Extensive measures have been taken to ensure the validity and accuracy of the data and resulting analyses.

The following are some of the descriptive characteristics of the ME-II study population:

Of the over 900 subjects:

- Essentially all have valid blood measurements
- Essentially all have data on genetic polymorphisms (except the control factory)
- Over 600 have personal exposure data, with the remainder having estimated concentrations based on similar exposure group analyses

The exposure data are distributed as follows:

- >50 ppm, approximately 27%
- >20 ppm, approximately 55%
- >1 ppm, approximately 83%
- <1 ppm, approximately 17%

The workers by factory are distributed as follows:

- 147 are from the Jinji factory

- 129 are from the Jinsai Pharmaceutical factory
- 361 are from the Shanghai Rubber factory
- 28 are from the Xinhui Rubber factory
- 412 are from the Shanghai Shoe factory

Metabolite analysis is ongoing. Urine and blood samples have been collected from 810 individuals and stored for future analysis. Urinary and blood metabolite data from more than 600 individuals was collected using a method derived by the Fudan University, School of Public Health. However, in independent analyses we determined it to be unable to accurately measure metabolite concentrations in spiked samples from unexposed volunteers. As a result, we have developed a modified method for analysis of benzene metabolites in human samples and have validated that this method is capable of accurately determining metabolite concentrations from spiked samples across an appropriate range consistent with the exposures described above. We are currently analyzing pre- and post- shift urine for a subset of 150 workers with detailed exposure information. This will be followed by analysis of blood metabolites for the same individuals. The analytical laboratory is on track to support completion of the EA and ME projects.