

To: BenzConsort-OC@listserve.api.org <BenzConsort-OC@listserve.api.org>;
BenzConsort-TC@listserve.api.org <BenzConsort-TC@listserve.api.org>; BHRC Communications Committee
<benzconsort-cc@listserve.api.org>
From: Russell White <whiter@api.org>
Cc:
Bcc:
Received Date: 2007-07-15 18:30:55 GMT
Subject: Shanghai Health Study - mid-year report from Drs. Irons and Gross

FYI

From: Ann.Louden@UCHSC.edu [mailto:Ann.Louden@UCHSC.edu]
Sent: Friday, July 13, 2007 2:48 PM
To: Russell White
Cc: jmricewas@aol.com
Subject:

Dear Russell,

On behalf of Drs. Irons and Gross, enclosed you'll find the scientific progress report for July 2007. I am also attaching a copy of our recent publication entitled " The TNF* 238A polymorphism is associated with susceptibility to persistent bone marrow dysplasia following chronic exposure to benzene" which has been accepted for publication this fall in Leukemia Research.

Please call if you have questions or problems opening these documents.

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

Attachments:

Lv_2007.pdf
SHS PR Jul2007 (final).pdf

PROGRESS REPORT

July 2007

Shanghai Health Study

Richard D. Irons*
Sherilyn A. Gross

- I. ANALYSIS OF DISEASE PROGRESSION FOR APLASTIC ANEMIA, MYELOYDYSPLASTIC 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 A.R. Schnatter, T.W. Armstrong and Y. Zhou

I. JCML: Disease Progression (DP)

Case Contact

Between August 8, 2003 and May 31, 2007, the laboratory processed 3434 new cases. Figure 1 illustrates the rate of case contact per month between June 2005 and May 2007. The decreased rate of case contact in the March 07-April 07 time frame relative to past years was due to an interruption in normal laboratory activities brought about by a disruption in study funding.

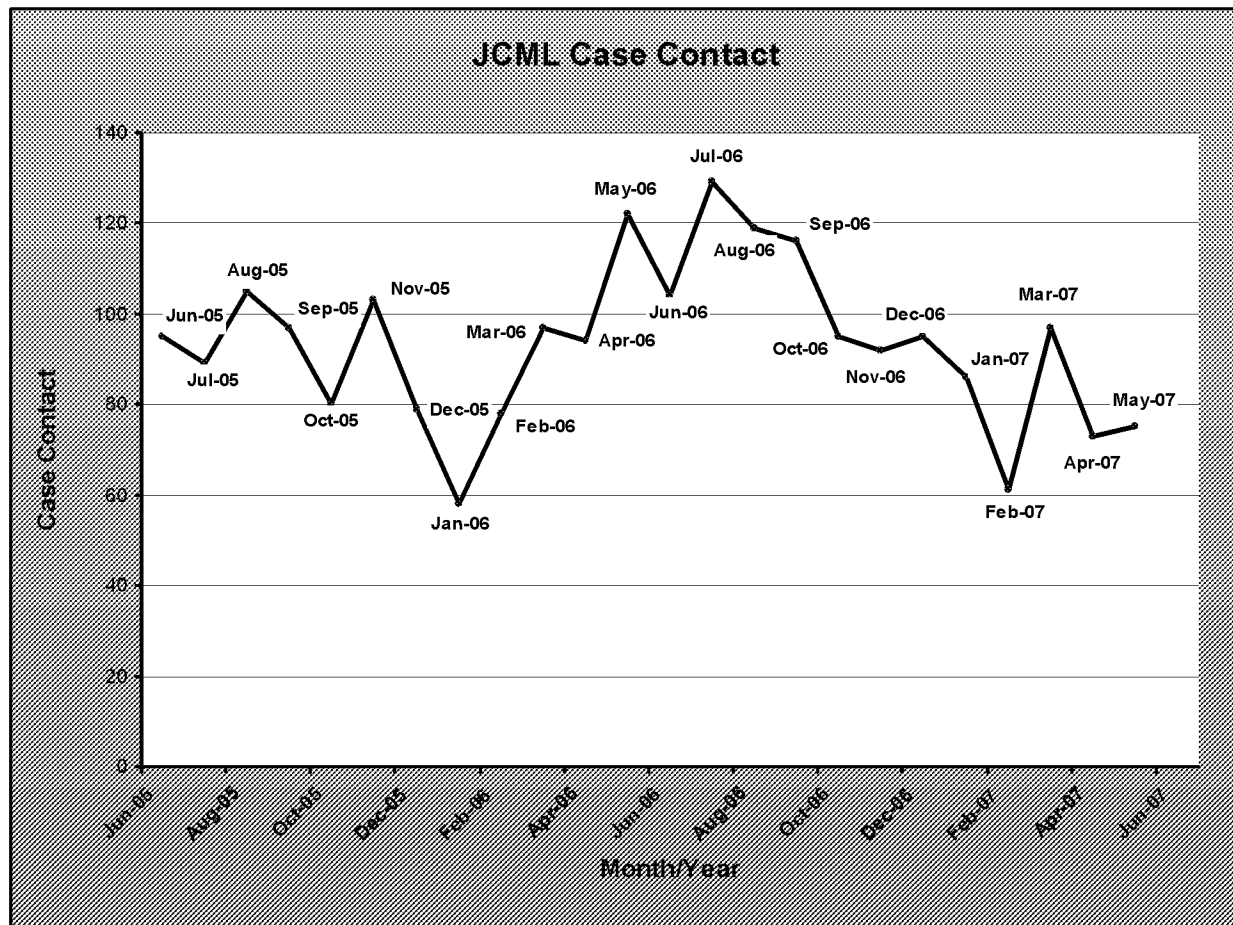


Figure 1. History of JCML Monthly Case Contact as of June 2005

Case Accrual based on WHO Criteria

For AML, 681 cases have been diagnosed according to WHO criteria and have documented informed consents. Of those 681 AML cases, 644 questionnaires have been validated and 545 have reached the preliminary exposure-assessment -completed status. Controls have been selected, informed consent documented and questionnaires validated for at least 646 of the AML cases. As of May 31st, at least 585 AML cases have assigned controls with preliminary EA completed.

For lymphoid neoplasms, 504 cases have been diagnosed according to WHO criteria and have documented informed consent. A total of 457 questionnaires have been validated and 394 of these have reached exposure-completed status. Controls have been assigned, informed consent documented and questionnaires validated for at least 456 of these cases, and preliminary exposure assessment completed on controls for approximately 410 cases. The recruitment of lymphoid cases is scheduled to continue through December 31, 2008. However, routine hematology services, accrual of new hematology cases and follow-up activities for DP will end this month.

Table 1. Current Study Cases Diagnosed as of May 31st, 2007.

Classification	Case Accrual (5/31/07)
AML	681
Lymphoid Neoplasms	504
MDS	586
AA	136
BID*	59

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

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 May 2007, the laboratory has evaluated a total of 255 follow up cases.

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 (5/31/07)
Cytopenias	131
CML	90
Nutritional Deficiencies	294

Quality Assurance/Quality Control

IC/EA documentation

Implementation of procedures to remediate documentation of IC's at the Tumor Hospital have been generally successful. To date, Tumor Hospital staff have contacted a total of 144 cases of lymphoid neoplasms for which IC could not be documented. Informed consents have been signed, questionnaires have been administered and new controls assigned for 65 of these

cases. Decisions are pending on 26 of the subjects contacted and 11 subjects have declined further participation. Efforts continue to contact and recruit additional cases with outstanding documentation. Despite the interruption in laboratory operations, the recruitment of new lymphoid cases from Tumor Hospital totaled 69 from December 2006 through June 2007.

Publications

Our studies to identify genetic polymorphisms associated with benzene-induced bone marrow injury have continued. These studies have resulted in the discovery that a specific genetic variation in an important inflammatory cytokine, TNF- α (TNF- α 238A), influences susceptibility to the development of benzene induced dysplasia (BID) and provides independent molecular confirmation of our previous observations that inflammation plays an important role in the development of long term bone marrow injury associated with benzene. These findings further suggest that cell-specific alterations in TNF- α expression may promote clonal selection in the evolution of MDS and AML (Lv et al (2007) "The TNF- α 238A polymorphism is associated with susceptibility to persistent bone marrow dysplasia following chronic exposure to benzene," *Leukemia Res.* (Online www.sciencedirect.com.)

II. Exposure Assessment

Sector Analyses and Literature Review

Several 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 last meeting was on June 21, and primarily covered progress in information assembly for the Job/Industry Sector-Time-Exposure Matrix for the CC/DP studies. Commonly seen industry and task combinations have been organized according to similar work/materials, summarized, and discussed with Drs. Herrick and Cherry. This is an evolution of the jobs/industry categories identified earlier that have been guiding assembly of information for the CC/DP study matrix.

A draft manuscript on the paint making and paint using segments was completed and is currently in SRP review. Additional reports on printing and glues/adhesives are nearly complete in Chinese. The review of solvent and glue composition has yielded limited useful information to date, and the precise compositional information for benzene content of these materials remains elusive. Efforts to assemble compositional information continue, but alternative approaches based on information outside of China may be required. The summary of the Western literature described in a prior progress report will be a central part of this alternative.

Sampling and Analytical Methods Comparison

A project is underway to 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 disruptions in project funding have limited progress made on this rather important component of the benzene data analysis. Information from the

comparison study is needed prior to any substantial work on statistical analysis of the benzene regulatory (i.e. IPHS) database.

Exposure Simulations

Data analysis and report preparation continues for the interior redecoration painting and small part degreasing simulations summarized in the previous progress report. Optimal use of the data from the simulations depends to a large degree on information about the time trends and changes in composition for paint solvents and solvents used in degreasing. To date, the availability of compositional information has been limited due to lagging of science and technology development on product quality controls. Although information does exist for at least for some time periods and for some relevant materials, access has been severely restricted. As described above, efforts to assemble composition information will continue.

Questionnaire Administration and Analysis

The CC/DP exposure assessment process, which has been described in previous reports, is again outlined in Figure 2. To date, 8300 EA questionnaires have been collected, 8000 entered into the database, 7600 have been validated and 7300 have had preliminary EA completed. 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.

Translations

Progress on translations continues on track with a total of 19,749 out of 24,183 work history entries having been updated during the last 6 months. (A worker with a single job-exposure scenario = 1 work history entry; a worker with 2 job-exposure scenarios = 2 work history entries, etc.)

CC/DP Exposure Assessment for PROBABLE “BENZENE” EXPOSED

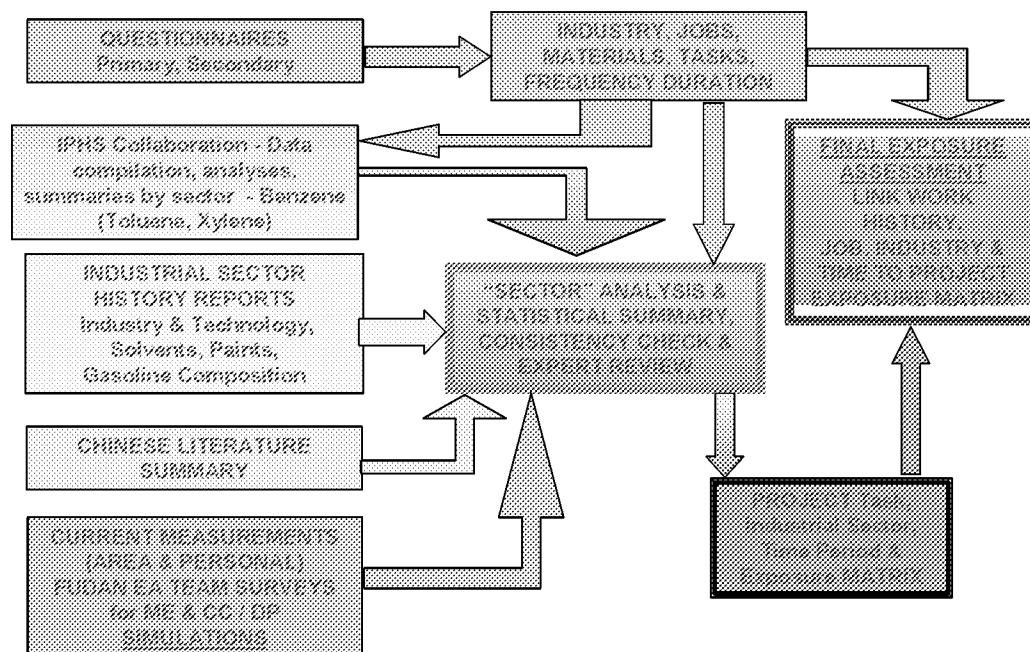


Figure 2. CC/DP Exposure Assessment for Probable “Benzene” Exposed.

III. Molecular Epidemiology (ME)

Another visit and survey of the Shanghai rubber plant operations was completed in early June. As part of this visit, IH samples were split to evaluate variability and/or bias in sampling media and laboratory analysis procedures for benzene in air. Urine was collected for the majority of the workers for determination of urinary benzene metabolites. This will complete the fieldwork for the ME Phase II study.

To date, over 1000 individual subjects have been recruited to the Phase II study from 5 different factories representing the rubber, pharmaceutical, asbestos/rubber composites and shoe manufacturing industries. A subset of these workers have been evaluated up to three separate time periods, in three different seasons, and in three different years, to establish a more accurate exposure profile. It is likely that publications on the ME Phase II study will consist of somewhat fewer than 1000 subjects since not all data (metabolites, exposure and outcome) is available for all workers. Notwithstanding, the power of the study should be considerable compared to past efforts in the literature. 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 an effort is underway to independently validate analytical methodology used in the analysis of benzene blood and urinary metabolites.

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From: Russell White <whiter@api.org>
Cc: jmricewas@aol.com <jmricewas@aol.com>
Bcc:
Received Date: 2007-07-17 13:25:14 GMT
Subject: RE: Shanghai Health Study - mid-year report from Drs. Irons and Gross

FYI - Dr. Gross confirmed that there was a typo in the report and accrual of cases of lymphoid neoplasms will end this year (2007), not 2008 as indicated in the report. A corrected report is attached.

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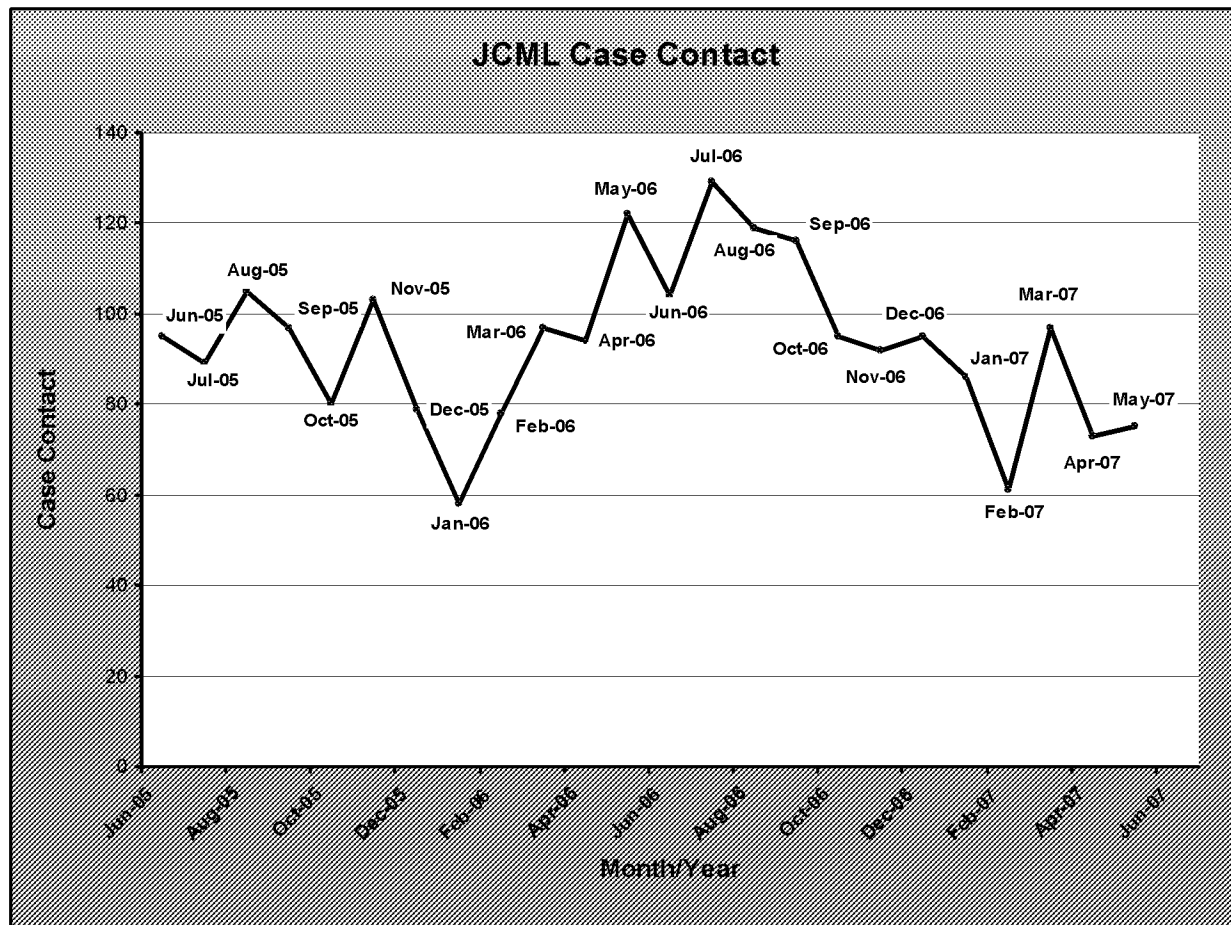


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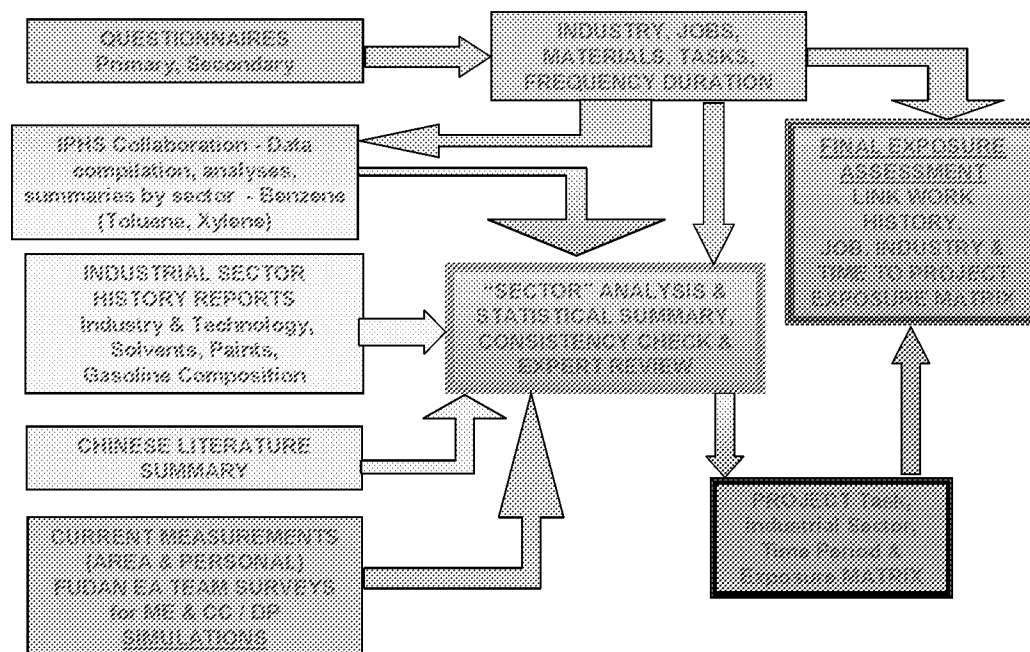


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