

SHANGHAI HEALTH STUDY

Main Messages for use with Media

As part of ongoing individual product stewardship and safety and health programs, a consortium of petroleum and chemical companies has sponsored an independent, scientifically rigorous, research project to further the current understanding of the human health effects of benzene.

The study is a project of Fudan University¹, the University of Colorado Health Sciences Center, Applied Health Sciences, Inc. and Cinpathogen, Inc. Other participants in China include the Shanghai Municipal Center for Disease Prevention and Control and the Shanghai Institute for Public Health and Supervision. The research protocols were subjected to independent reviews by outside experts, including reviews of their consistency with international ethical standards and reviews by an expert scientific panel. The research protocols also have been approved by independent review boards at Fudan University and the University of Colorado.

A state-of-the-art clinical and molecular laboratory was established on the Fudan University campus. The lab supported the research project and the Shanghai medical community and the Fudan-Cinpathogen Clinical & Molecular Research Center will remain at Fudan once the project is completed. This sustainable technology transfer was an important aspect of the project design.

The results of this study are being published in scientific journals. Details of the findings will be presented there and further information may be produced by the investigators over the coming years.

The companies that funded this study had no role in the design or operation of the research and analyses conducted. This was overseen by an independent Scientific Review Panel. Additionally, an Ethics Review Panel was established to oversee those aspects of the study.

¹ Fudan University, located in Shanghai, China, is one of the oldest, most prestigious and most selective universities in the People's Republic of China. It includes 77 research institutes, 112 cross-disciplinary research institutes and 5 national key laboratories. Fudan has a high-level research faculty of over 2,400 full-time teachers and researchers, including 1,350 professors and associate professors, 30 academicians of the Chinese Academy of Sciences and the Chinese Academy of Engineering, nearly 660 doctoral supervisors,

SHANGHAI HEALTH STUDY:
An independent, scientifically rigorous study

Frequently Asked Questions

Q: Who funded this study?

A: The funding companies are **BP, Chevron, ConocoPhillips, ExxonMobil, and Shell Chemical**, with additional support from Marathon.

Q: Why was the study funded?

A: The goal of the study is to contribute to, and advance, the accepted body of scientific research and knowledge of benzene-induced disease.

- The project's purpose is to gain a more refined understanding of the relationship between benzene exposure and potential associated health risks.
- Beyond advancing knowledge of benzene toxicology, the study will further assist the contributing companies in their continuing efforts to provide high-quality product stewardship and continuous improvement of their risk management programs.

Q: Who conducted the research?

A: The study is a project of Fudan University, the University of Colorado Health Sciences Center, Applied Health Sciences, Inc. and Cinpathogen, Inc. Other participants in China include the Shanghai Municipal Center for Disease Prevention and Control and the Shanghai Institute for Public Health and Supervision.

Q: Where was the study conducted and why?

A: In Shanghai, China. The data from a wide range of historic benzene exposures in China provide a significant opportunity to conduct meaningful research on the health effects of human exposure to benzene.

Q: When was the study conducted?

A: The study was initiated in 2000 and will be completed in 2009; patient data collection took place from 2003-2007. Publication of the results is ongoing and will continue.

Q: How was the study conducted?

A: The independent investigators conducting the study have had full control over the study, including design, research, and all interpretations and conclusions that may be drawn from the data when the study is completed.

The study has been designed to withstand rigorous scientific peer review.

The study protocols, including data management processes, have met the rigorous requirements of two separate Institutional Review Boards (IRBs) which govern University research on human subjects, one at the University of Colorado and one at Fudan University. The research program also has the approval of an independent Scientific Review Panel of experts and an independent ethical review.

- Study protocols, including data management processes, were addressed with the assistance of independent Scientific Review and Ethics Review Panels. Both panels have remained available to the investigators throughout the research program.
- The independent Scientific Review Panel, composed of international experts in relevant scientific disciplines, endorsed the research protocols following several reviews and revisions.
- The independent Ethics Review Panel thoroughly reviewed the study protocols (e.g. informed consent, data management) to ensure they met international standards for human research. The panel consists of bioethicists from the U.S., China, and Europe.

Q: What did the study do?

A: A state-of-the-art clinical and molecular laboratory was established on the Fudan University campus. From 2003-2007, this study funded the collection and analysis of more than two thousand cases of blood disease in the Shanghai area. Patients with blood diseases in the Shanghai area were referred to the study laboratory for evaluation and diagnosis. Estimates of personal exposures to benzene were also made. Detailed and thorough analysis and interpretation of the data are underway by the researchers.

Q: What have the researchers found?

A: Since 2005, the independent researchers have been presenting information on the study design to a variety of scientific audiences. **The investigators will present findings from the study at the September, 2009 Munich Benzene Symposium.** Those findings have been and will continue to be published in the peer-reviewed literature. Further detail can be provided by the appropriate Principal Investigator; see the Principal Investigator Contact Information list.

Q: What will happen to the laboratory after the study?

A: The lab, which has supported the research project, the Shanghai medical community and the Fudan-Cinpathogen Clinical & Molecular Research Center, **will remain at Fudan** once the project is completed.

Q: How much did the study cost?

A: While the funding of specific grants and contracts under this study is confidential, **more than \$30 million** has been spent on this effort.

Q: Why has the study been so expensive?

A: This is an extremely thorough, complex study. It has involved:

- Establishment of a state-of-the-art world class laboratory
- Recruitment of thousands of cases over many years
- Planning and conduct of three distinct research studies.

Year	Shanghai Health Study Timeline
1999	• Preliminary research design and feasibility estimate developed based upon site visits by Principal Investigators and industrial hygiene personnel
2000	• Study protocols started by the University of Colorado, Applied Health Sciences, and Fudan University • Scientific Review Panel (SRP) established and chaired by Dr. Rice • Ethics Review Panel (ERP) established and chaired by Dr. Brody
2001	• Renovation of laboratory facilities at Fudan University started
2002	• Case-control study protocol approved by SRP and ERP
2003	• Disease progression study protocol approved by SRP and ERP • Molecular epidemiology study protocol approved by SRP and ERP • Patient enrollment begins in August
2004	• Study design and goals presented at Benzene 2004 Conference in Munich
2005	• First SHS publication; Chronic exposure to benzene results in a unique form of dysplasia. <i>Leukemia Research</i>. 2005 Dec;29(12):1371-80. • Public symposium held at Georgetown University to discuss the SHS
2006	• Case accrual and exposure assessment continue
2007	• Case accrual and exposure assessment activities conclude • 722 cases of AML and 646 cases of lymphoid neoplasms accrued for case-control study
2008	• Independent quality assurance and data analysis conducted
2009	• Results presented at the Benzene 2009 Conference in Munich

Science and the Shanghai Health Study

Summary of Current Benzene Science

The major effects of benzene are chronic (long-term) impacts on the body's blood forming tissue. At high enough exposures, benzene damages the bone marrow and can cause a decrease in red blood cells, leading to anemia. Benzene is also a cause of a particular type of leukemia, acute myelogenous leukemia (AML).

Shanghai Health Study

- Preliminary research design and feasibility studies based upon site visits by Principal Investigators and industrial hygiene personnel in 1999; initial site visits documented
 - Relatively high exposure levels
 - Sufficient numbers of cases of disease to perform valid studies
 - Willing scientific collaborators who are research oriented
- Protocols for three closely related studies were developed:
 - Study 1, "Case Control Study" uses a common epidemiological study design, to examine the risk of AML and lymphoid cancers like Non-Hodgkin Lymphoma (NHL) among benzene exposed workers and attempts to determine the dose response curve in the event an association is seen. Both cases and controls were prospectively collected. This study will:
 - ✓ Develop exposure information based upon historical workplace monitoring information and questionnaire
 - ✓ Explore other potential causal factors for AML and lymphoid neoplasms.
 - ✓ Include information on lymphoid and AML subtypes
 - Study 2, "The Disease Progression Study" is a prospective investigation of the relationship between non-cancer bone marrow diseases (such as MDS, AA, or "benzene poisoning") and benzene induced AML. It will examine:
 - ✓ Whether benzene-induced AML exhibits a molecular pattern that is different than spontaneous AML
 - ✓ What is the specific mechanism by which benzene causes leukemia
 - ✓ Are there biological markers of benzene induced AML?
 - Study 3, "The Molecular Epidemiology Study" is a study to examine whether there is a quantitative relationship between benzene exposure and potential early indicators (biomarkers) of both exposure and effect. It will seek to answer:
 - ✓ What levels of benzene are associated with biomarkers of exposure and/or disease?
 - ✓ Is there an association of blood effects with genetic polymorphisms?
 - ✓ Do biomarkers of exposure validate workplace airborne exposure measurements of benzene?

The Three Studies Meet Several Technical, Ethical and Cultural Challenges

- Technical – Studies are large and incorporate the latest technology including the WHO 2002 criteria for classification of lymphohematopoietic cancers. A Scientific Review Panel made up of leading experts from a number of fields relevant to these studies has reviewed and endorsed the research protocols. Additionally, the protocols have been reviewed and approved by Institutional Review Boards (IRBs) both in the US and China.
- Ethical - Study protocols meet international standards as reviewed and endorsed by an Ethics Panel consisting of leading international ethics experts. Subjects and participating communities benefit from having participated in the study through expert diagnosis and evaluation of blood disorders and confidentiality is preserved.
- Cultural –Collaborators on these studies included researchers from the Medical School at Fudan University, the Institute for Public Health Supervision, and the Shanghai Municipal Centers for Disease Control and Prevention (the latter two are responsible for occupational exposure monitoring and enforcement in Shanghai).
- In summary these studies were a significant opportunity to obtain a better understanding of the mechanism of benzene induced disease in humans; as the results of the studies are published, the knowledge may enhance the current assessment of the impacts of benzene exposure on health.

What Has The Shanghai Health Study Accomplished?

- From 2003-2007, this study funded the collection and analysis of more than two thousand cases of blood disease in the Shanghai area. Measurements and estimates of exposures to benzene were also made. Detailed and thorough analysis and interpretation of the data are underway by the researchers.
- The results of the case-control study will be presented at the Benzene 2009 Conference and later published in Chemical-Biological Interactions as part of the Conference proceedings. Additional publications are anticipated.
- Some results from the Molecular Epidemiology and Disease Progression studies have already been published. Additional data and conclusions will be presented at the Benzene 2009 Conference and published as part of the Conference proceedings. Additional publications are anticipated.

Thus far, publications from the Shanghai Health Study are as follows:

Characterization of Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma (CLL/SLL) in Shanghai, China: Molecular and Cytogenetic characteristics, IgV gene restriction and hypermutation patterns.

Irons RD, Le A, Bao L, Zhu X, Ryder J, Wang XQ, Ji M, Chen Y, Wu X, Lin G.
Leukemia Research. 2009 May 8. Epub ahead of print

Adult precursor B lymphoblastic leukemia in Shanghai, China: Characterization of phenotype, cytogenetics and outcome for 137 consecutive cases.

Bao, L. Gross, SA, Ryder, J, Wang, X-Q, Ji, M, Chen, Y., Yang, Y, Zhu, S, and Irons, RD

International Journal of Hematology. 2009 Sep;89(4):431-7. Epub 2009 Mar 26.

A Prospective Study of 728 Cases of Non-Hodgkin Lymphoma from a Single Laboratory in Shanghai, China.

Gross SA, Zhu XZ, Bao L, Ryder J, Le A, Chen Y, Wang XQ and Irons RD. (2008)
International Journal of Hematology. 2008 Sep;88(2):165-73. Epub 2008 Jul 23.

The TNF- α 238A polymorphism confers susceptibility to persistent bone marrow dysplasia following chronic exposure to benzene.

Lv L, Kerzic P, Lin G, Schnatter AR, Bao L, Yang Y, Zou H, Fu H, Ye X, Gross SA, Armstrong TW and Irons RD

Leukemia Research. 2007 Nov;31(11):1479-85. Epub 2007 Mar 23.

Aggressive NK Cell Leukemia: Report of a Chinese Series and Review of the Literature.

Ryder J, Wang X, Bao L, Gross SA, Fu H, Irons RD

International Journal of Hematology. 2007 Jan;85(1):18-25.

Prevalence of MDS subtypes in Shanghai, China: A comparison of the World Health Organization and French American British Classifications.

Irons RD, Wang X-Q, Gross SA, Bao L, Ryder J, Chen Y, Chen H, Sun H, Zhou J, Ji M, Du X, Fu H, Lin G

Leukemia Research. 2006 Jul;30(7):769-75. Epub 2005 Dec 6.

Prospective study of 174 de novo acute myelogenous leukemias according to the WHO classification: subtypes, cytogenetic features and FLT3 mutations.

Bao L, Wang X-Q, Ryder J, Ji M, Chen Y, Sun H, Yang Y, Du X, Kerzic PJ, Gross SA, Yao L, Lv L, Fu H, Lin G and Irons RD

European Journal of Haematology. 2006 Jul;77(1):35-45. Epub 2006 Mar 27.

Chronic exposure to benzene results in a unique form of dysplasia.

Irons RD, Lv L, Gross SA, Ye X, Bao L, Wang X-Q, Ryder J, Armstrong TW, Zhou Y, Jiao L, Le A-T, Kerzic PJ, Ni W and Fu H

Leukemia Research. 2005 Dec;29(12):1371-80. Epub 2005 Sep 23.

Principal Investigators for the Shanghai Health Study

Richard D. Irons, Ph.D, DABT Cinpathogen, Inc. 4800 Baseline Road, #-104 PMB253 Boulder, CO 80303 Tel: (303) 381-2543 richard.ironson@cinpathogen.com	Principal Investigator for Disease Progression and Molecular Epidemiology studies. Key contact for laboratory operations and case collection.
Sherilyn A. Gross, Ph.D. Health Sciences Center University of Colorado Campus Box C238 4200 East Ninth Avenue Denver, CO 80262 Tel: (303) 724-3579 Sherilyn.Gross@UCHSC.edu	
Otto Wong, Sc.D., F.A.C.E. Applied Health Sciences P. O. Box 2078 San Mateo, CA 94401 Tel: (650) 347-7898 OttoWong@aol.com	Principal Investigator for Case Control Study.
Fu Hua, MB, MPH, PhD Deputy Dean and Professor School of Public Health Fudan University P.O. Box 248 138 Yi Xue Yuan Lu Shanghai, 200032 PR China hfu@fudan.edu.cn	

MEMBERS OF THE SCIENTIFIC AND ETHICS REVIEW PANELS FOR THE SHANGHAI HEALTH STUDY

Scientific Review Panel

*Jerry Rice	Georgetown University, USA
Richard Albertini	University of Vermont, USA
Harvey Checkoway	University of Washington, USA
John Cherrie	Institute of Occupational Medicine, UK
Helmut Greim	Technical University of Munich, Germany
Robert Herrick	Harvard School of Public Health, USA
Richard Larson	University of Chicago, School of Medicine, USA
Guilan Li	Chinese Center of Disease Control and Prevention, China
Howard Rockette	University of Pittsburgh, USA

Ethics Review Panel

*Juhana Idanpaan-Heikkila	Council for Int'l Organization of Medical Sciences (WHO), Switzerland
Ellen Clayton	Vanderbilt University, USA
Paul Lombardo	Georgia State University, USA
Zong liang Xu	Fudan University, China
Baruch Brody	Baylor College of Medicine (<i>Retired</i>)

*chairman

From: Howard Feldman [Feldman@api.org]

Sent: Monday, December 07, 2009 11:03 AM

To: BenzConsort-OC@listserve.api.org; BenzConsort-TC@listserve.api.org; BHRC Communications Committee; Karen Matusic; Grothe, Janet D; Johnson, Rich

Cc: Bob Greco; Kyle Isakower; Kathy Lewis

Subject: Final SHS Communications Package

Attached is the November 30, 2009 final version of the Shanghai Health Study Communications Package.

Howard J. Feldman

Director

Regulatory & Scientific Affairs

1220 L Street, NW

Washington, DC 20005-4070

USA

Telephone 202-682-8340

Fax 202-682-8270

E-mail feldman@api.org

