

Proposed Studies on the Risk of Benzene-Induced Diseases in China

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Goal: To form a consortium to fund research on benzene-exposed workers in China.

Purpose: To gain an accurate understanding of the true relationship between benzene exposure and the risk of certain hematopoietic diseases. This study would lead to improved benzene-driven, health-based regulatory (e.g., ambient air, water & occupational) standards worldwide, by providing the regulatory and scientific communities with information for more accurate assessment of the risks from exposure to benzene.

A unique set of circumstances exists at this point in time in Shanghai to conduct meaningful benzene research. These include a database of occupational exposures in a different regulatory environment, and willing and qualified co-investigators influential in local scientific medical, and regulatory establishments. Therefore, questions that have plagued benzene health risk assessment for decades appear to be answerable in Shanghai.

- High exposures
- Benzene-induced disease
- Good records since 1970s

- Technology sophistication
- Willing collaborators
- Influential contacts

1940's Exposures

21st Century Technology

Unique, unparalleled
research opportunities

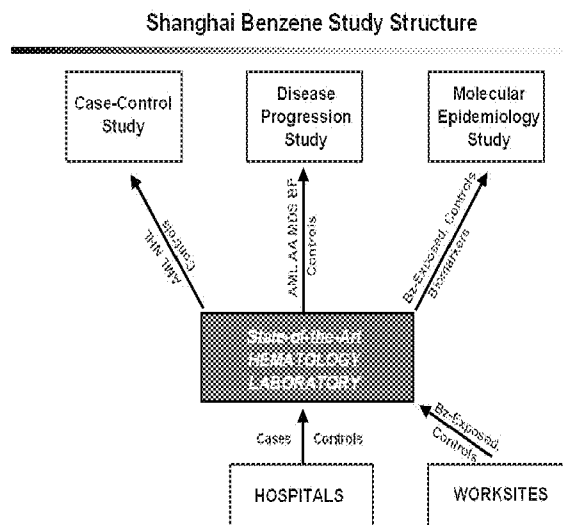
Challenges: The proposed studies meet several technical, ethical, and cultural/political challenges.

- **Technical** - In order to stand up to scientific scrutiny, studies must be large, well-managed, and incorporate the latest technology. State-of-the-art research is absolutely necessary to make real progress in developing sound benzene risk assessments.
- **Ethical** - To address the ethical issues, the study protocols have all undergone a thorough analysis to ensure that: the subjects and participating communities benefit from having participated in the study; that confidentiality is preserved, and that researchers are working with local regulatory authorities to improve worker safety. An Ethics Panel is part of the oversight for the project and includes a Chinese bioethicist.
- **Cultural/Political** - In order to address the realities of doing research in China, collaborators on these studies include researchers from the Medical School at Fudan University, and the Shanghai Municipal Centers for Disease Control and Prevention (responsible for occupational exposure monitoring and enforcement).

Benefits: Information gained from this project will have a direct relevance for worldwide regulatory standards designed to protect workers and the general population from benzene-induced disease. These include air and water quality standards, as well as hazardous waste and site remediation standards. These studies will assist contributing companies in achieving the highest product stewardship goals and in oversight of their risk management programs.

The Studies: Three inter-related studies have been proposed for this project:

- **Case-Control Study** - A hospital-based case control study to investigate the potential relationship between benzene exposure and both Non-Hodgkins Lymphoma (NHL) and Acute Myelogenous Leukemia (AML), including an attempt to quantify the potency of benzene for the AML response.
- **Disease Progression Study** - A hospital/clinic-based investigation of the relationship between non-cancer diseases of the bone marrow and AML (cancer) to determine if effects on bone marrow progress through non-cancer stages to an ultimate leukemia. This study would also attempt to define the shape of the dose response for possible "precursor" diseases and could result in characterization of unique identifiers of benzene-induced AML.
- **Molecular Epidemiology Study** - Investigate if there is a quantitative relationship between benzene exposure and potential early indicators of both exposure and effect in a focused population of workers.



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Costs: The estimated costs for the project were derived after careful consideration of all of the technical, ethical, and political issues. (inflation has been incorporated into the estimate).

Total Cost Estimate (2001 U.S. Dollars)	
Seed Monies	\$500,000
Study Costs	
Case-Control Study	\$1,761,000
Disease Progression Study	\$3,494,000
Molecular Epidemiology Study	\$3,275,000
Hematological Laboratory in Shanghai	\$8,340,000
External Communications	\$1,000,000
Other Costs (Administrative, Travel, Ethics Panel, Scientific Oversight Panel)	\$1,341,000
GRAND TOTAL	\$19,713,000

Funding: Funding for the project will be handled by a consortium of interested stakeholders, with shares determined by size of the benzene related operations of the contributing organization. The proposed funding formula was devised based on the assumption that most of the support will come from the petroleum and petrochemical industries. It is anticipated to take five years to complete the project, and that the costs will be highest in the first years of the project.

Proposed Funding Formula Share Determination

Shareholder Category	Shares
U.S. Refiner (based on U.S. refinery capacity)*	
Small ($\leq 500,000$ bbl/day)	1
Medium ($>500,000$ and $\leq 1,500,000$ bbl/day)	2
Large ($> 1,500,000$ bbl/day)	3
Non-U.S. Refiners (no U.S. refineries)	1
Free-Standing Chemical Co. (No refineries)	2
Upstream Company (No refineries)	1
Other (trade association, government, NGO)	Negotiable

*U.S. refinery capacity will be determined based upon refinery ownership as of October 1, 2000. Capacity will be calculated using the Oil and Gas Journal's 2000 Pennwell Directory.

Example Funding for One Share By Project Year*

Study Year	Percent of Costs	Cost Per Share
1	30	\$422,400
2	25	\$352,000
3	15	\$211,200
4	15	\$211,200
5	15	\$211,200
Total:		\$1,408,000

*Assumes that there are a total of 14 shares at approximately \$1,408,000 per share. Costs per share may increase or decrease dependent upon participation level (i.e., total number of shares).

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For Information

API Executive Committee

Issue: Continued funding shortfall for the industry-sponsored research project in China to study the potential health effects of benzene.

Background: There is continued concern with the potential health effects of benzene. Approximately three years ago, industry researchers became aware of information maintained by the Chinese government in Shanghai regarding benzene exposures of workers and their health histories. Given the high quality of the occupational exposure records in Shanghai, this is viewed as a unique opportunity to study the relationship between exposure to benzene and the risk of certain blood diseases. The Benzene Health Consortium is sponsoring a five-year program that should significantly decrease the degree of uncertainty surrounding these risks. There is a significant degree of support for this project within China as evidenced by the active participation of Chinese researchers, physicians and occupational regulatory agencies. Independent multinational, multidisciplinary scientific and ethics review panels have been involved in protocol development and will actively participate in overseeing the project. The study will provide industry and the scientific and regulatory communities with information in order to more accurately assess the risks from exposure to benzene, enhancing product stewardship.

Project Status: Three inter-related studies are underway:

1. Case-Control Epidemiology Study
2. Disease Progression Study
3. Molecular Epidemiology Study

Renovation of space for a clinical hematology laboratory at Fudan University in Shanghai is complete. Purchase and installation of capital equipment is underway and intensive training of Chinese laboratory technicians is in progress. The laboratory startup activities are on track to be able to begin processing samples from study participants in the 1st quarter of 2003. Previous and current Shanghai workplace exposures are being evaluated and training of exposure assessment technicians is underway. Legal and public affairs expertise has been retained to facilitate Consortium activities.

Funding status: Five companies have provided initial funding for the study. These companies (BP, ChevronTexaco, ConocoPhillips, ExxonMobil and Shell Chemical Company) have committed \$16.5 million. Based on the protocol enhancements recommended by the independent scientific and ethics review panels, the Consortium Business Oversight Committee approved a \$22.8 million program. To address the shortfall, other US and non-US companies within the petroleum industry, chemical sector, and non-petrochemical industries have been approached. To date, no additional entities have joined. The Consortium members are currently executing a plan drafted in September to approach additional companies by the end of 2002. Despite the planned efforts, the likelihood of identifying additional sponsors to cover the shortfall is believed to be small. Therefore, we anticipate the need to seek additional

guidance from the Executive Committee in early 2003 on ways to address the funding shortfall.