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Proposed China Consortium Committee Structure

For Presentation at
August 31, 2000 Consortium Development Meeting

The following is intended as a draft description of the major duties, roles and makeup of committees that could function as the administrative, scientific, and ethics oversight components of the China Benzene Research Consortium. This draft is intended for discussion only, and does not represent the final, or recommended committee structure or responsibilities.

Please see the attached flow chart for a schematic of the reporting relationships of the committees described below.

COMMITTEES

Business Oversight Committee

Membership: One member from each sponsor company. The Chairman of the Technical Oversight Committee is *ex officio* member of this committee, non-voting unless also designated as full member of this committee.

Input: The Business Oversight Committee receives input from the Technical Oversight Committee regarding the technical progress of the research and recommendations for research related expenditures, and from the Ethics Review Board regarding recommendations for bioethics related issues.

Responsibilities: The Business Oversight Committee shall be the ultimate administrative authority for the consortium and shall make all final decisions regarding budget, reporting and interaction with the Chinese authorities. The Business Oversight Committee shall have final approval over the membership of the Ethics Review Board and over the membership of the Scientific Review Board subsequent to the recommendation of the Technical Oversight Committee.

The Business Oversight Committee shall report Annually to the member companies on the financial status of the consortium. All expenditures of the consortium shall be approved or delegated by the Business Oversight Committee.

The Business Oversight Committee shall be responsible for TSCA 8(e) reporting on behalf of the consortium. This role in no way limits the ability of individual members of the consortium from filing individual 8(e) submissions if they deem it appropriate.

Technical Oversight Committee

Membership: The membership of the Technical Oversight Committee shall include one member from each contributing member of the consortium. (Outside entities such as governmental agencies or NGOs could have a place on this committee subject to approval of the Business Oversight Committee.)

Input: The Technical Oversight Committee shall receive semiannual reports from the principal investigators regarding the progress of research. This committee shall also receive reports from any Quality Assurance activities undertaken during the course of the research. This committee would receive recommendations from both the Ethics Review Board and the Scientific Review Board regarding the conduct of research and, in the case of the latter board, the acceptability of proposed manuscripts and abstracts.

Responsibilities: The Technical Oversight Committee shall act as the technical consultant to the Business Oversight Committee of the consortium. This committee would review all manuscripts for publication and abstracts of presentations stemming from the consortium research and advise the Business Oversight Committee on the validity and interpretation of the results received from the principal investigators. This committee shall be responsible for recommending protocol alterations, abstracts of presentations and manuscripts for publication to the Scientific Review Board for approval.

Scientific Review Board:

Membership: Internationally recognized experts in scientific/medical fields that are recommended by the Technical Oversight Committee and approved by the Business Oversight Committee. There are also potential seats on the Committee for other stakeholders as approved by the Business Oversight Committee. The chair of the Ethics Review Board shall also be a member *ex officio* of the Scientific Review Board.

Input: The Scientific Review Board shall receive progress reports from the principal investigators on at least a semi-annual basis. The Scientific Review Board shall meet annually to receive a report from the Principal investigators on the progress of the research relative to the proposed protocols. Otherwise, the Scientific Review Board shall meet in person or by conference call as deemed necessary to carry out their duties. The Scientific Review Board shall consult with the Ethics Review Board regarding the ethical conduct of research under this program.

Responsibilities: It shall be the responsibility of the Scientific Review Board to approve the initial research protocol and all significant protocol changes thereafter. The Scientific Review Board based upon the decision of the chair of that group shall determine what protocol changes are considered significant. These approvals shall be transmitted via the Technical Oversight Committee to the Business Oversight Committee for final acceptance. The Scientific Review Board shall approve all manuscripts for publications and all abstracts for presentation by whatever medium that include data generated as part of this research project.

Ethics Review Board:

Membership: Determined by the Business Oversight Committee. This Board should include at least one recognized bioethicist from the United States, The European Union and the Peoples Republic of China. This board should also include one or more representatives of the community under study. The Chair of the Scientific Review Board shall be an *ex officio* member of the Ethics Review Board.

Input: The Ethics Oversight Board will receive input from the Technical Oversight Committee and the principal investigators regarding proposed research and from the NGO Liaison Committee regarding actions to address bioethics issues raised by this research.

Responsibilities: The Ethics Review Board shall be responsible for recommending all actions by the consortium that are intended to ensure that all research performed by the Consortium shall conform to ethical standards as identified by the Ethics Review Board and approved by the Business oversight Committee. The Ethics Committee shall maintain close communication with the Scientific Oversight Committee to ensure that the implementation of all research protocols is consistent with ethical standards as defined above. To this end the Ethics Review Board shall meet Annually to review the progress of research and to assure itself that the research is being conducted in a manner consistent with the approved ethical guidelines.

NGO Liaison Committee:

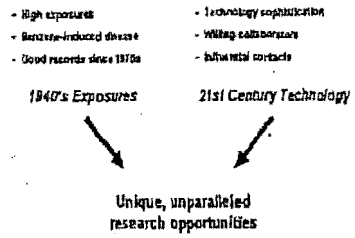
Membership: At a minimum the membership of the Non-Governmental Liaison Committee (NGO Liaison Committee) shall consist of a member of the Business and Technical Oversight Committees, a member of the Ethics Review Board and a member of each outside agency with which the Consortium is affiliated.

Responsibilities: The NGO Liaison Committee shall exist for the purpose of addressing bioethical issues raised by the research program of the Consortium that can met by collaboration with entities other than governmental regulatory bodies or industry associations. The NGO Liaison Committee shall recommend programs and a budget to the Business Oversight Committee to address these issues.

Input: The NGO Liaison Committee shall consult with the Ethics Review Board regarding programs to address bioethics issues.

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

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 disease. This study would lead to improved benzene-driven, health-based regulatory standards by providing the regulatory and scientific communities with information for more accurate assessment of the risks from exposure to benzene.

Opportunities: A unique set of opportunities exists at this point in time in Shanghai to conduct meaningful benzene research, including high occupational exposures that do not exist anywhere in the West, willing co-investigators influential in local scientific, medical, and regulatory establishments. Therefore, questions that have plagued and confounded benzene health risk assessment for decades appear to be answerable in Shanghai.

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 changing the existing benzene risk assessment paradigm.
- Ethical - To address the ethical issues, the study protocols have all undergone a thorough analysis to ensure that the subjects are appropriately compensated for their participation; that both the subjects and communities benefit from having participated in the study; and that worker safety will improve. 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, the Shanghai Municipal Centers for Disease Control (responsible for occupational exposure monitoring and enforcement).

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

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Benefits of Extensive Collaboration

CHINESE PERSPECTIVE	U.S. PERSPECTIVE
• Imports from the West ➢ Study Methods Expertise ➢ Leading Technology & Know-How	• Required to Navigate Socio-Political Infrastructure
• Enhances Professional Advancement - Publications	• Ensures Adequate Participation
• Broadens Training Opportunities	• Enhances Study Impact, Relevance
• Allows Greater Autonomy in Future	• Improves Business-Regulatory Interface in China

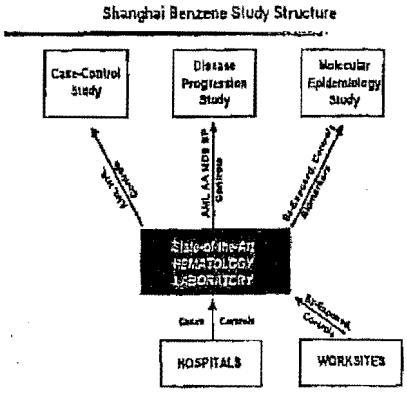
Benefits:

Information gained from this project will have a direct, cross-media impact upon 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. The information gained from these studies will assist contributing companies in achieving product stewardship goals and will be useful in defending the industry's risk reduction programs. Additional benefits from this collaborative approach are outlined below.

Proposed Studies on the Risk of

Benzene-Induced Diseases in China

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 these "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 benzene exposed workers.

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

Costs: The estimated costs for the project were derived after careful consideration of all of the technical, ethical, and political issues. Therefore, the estimated costs are fairly stable and are not anticipated to

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

increase by much (inflation has been incorporated into the estimate).

Funding: Funding for the project will be handled by a consortium of interested stakeholders, with shares determined by size 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.

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 decre (i.e., total number of shares).

Proposed Funding Formula
Share Determination

Shareholder Category	Shares
U.S. Refiner (based on U.S. refinery capacity)*	
Small (≤ 500,000 bbl/day)	1
Medium (>500,000 and ≤ 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 ca Journal's 2000 Pennwell Directory.

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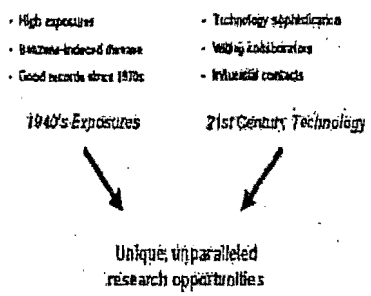
Proposed Studies on the Risk of Benzene-Induced Diseases in China

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.



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.
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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 product stewardship goals.

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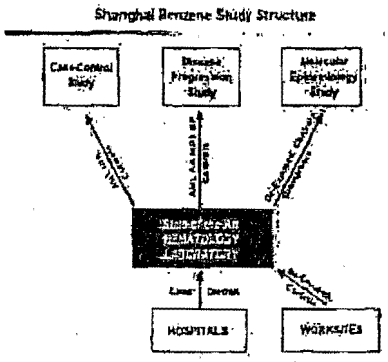

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Q & A
Studies of Benzene in China

The purpose of this document is to outline the answers to the questions most frequently asked regarding these studies.

Glossary of Terms

AML (Acute Myelogenous Leukemia): The hematopoietic disease most commonly associated with exposure to benzene. This relationship has resulted in benzene's classification as a human carcinogen.

Hematopoiesis: The formation of blood and blood cells, including red & white blood cells and platelets.

NHL (Non-Hodgkins Lymphoma): Complex spectrum of malignancies of lymphoid tissues, most often arising in the lymph nodes.

NCI/CAPM (National Cancer Institue/Chinese Academy of Preventative Medicine) - The authors of a previous set of studies in China that found NHL associated with benzene exposure, the first study to show such a linkage.

SMCDC (Shanghai Municipal Centers for Disease Control) - The Shanghai governmental agency responsible for occupational exposure monitoring and enforcement

Q. For the Case Control Study of NHL, why not just perform a retrospective study; would that not be a quicker and much less expensive way to get the same information?

A. First and foremost, is the lack of complete and verifiable diagnoses from a simple retrospective study. A number of other conditions can mimic NHL, and misdiagnosis is easy in the absence of sophisticated diagnostic procedures. Diagnostic samples are not routinely kept in China and there would be no opportunity to confirm diagnoses for most cases. Secondly, assessment of exposure and confounding risk factors is complicated in a retrospective study. In the case of deceased patients, details of lifestyle and work history must be obtained from relatives or other workers. Taking cases prospectively reduces the distance in time that one needs to go back in order to get needed exposure records.

Q. The diagnostic laboratory is a major expense. Why is it necessary? Why can't we just do a standard case-control study?

A. Non Hodgkin's Lymphoma (NHL) is an aggregate category of ca. 20 distinct lymphocytic diseases. In order to perform an NHL study that conforms with the current diagnostic schema, the subtype of NHL should be known. These subtypes are distinguished by morphological appearance and characterization of cell surface markers by sophisticated immunochemical techniques. A number of viral infections are known risk factors for some forms of NHL. For example, hepatitis C which is common in China. The presence of the planned laboratory on site in Shanghai assures us of consistent, state-of-the-art diagnostic capabilities under our control without the necessity of the logistic and bureaucratic nightmare entailed in shipping human tissue samples to the US for testing.

Thus the laboratory is an essential and required feature of this program. Besides providing uniform, state-of-the-art diagnoses, it provides the necessary technology to control for many potentially confounding factors (e.g., cell type, viral infections) that could affect the results of this study. This will allow us to provide more insight on the relationship, if any, between benzene and NHL than previous studies such as the NCI/CAPM study.

Q. Why are we including AML in the Case-Control study. AML is also in the Disease Progression study. Isn't this a duplication?

A. Including AML, which we would expect to see associated with benzene exposure, provides a positive control to defend against criticisms that our methodology was somehow not adequate to see associations that do exist. There is some overlap in that the Case-Control study will serve as one source of AML cases in the Disease Progression study.

Q. One of the reasons for pursuing the Molecular Epidemiology study is that the Chinese officials in Shanghai have requested this type of data; why can't they use the existing NCI/CAPM study results?

The NCI/CAPM study was roundly criticized for not providing a good measure of actual exposure; for not accounting for exposures to multiple chemicals; for assuming that all AML, NHL, and other blood-related diseases were caused by exposure to benzene alone; and with poor study design that did not account for confounding factors (e.g, smoking) and other factors. USEPA has taken the position that this study cannot be used to calculate a quantitative cancer risk from benzene exposure. This is precisely the reason this study will be so important.

The Chinese base their occupational standards on measurable effects on people, and not on mathematical modeling of hypothetical risks as is typical in the U.S. and Europe. The NCI/CAPM studies did not provide them with the type of data upon which to base a change in their current standards. Their current standard is based on a decrease in white blood cell counts rather than leukemia. They are interested in the Molecular Epidemiology Study which is intended to provide an objective, measurable indicator of risk.

Q. Why are we taking on the expense of providing laboratory diagnostic services for hematopoietic diseases in Shanghai hospitals during the course of the study?

A. These services provide crucial benefits to the consortium research in two areas:

- Research Data – As the central diagnostic laboratory we will assure the quality and consistency of the diagnostic data. This role assures access to blood and bone marrow samples from study participants. Without this role we would have to seek permission to perform a second procedure to obtain these tissues for the research. Patients would be reluctant to undergo such a second procedure, which would complicate obtaining large numbers of participants.
- Bioethics – Providing this higher level of diagnostic information to hospital physicians improves the level of patient care which addresses the ethics standard that the study benefit participants and the general community in which the research is performed.

Q. If the Chinese are going to be the major beneficiaries of this research, shouldn't they contribute to the project?

A. Although the Chinese are not providing direct monetary contributions, they will be contributing in-kind support. The laboratory space allocated to the project has been provided by Fudan University. The funds provided by API for the laboratory space have gone toward renovation of that space to make it acceptable for the purposes of this study, but we will not pay any rent for the use of the space during the period of our studies. The considerable resources of the Shanghai Municipal Centers for Disease Control (SMCDC) have been offered freely, including use of their database to identify facilities and individuals to include in the study as well as laboratory support for industrial hygiene monitoring analyses necessary to the study. And most pointedly, the Chinese provide access to the subjects, without whom it would be impossible to conduct such a study.

Q. Why is this being undertaken primarily by the petroleum industry, and why have other industries and/or international companies not been approached to help fund this research?

A. API has long taken a lead role in benzene health effects research. Other industries are being approached to help in this effort, as are international petroleum companies and trade associations. Presentations have been made to CONCAWE, IPIECA, and CEFIC. At least one of our major supporters, BP, is headquartered outside the United States.

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February 28, 2001