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From: George Woodall <Woodallg@api.org>
Cc:
Bcc:
Received Date: 2001-02-28 01:20:08 GMT
Subject: Informational materials available

Benzene Consortium Stakeholders.

Two of the informational documents we have been developing are completed and have been placed on the Consortium web page for your use. The web page is password protected. The document titles below have been linked to these documents on the web. I have also attached these documents to this e-mail.

* Proposed

<<http://www.api.org/benzene-consortium/Information/OnePagerFINAL.doc>>

Studies on the Risk of Benzene-Induced Diseases in China - A two page document designed to be copied double-sided onto one page. Very general in nature, this document includes estimated costs and a simple description of the draft funding formula.

* Ethics

<<http://www.api.org/benzene-consortium/Information/EthicsOnePagerFINAL.doc>>

Considerations and Status of Resolution - A brief description of the ethical issues that have been considered in the process of developing the study protocols and the status of steps taken to resolve those issues.

Both of these documents have been reviewed thoroughly, including a legal review; however, constructive criticism is always welcome.

We are continuing work on several other documents in this series, including:

1) a Q&A document that answers many of the more common questions we have been receiving during management briefings; 2) a more detailed Overview document; 3) a draft Consortium Structure document that goes into detail on how the consortium may be structured, depending on the decisions of the Executive Committee following Consortium formation; and 4) a PowerPoint presentation that provides most of the information in the other documents. These documents will also be placed on the web page as they are completed and approved for use.

Thank you,
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Attachments:

EthicsOnePagerFINAL.doc
OnePagerFINAL.doc

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

Page 1

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.

Opportunities: A unique set of opportunities exists at this point in time in Shanghai to conduct meaningful benzene research, including a database of occupational exposures in a different, regulatory environment, willing and qualified 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.

- 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

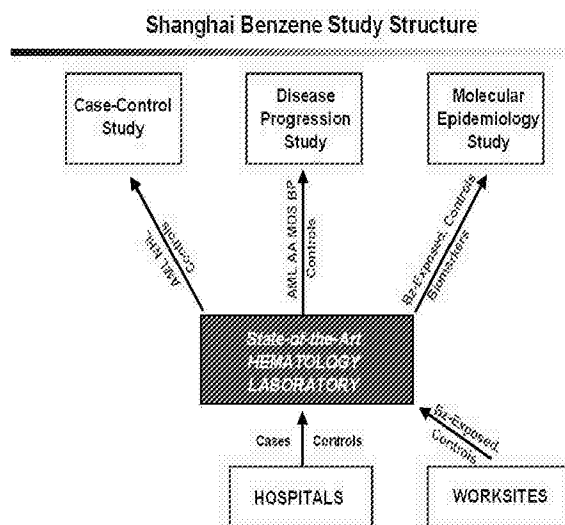
Challenges: The proposed studies meet several technical, ethical, and cultural/political challenges.

- **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 changing existing 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, cross-media 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 and will be useful in defining industry's risk reduction 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 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.



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

Page 2

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).

For more information contact:	Lorraine Twerdok (API) at (202)682-8344 or twerdokl@api.org ; or Patrick Beatty (Chevron) at (510)242-7037 or pwbe@chevron.com
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Proposed Studies on the Risk of Benzene-Induced Diseases in China

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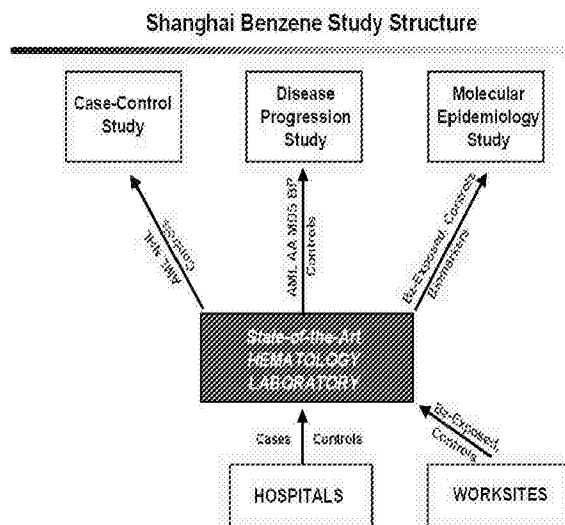
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The purpose of this document is to outline the answers to the questions most frequently asked regarding these studies.

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 Institute/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