

Shanghai Health Study Review and Update

Shell Steering Team
16 November 2004

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Shanghai Health Study

- Benzene Toxicology and Regulations
- Shanghai Health Study (SHS) providing an opportunity to clarify scientific issues
- Status of the study
- Benzene Health Research Consortium Organization
- Shell participation
- Current challenges
- Shell Steering Team

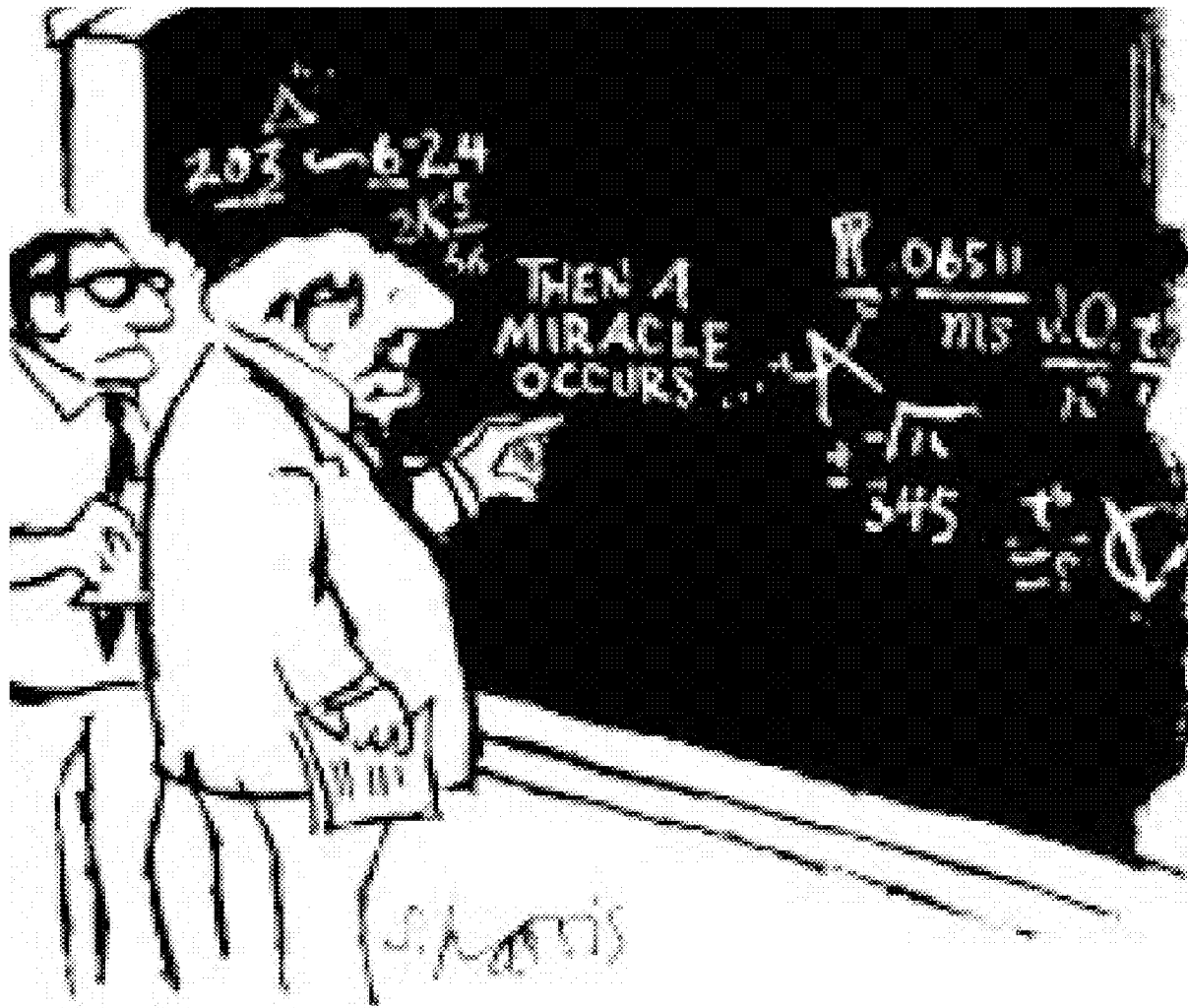
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Benzene Toxicology & Regulations

Benzene Toxicology

- Toxic chemical management :
 1. Hazard Identification
 - what are the hazards, regardless of exposure?
 2. Risk Characterization
 - dose response – what is a safe dose?



"I think you should be more explicit here in step two."



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Benzene Toxicology & Regulations

Benzene Toxicology – the hazard

- Benzene Is . .
 - A recognized - *known* - human carcinogen
 - Acute Myelogenous Leukemia (AML)

Benzene Toxicology & Regulations

Benzene Toxicology – Risk Characterization

- The effects of exposure depend on:
 - dose
 - duration
 - other exposures
 - personal traits and habits
 - genetic susceptibility

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Benzene Toxicology & Regulations

Benzene Toxicology – Previous Study Summaries

- Pre-1997
 - Acute Myelogenous Leukemia (AML) associated with benzene
 - Not seen at exposures < 1ppm
 - Clear observations at exposures > 20 ppm
 - Insufficient data at 1-20 ppm to clearly assess risk
 - All steps required for induction of cancer have not been determined

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Benzene Toxicology & Regulations

Benzene Toxicology – Previous Study Summaries

- National Cancer Institute (NCI) Shanghai Study
 - Case-control study published in 1997
 - Benzene associated with AML and **Non Hodgkin's Lymphoma (NHL)**: unusual association with a non-AML cancer
 - Study design did not add to understanding of threshold (lowest exposure group was 10 ppm or less)

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Benzene Toxicology & Regulations

Benzene Toxicology – Previous Study Summaries

- Australian Institute of Petroleum (AIP)
Health Watch Study
 - Case-control study released in 2001
 - Association with **all leukemias**, including chronic lymphocytic leukemia (CLL)
 - Leukemia association reported at **lower exposure levels** than prior studies.
 - No association with NHL or multiple myeloma

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Benzene Toxicology & Regulations

Benzene Toxicology Summary

- Known:
 - Acute Myelogenous Leukemia
- New studies information
 - Non-Hodgkin Lymphoma
 - All leukemias
 - Cancers associated at lower exposures than previously recognized

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Benzene Toxicology & Regulations

Benzene Regulations - Work place exposure

- Benzene Is . .
 - Tightly regulated although worldwide standards vary:
 - Work place exposure levels in the range of 0.4 – 10 ppm
 - Regulations in the US via the Clean Air Act might limit community levels to as low as 40 ppt.

Shanghai Health Study

An Opportunity

SHS designed to qualitatively and quantitatively address these issues:

- What other Lymphoid or Hematopoietic Diseases might be associated with benzene exposure?
- At what exposure level/threshold are there effects?
- What is the progression of disease from exposure to cancer?
- Are there biomarkers to help identify exposure and potential disease?

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Shanghai Health Study

An Opportunity

Purpose:

- To gain a quantifiable understanding of the relationship between benzene exposure and potential development of associated hematopoietic diseases/cancer risks
 - Researchers using cutting-edge technologies to advance the understanding of benzene-induced disease

Shanghai Health Study is 3 Studies

**AML/NHL
Case Control
Study**

**AA/MDS/AML/BP
Disease
Progress
Study**

**Molecular
Epidemiological
Study
of Benzene
Exposure**

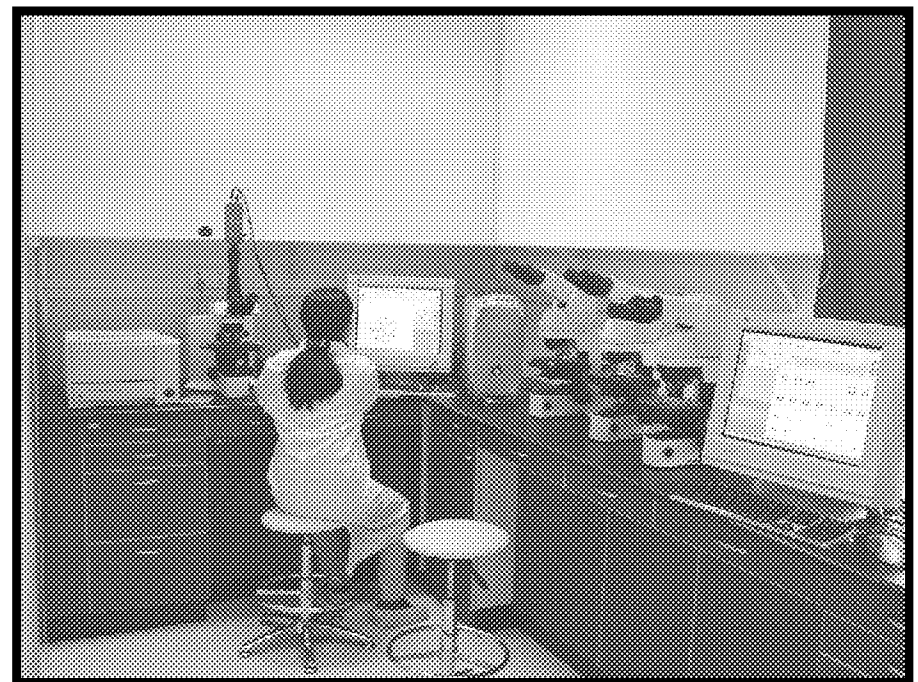
**Joint Sino-US Clinical and Molecular Laboratory
(JCML)**

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SHELL-MCCLURG-068103

Joint Sino-U.S. Clinical and Molecular Laboratory



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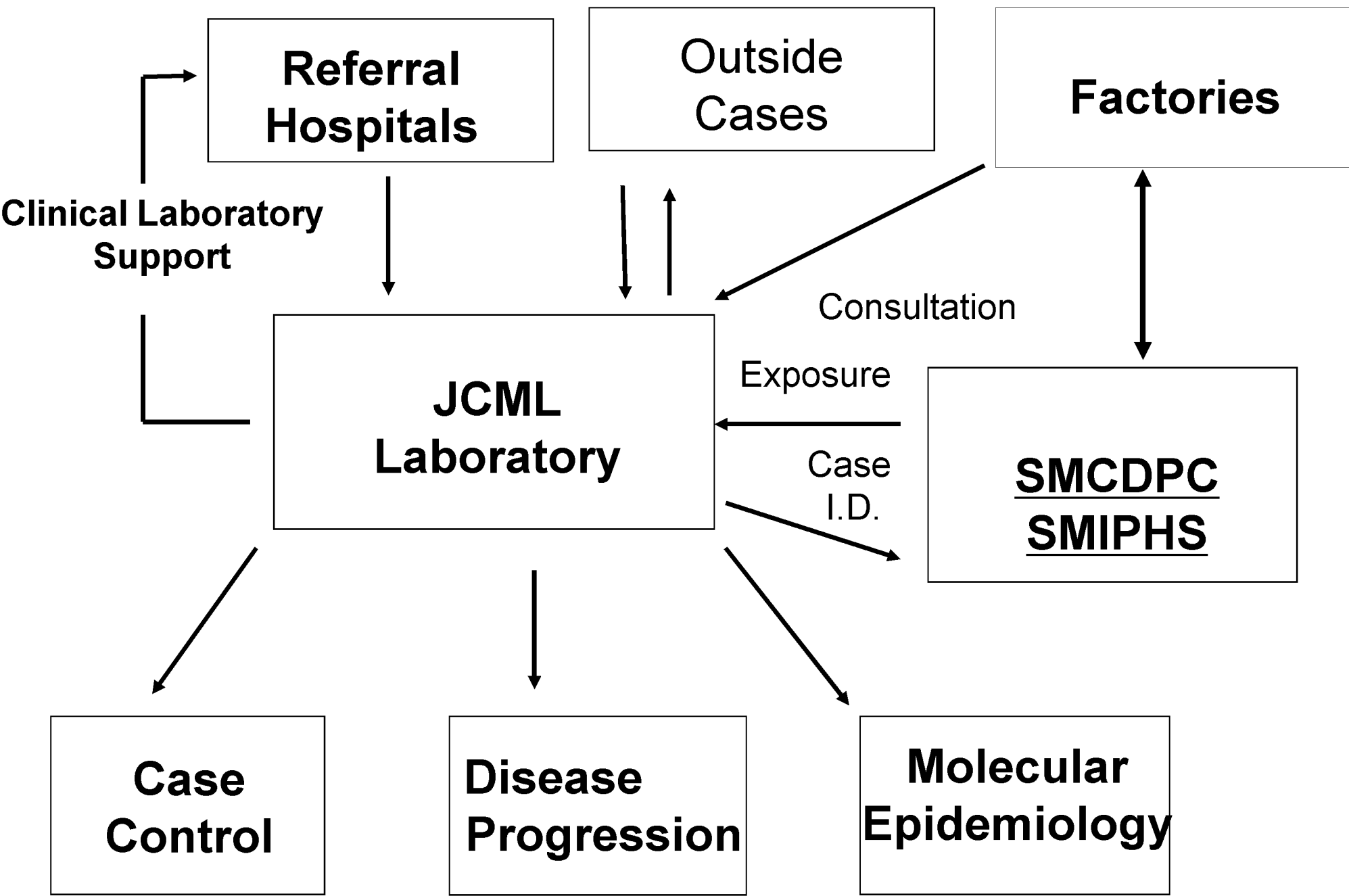
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Joint Sino-U.S. Clinical and Molecular Laboratory

- State-of-the-art laboratory on Fudan University campus
 - Meets international standards
 - Supports the study, Shanghai medical community and will remain at Fudan
- Technology transfers
 - Chinese staff trained at University of Colorado
 - U.S. researchers working with Chinese colleagues and government officials

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Shanghai Health Study

An Opportunity

SHS Elements:

- 3 Studies
 - Case Control Study
 - Disease Progression Study
 - Molecular Epidemiology
- Quality Science
- Study Participants
- Study Timeline

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Study #1 - Case Control Study

- Prospective epidemiology study to determine risk of AML and NHL, among benzene exposed workers
- Data collected will allow analysis of potential other causal factors for NHL
- Estimate 4-5 years to obtain 450 AML and 450 NHL patients into study
- Improved exposure assessment based on historical and concurrent workplace monitoring and questionnaire

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Study #2 - Disease Progression

- Prospective study on relationship of non-cancer bone marrow disease and benzene-induced AML
 - Is benzene-induced AML different from spontaneous AML by unique cellular markers?
 - Does AML involve a progression through one or more non-cancer states?
- Research methods:
 - questionnaires, interviews, review work histories
 - examine blood, breath, urine study/evaluate potential biomarkers

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Study #3 – Molecular Epidemiology

- Prospective study of establish quantitative relationship between exposure and effect
 - Do low benzene exposures cause blood effects?
 - Is there an association of blood effects and genetic susceptibility?
 - Do biomarkers of exposure accurately reflect workplace exposures?
- Healthy workers at sites with varying levels of benzene exposure will participate; extensive lab work, including genetic tests, will be conducted

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Quality Science

- Institutional Review Boards (IRBs) approved Protocols
 - Govern use of human subjects
 - U.S. and China independently
- Shanghai Health Study Panels
 - International Ethics Review Panel
 - 4 members representing 3 global regions
 - International Scientific Review Panel
 - 10 members; 6 scientific disciplines
 - Involved during entire project

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Shanghai Health Study

An Opportunity

Study Participants

Principal Investigators

Dr. Richard Irons, U of Colorado Health Sciences Center
Dr. Otto Wong, Applied Health Sciences
Dr. Fu Hua, Fudan University

Collaborators

ExxonMobil Biomedical Sciences

Chinese Participants

Fudan University School of Medicine
30 area Shanghai hospitals
Shanghai Municipal Center for Disease Prevention
Shanghai Hematology Society
Shanghai Pathology Institute for Public Health Supervision
Shanghai Public Health Bureau

Internal Review Boards

U of Colorado, Fudan University, Applied Health Sciences

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SHS Timeline

- 2001
 - Consortium established to fund the study; Protocols reviewed
- 2002
 - Questionnaire development, pilot testing; Key laboratory personnel trained
- 2003
 - Laboratory completed; 1st Annual Meeting; Case recruitment began – 4th quarter
- 2004
 - Preliminary data; 2nd Annual Meeting; International Benzene Symposium Presentations
- 2005 → 2007
 - Research, data analysis; Results published as studies completed

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SHS – Current Status

- **Study structure is a big success**
 - 2 annual meetings held
 - Scientific & Ethics Review Panels engaged
- **Study is progressing**
 - In year 2 of anticipated 4-year study
 - Laboratory is operating smoothly
 - Cases being accrued
 - 30 Shanghai hospitals referring cases
- **Study presentations**
 - International Benzene Symposium, Munich, Oct 2004
 - Papers to be published

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SHS – Major Accomplishments

- Set the standard for epidemiology studies
- Study being conducted using WHO cancer classifications for the first time
- Study infrastructure

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Benzene Health Research Consortium

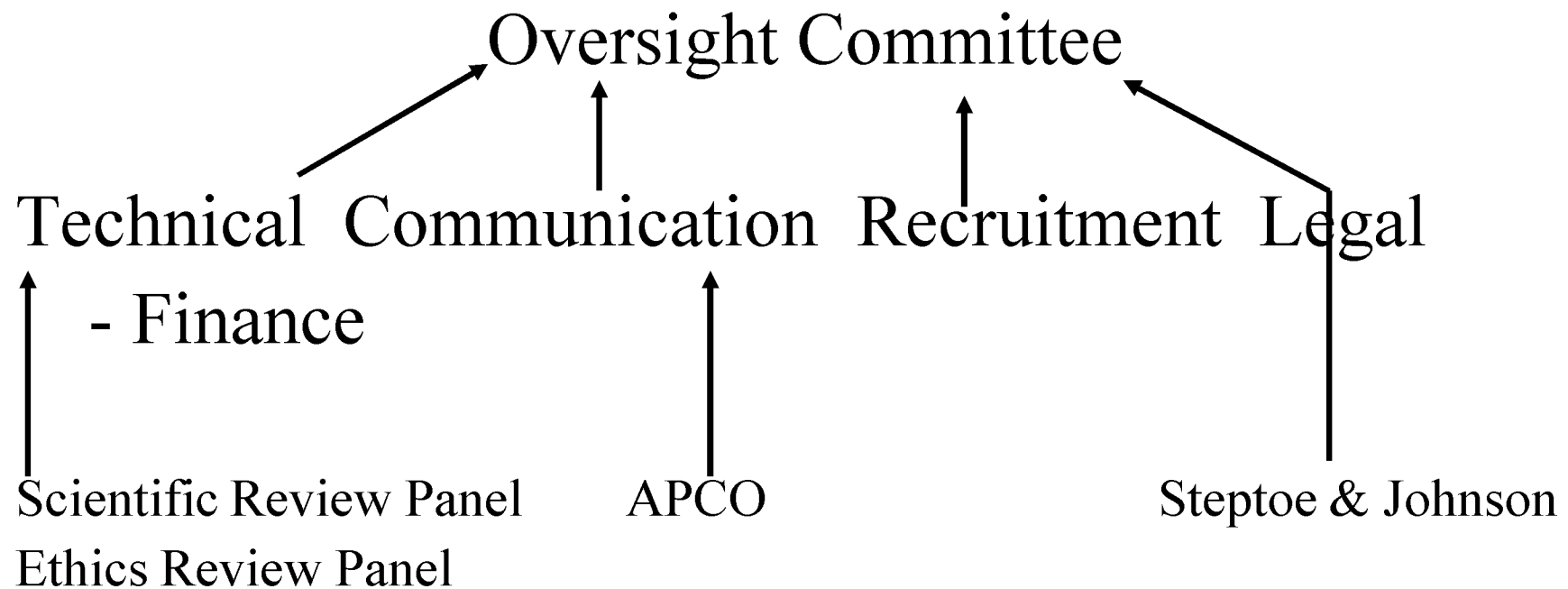
SHS Sponsors

- A consortium of petroleum and chemical companies concerned about understanding the human health effects of benzene
 - BP
 - ChevronTexaco
 - ConocoPhillips
 - ExxonMobil
 - Shell Chemical
 - with additional funding from Marathon Ashland
 - Project Administrator: American Petroleum Institute

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Benzene Health Research Consortium Structure



API Administrative Support

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SHELL-MCCLURG-068117

Benzene Health Research Consortium

Shell Participation

- Consortium leadership positions:
 - Patsy Clegg Oversight Committee Chair
 - Stuart Cagen Technical Vice-Chair
Finance Committee Chair
 - Shan Tsai Adjunct Professor, Fudan University
 - Sarah Colletti Communications Committee

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Shell Intentions for Project and Outreach

- **Shell** intentions based on:
 - Product stewardship needs for hazard and risk clarity.
 - Protecting reputation – in China and around the world.
 - Protect relationships/investments in China.
 - Meet commitment to transparency and ethics.
 - Protect credibility of project and participants.
 - Raise awareness and understanding of the project.
 - Secure buy-in and constructive feedback into the process.

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Current Challenges

- Short Term: Getting the study done
 - Exposure Assessment
 - Operating costs
- Longer Term
 - Laboratory Sustainability & Disengagement

Current Challenges

- **Exposure Assessment** is a greater challenge than expected
 - Quality & capability of resources on the ground in China
 - Cooperation of Chinese agencies

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Current Challenges

- **Budget Implications**

- Current Budget: 20.8 MM
- Request for additional \$: 3.3 MM

- Budget Solution Proposals

- Funding reallocation: 0.6 MM ?
- Additional Funding sought:
 - BP 1.7 MM
 - ILSI ?
- Study prioritization: ?

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Current Challenges

- **Laboratory Sustainability & Disengagement**
 - Lab belongs to Fudan University;
Expecting university decision as to
management by year end.
 - Uncertainty as to future role of lab
after study concludes.
 - Consortium is working on options

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Current Challenges

Conclusions:

- Ensure that a robust study is completed
- Continue efforts to reprogram and reallocate funds
- Lab sustainability

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SHS - Shell Steering Team

- Business
 - Nancy Sullivan, Business sponsor – Emeritus
 - Stacy Methvin, Americas Base Chemicals VP
 - Contracts and Funding
 - Harshad Topiwala, APME Base Chemicals VP
 - Business Focal Point
 - Bill Colquhoun, EUAF Base Chemicals VP
- SOPUS
 - David Sexton, Portfolio Planning & Development
- External Affairs
 - Nick Wood, EA Manager for Shell in China
 - Sarah Colletti, EA Manager for the Americas
- Issue Management
- Legal
 - John Schmid
- Finance
 - Tarita Samuel
- HSE
 - Susan Tholstrup, HSE sponsor
 - Patsy Clegg, Oversight Committee
 - Stuart Cagen, Technical & Finance Committees
- Medical
 - Shan Tsai, Technical Committee

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SHS - Shell Steering Team Charter

PURPOSE: The purpose of the Shell Steering Team is

- Set the strategy
- Provide guidance to Shell staff on the Benzene Health Research Consortium committees
- Provide internal Shell communication on the progress of the study
- Issue Management
- Provide resources to support the study

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SHS - Shell Steering Team

Path Forward:

- Next Meeting
- Next communication
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