From:	Cagen, Stuart Z SCC-CF-SS <stuart.cagen@shell.com>
Sent:	Friday, November 12, 2004 7:48 PM (GMT)
To:	'shan tsai' <shantsai@hotmail.com>; Clegg, Patsy M SCC-CHSE-PC <patsy.clegg@shell.com>; Tsai, Shan P SHLOIL-SHS <Shan.Tsai@shell.com>
Subject:	RE: draft presentation for your review
Attach:	Shanghai Health Study review and update 16 November 2004.ZIP

New version for your review.
Slightly reduced and I have incorporated most of Shan's suggestions. Note I have kept 20 ppm as the 'threshold' value, not 5 ppm as Shan has suggested but I have changed the language from risk to association...
Comments ? Perhaps we should talk sometime on Monday.
Stuart
Stuart Cagen
Shell Chemical LP
One Shell Plaza, 910 Louisiana, Houston, TX 77002-4916
Tel: +1 713 241 1407 Fax: +1 713 241 3325 Other Tel: +1 832 646 3987
Email: stuart.cagen@shell.com
Internet: http://www.shell.com/chemicals
-----Original Message-----
From: shan tsai [mailto:shantsai@hotmail.com]
Sent: Thursday, November 11, 2004 12:09 AM
To: Cagen, Stuart Z SCC-CF-SS; Clegg, Patsy M SCC-CHSE-PC; Tsai, Shan P SHLOIL-SHS
Subject: RE: draft presentation for your review
Stuart,
The presentation materials look very good. I have only a few suggestions:
1. Epidemiology Conclusions Pre-1997: the clear risk at exposures is too high. May need to lower to >5ppm. Also change issufficient data to 1-5 ppm
2. Austrilian study - Add "at lower level of benzene exposure" after the first bullet of that slide
3. In the How is the SHS Distinct - what you mean by "the first-hand exposure reports"
4. In the Study #1 - Case Control Study, first bullet, delete "potentially"
5. Overall, too much detailed information in this presentation.
Shan
Taiwan
>From: "Cagen, Stuart Z SCC-CF-SS" <stuart.cagen@shell.com>
>To: "Clegg, Patsy M SCC-CHSE-PC" <patsy.clegg@shell.com>,"Tsai, Shan P
>SHLOIL-SHS" <Shan.Tsai@shell.com>,<shantsai@hotmail.com>
>Subject: draft presentation for your review
>Date: Tue, 9 Nov 2004 14:15:02 -0600
>
>
> <<Shanghai Health Study update 16 November 2004.ZIP>>
>
>
>Stuart Cagen

>
>Shell Chemical LP
>One Shell Plaza, 910 Louisiana, Houston, TX 77002-4916
>
>Tel: +1 713 241 1407 Fax: +1 713 241 3325 Other Tel: +1 832 646 3987
>Email: stuart.cagen@shell.com
>Internet: http://www.shell.com/chemicals
>
><< ShanghaiHealthStudyupdate16November2004.ZIP >>

Shanghai Health Study: review and update

16 November 2004

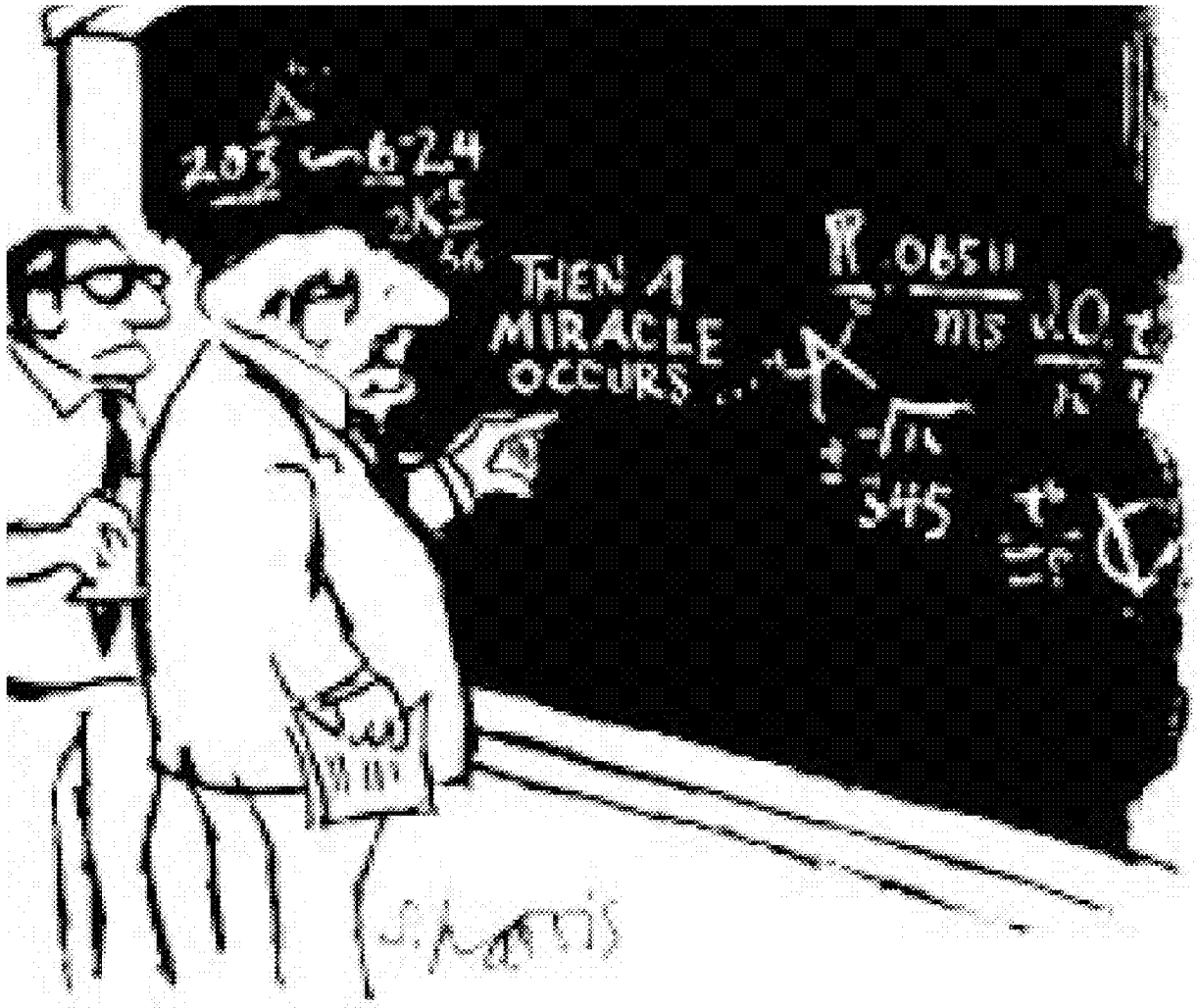
Shanghai Health Study

- Benzene toxicology and regulations
- Shanghai Health Study (SHS) providing an opportunity to clarify scientific issues
- Status
- Shell participation
- Current challenges

Benzene toxicology and regulations

- Two important steps in the management of toxic chemicals:

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."

Understanding Benzene Toxicity

Benzene toxicology and regulatory issues

- Two important steps in the management of toxic chemicals:

1) Hazard Identification – what are the hazards, regardless of exposure.
2) Risk characterization – dose response – what is a safe dose.

Benzene Is . . .

- Hazard Identification – what are the hazards, regardless of exposure:
  - A recognized - *known* - human carcinogen:
    - Acute Myelogenous Leukemia (AML)

Benzene Toxicity

- The effects of exposure to any hazardous substance depend on:
  - dose,
  - duration,
  - other exposures,
  - personal traits and habits,
  - genetic susceptibility

Epidemiology Conclusions 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
- Some steps are not dose-dependent and are governed by a threshold mechanism
- All steps required for induction of cancer have not been determined

Benzene Is . . .

- Tightly regulated although worldwide standards vary:
  - Work place exposure levels in the range of 0.5 – 10 ppm
  - Regulations in the US via the Clean Air Act might limit community levels to as low as 40 ppt.

Recent Epidemiological Studies

- National Cancer Institute Shanghai Study (NCI) – 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)

Recent Epidemiological Studies

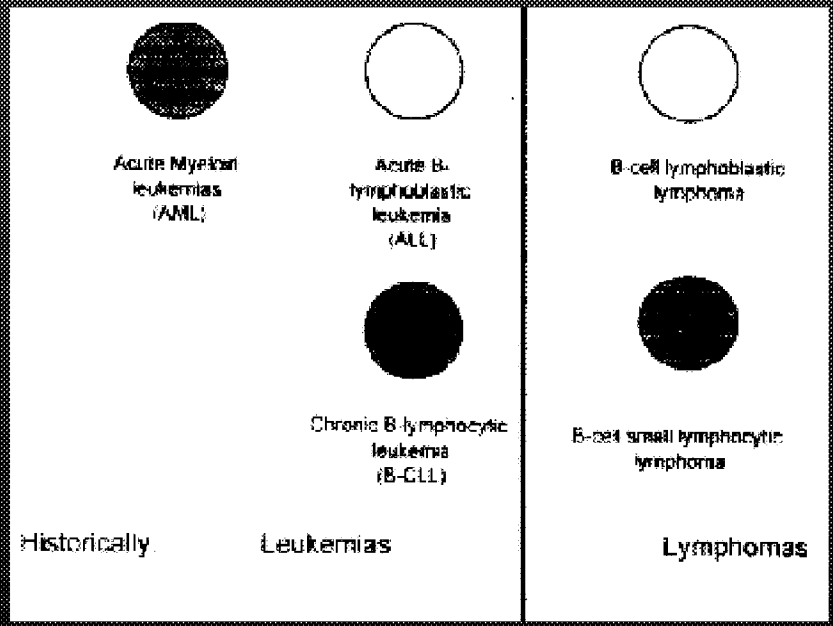
- Australian Institute of Petroleum's (AIP) Health Watch Study – case-control study released in 2001
  - Association with all leukemias, including chronic lymphocytic leukemia
  - Leukemia association reported at lower levels than prior studies.
  - No association with NHL or multiple myeloma

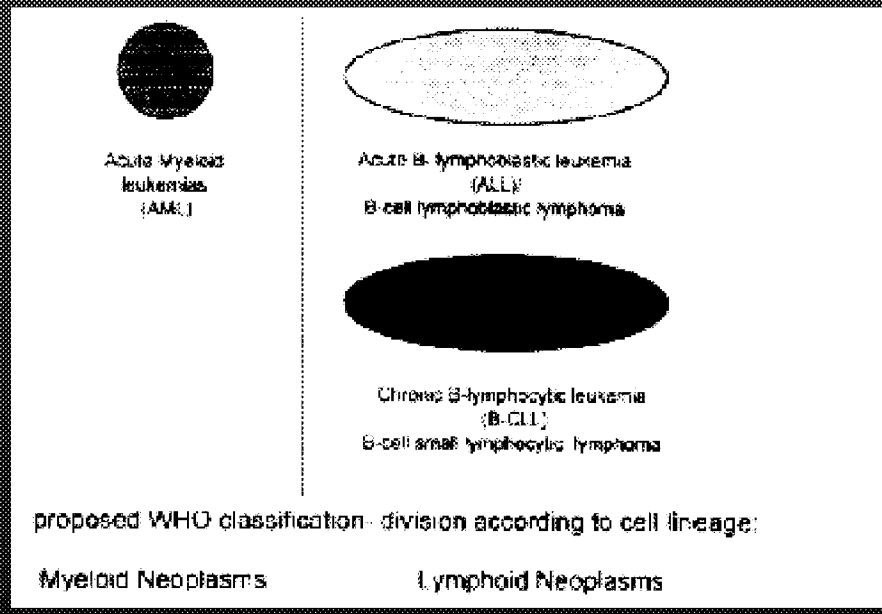
Benzene Is . . .

- Hazard Identification – what are the hazards, regardless of exposure:

  – A recognized - *known* - human carcinogen:
    - Acute Myelogenous Leukemia (AML)
    - Other Lymphoid or Hematopoietic Diseases have been suggested.

WHO Classification of Lymphoid and Hematopoietic Neoplasms





The older concept (left), that leukemias are fundamentally different from solid tumors of the same cell type, is replaced in the new WHO classification (right) in which lymphoid tumors of a given cell type are a single entity that may present either as leukemia or lymphoma.

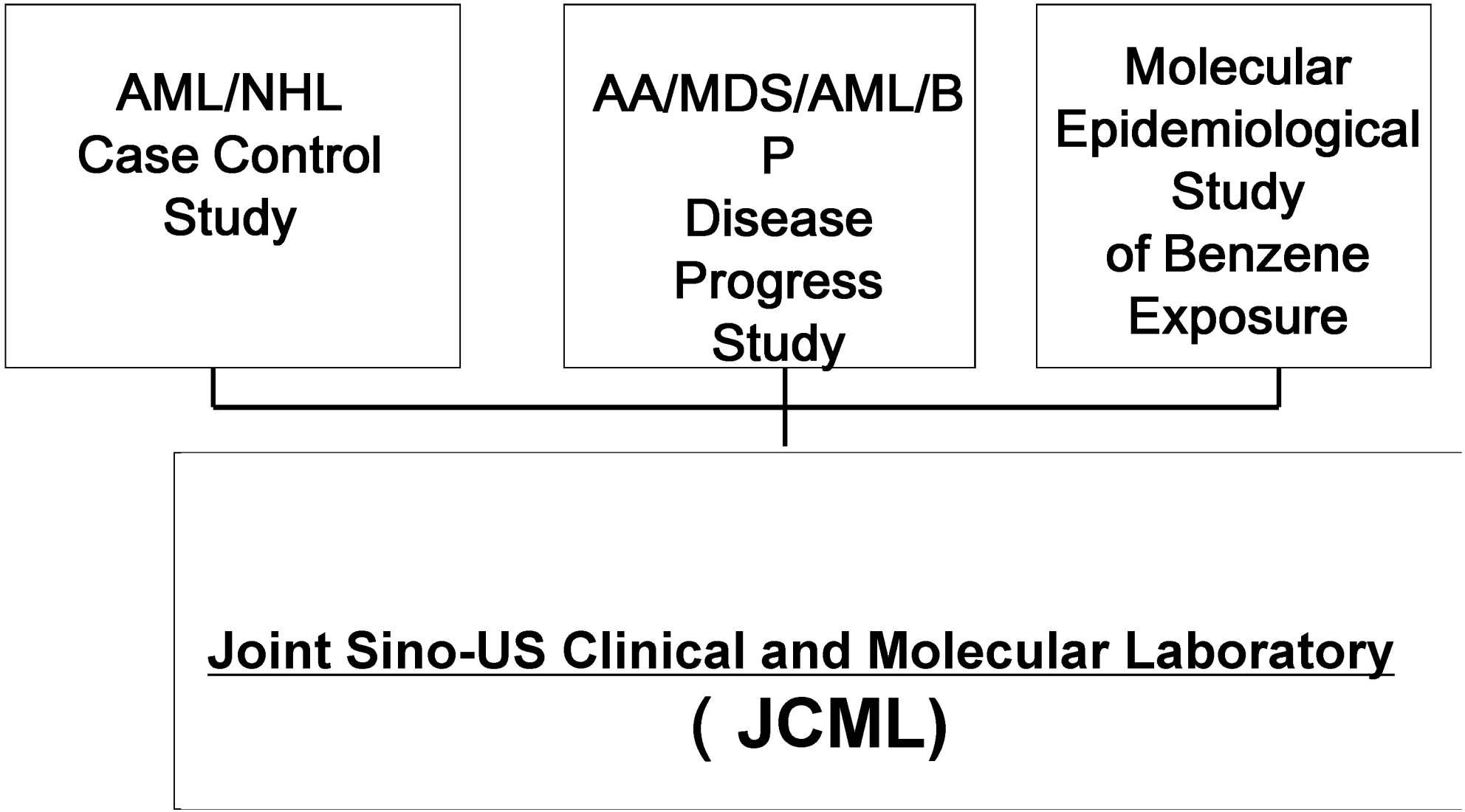
Current Science

- No definitive epidemiological evidence to define a threshold
- NCI and AIP studies conflict with earlier studies by associating benzene exposure with non-AML cancers
- Disease classification clarified
- SHS designed to qualitatively and quantitatively address these issues

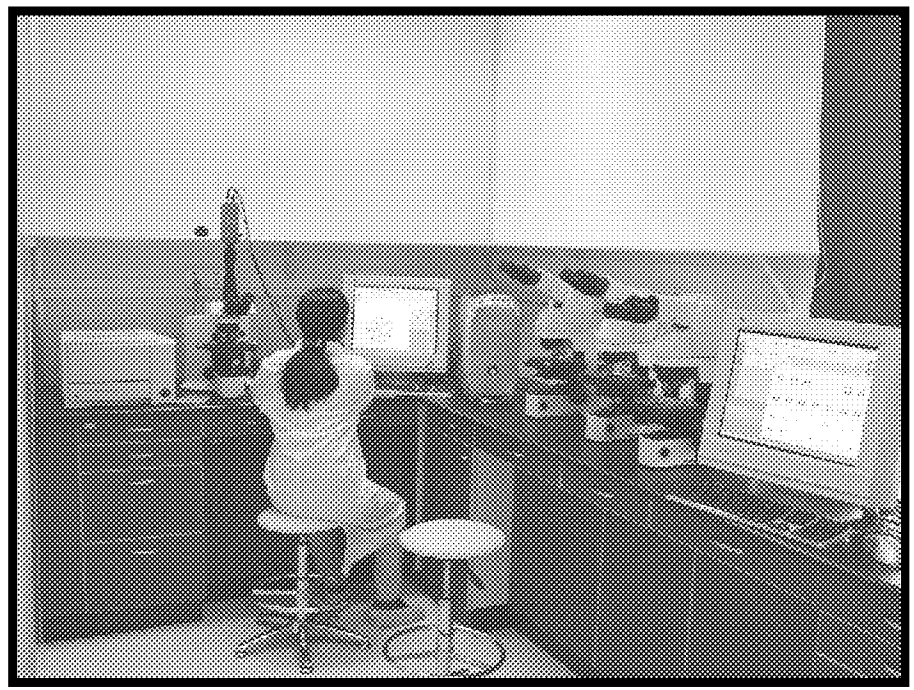
Shanghai Health Study Purpose

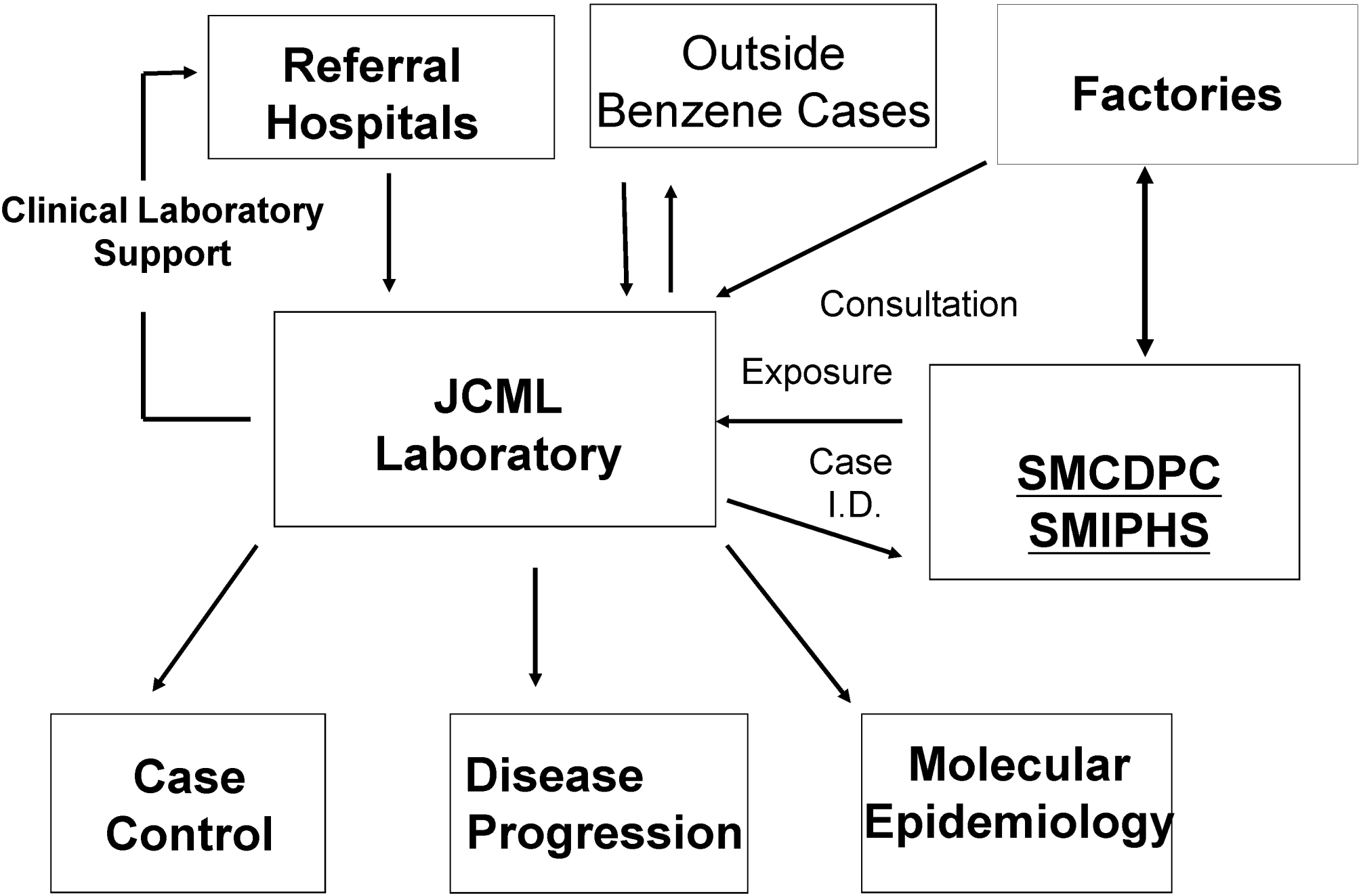
- To gain a quantifiable understanding of the relationship between benzene exposure and potential associated cancer risks
  - Researchers using cutting-edge technologies to advance the understanding of benzene-induced disease

Health Effect Study of Benzene in Shanghai



Sino-U.S. Joint Clinical and Molecular Laboratory




Referral Hospitals
Outside Benzene Cases
Factories
Clinical Laboratory Support
Consultation
JCML Laboratory
Exposure
Case I.D.
SMCDPC SMIPHS
Case Control
Disease Progression
Molecular Epidemiology

SHS Elements

- Case Control Study
- Disease Progression Study
- Molecular Epidemiology
- Quality Science
- Scientific Review Panels
- Current Status
- Scientific and Ethical Reviews
- Projected Timeline

Specific Study Goals

- Understand relationship, if any, between benzene exposure and development of specific hematopoietic diseases: AA, MDS, AML and NHL
  - Causation of specific diseases/subtypes
  - Mechanism of disease progression
  - Dose-response relationships
  - Identification of cofactors and confounders
  - Identification of biomarkers of exposure and disease progression

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 to 5 years to obtain 450 AML and 450 NHL patients into study
- Improved exposure assessment based on historical and concurrent workplace monitoring and questionnaire

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

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

Quality Science

- Protocols approved by external Institutional Review Boards (IRB's)
  - Govern use of human subjects
  - U.S. and China independently
- Shanghai Health Study panels
  - International Ethics Expert Panel
  - International Scientific Expert Panel
    - 10 members
    - 6 scientific disciplines
  - Involved during entire project

Shanghai Health Study

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

SHS Projected Timeline

- Questionnaire development, pilot testing in progress, 2002
- Key laboratory personnel trained, 2002
- Laboratory complete, 2003
- Laboratory opening, summer 2003
- Case recruitment began – 4th quarter, 2003
  - 1600 benzene exposed workers, 400 controls
  - Time necessary to identify qualified patients
  - Length of study may be extended if required
- Research, analysis expected 2003-2007
- Results published as studies completed

Sino-U.S. Joint Clinical and Molecular Laboratory (JCML)

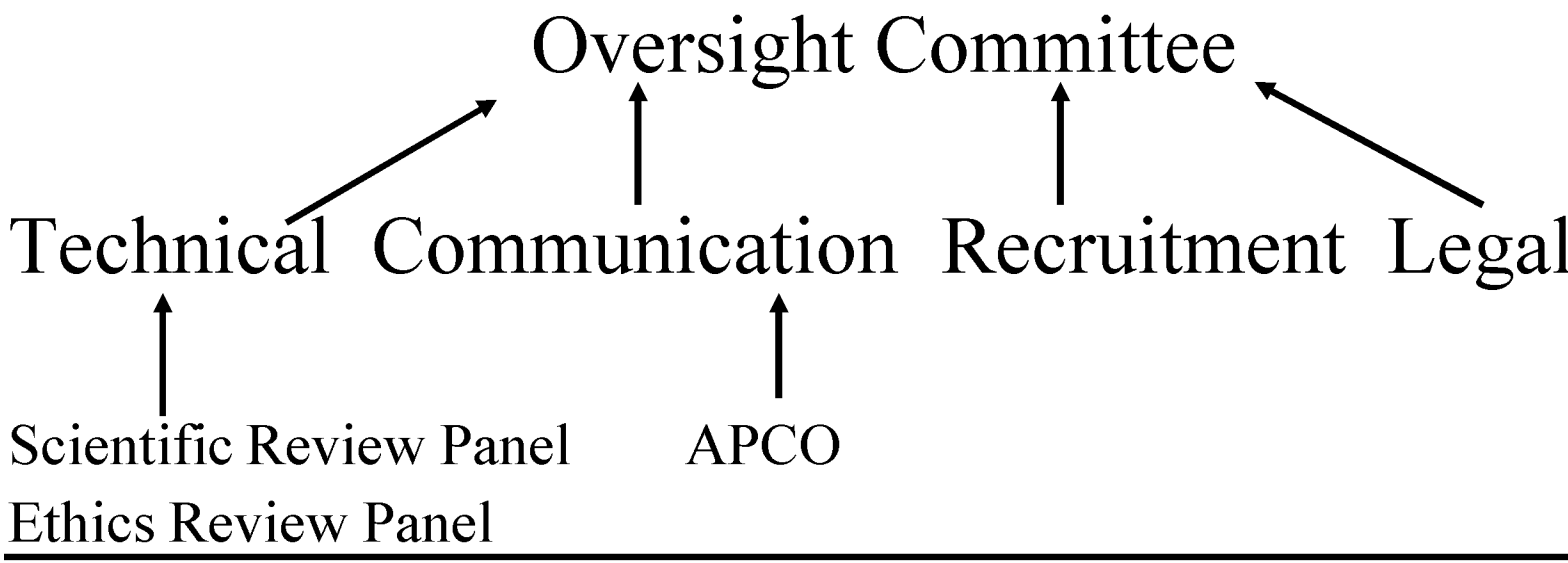
- State-of-the-art laboratory constructed on Fudan University campus
  - Built according to international standards
  - Lab will support the project, Shanghai medical community and remain at Fudan
- Technology transfers
  - Chinese staff receiving training at University of Colorado
  - U.S. researchers working with Chinese colleagues and government officials on methodologies, questionnaires, processes, etc.

Who is Sponsoring the SHS?

- 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

Sponsor infrastructure:
Shanghai Health Study Consortium

Organization



API Administrative Support

Shell participation

- Shell currently holding consortium leadership positions:
  - Patsy Clegg - consortium oversight committee Chair
  - Stuart Cagen - technical committee Vice-Chair and Chair of finance committee
  - Shan Tsai - adjunct professor, Fudan University
  - Sarah Colletti/Lauren Iannarone, communications committee

Shanghai Health Study
Shell intentions for project and outreach

- Shell intentions to be 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.

Current challenges

- Budget
- Exposure assessment
- Sustainability of the lab (JCML)

Shanghai Health Study

- Budget (approved November 2003): $ 21.08 M (Shell portion: $ 4.2 M)
- Supplemental funding request (November 2004): $ 3.3M (Shell portion not yet estimated)
  - Not currently approved by consortium
  - Due in part to initial study delays (eg., SARS in China)
  - Due in part to unexpected difficulties in program management via Shanghai partners, including limited access to locations with higher benzene exposures.

Shanghai Health Study

- Exposure assessment difficulties related to the level of active participation of Shanghai partners and more difficult than expected historical occupational data base.

- Exposure assessment issues possibly optimized but not solved with supplemental funding.

Shanghai Health Study

- Laboratory (JCML) sustainability beyond the study is currently a SHS sponsor consortium issue:
  - Sponsor consortium favors efforts to maintain the laboratory.
  - Laboratory brings a unique and important resource to the Shanghai medical community.
  - Financial sustainability of the laboratory is primarily the responsibility of the current owner (Fudan University).