

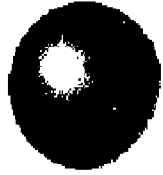
The Shanghai Health Study

Patsy Clegg

Chair, Oversight Committee

Shell Chemicals LP

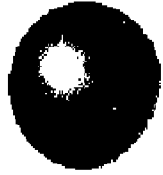
June 22, 2005



What is the Shanghai Health Study?

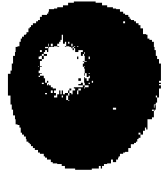
- ⊕ A long-term clinical study to investigate the potential causes and development of lympho-hematopoietic diseases (diseases of the lymphoid organs, blood and bone marrow) as related to benzene

- ⊕ A project of
 - ❑ Fudan University Medical Center - Shanghai, China
 - ❑ University of Colorado Health Sciences Center
 - ❑ Applied Health Sciences - an independent U.S. research firm
 - ❑ Chinese public health agencies
 - ❑ Shanghai hospitals



Path to developing the study:

- ⊕ Pre-97: Benzene exposure associated with AML
- ⊕ 97: NCI published conclusions from China study that:
 - AML develops at exposures lower than previously known – no threshold observed
 - Benzene is associated with NHL
- ⊕ 98-00: NCI Methodology criticized
Feasibility studies in Shanghai
- ⊕ 01: Australian Institute of Petroleum's (AIP)
Health Watch Study
 - Association with all leukemias, including chronic lymphocytic leukemia
 - No association with NHL or multiple myeloma
- ⊕ 01: Benzene Health Research Consortium formed to:
 - do a study to test conclusions
 - address questions of disease progression and biomarkers



The Shanghai Health Study is 3 studies

1. Case Control Study

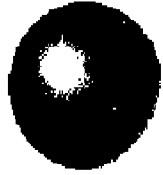
Traditional, prospective epidemiology study to determine risk of AML, NHL among benzene exposed workers
- 450 AML and 450 NHL patients into study

2. Disease Progression Study

Prospective study on relationship of non-cancer bone marrow disease and benzene induced AML

3. Molecular Epidemiology Study

Prospective study seeking to establish quantitative relationship between exposure and effect



The Shanghai Health Study

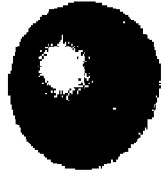
1. Case Control Study - Update

Traditional, prospective epidemiology study to determine risk of AML, NHL among benzene exposed workers

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As of YE04:

- Disease recruitment on track

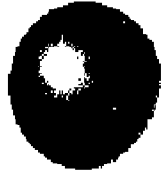


The Shanghai Health Study

2. Disease Progression Study - Update

Prospective study on relationship of non-cancer bone marrow disease and benzene induced AML

- Unique profile of MDS (myelodysplastic syndrome) identified in high-benzene exposed workers
 - Characterized as BIMDS (benzene-induced myelodysplastic syndrome)
 - MDS subtype profile established
 - Suggests that immune parameters have a much larger influence than originally thought
 - Both BIMDS and MDS-subtyping will appear as manuscripts

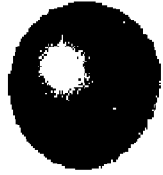


The Shanghai Health Study

3. Molecular Epidemiology Study - Update

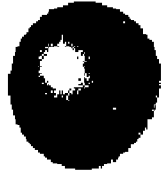
Prospective study seeking to establish quantitative relationship between exposure and effect

- Have successfully recruited several factories
- Records for over 1000 cases have been abstracted



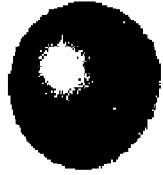
Uniqueness of Shanghai Study

- ⊕ Prospective research
 - ❏ Patients at participating hospitals suspected of having a lymphoid, blood or bone marrow disease are referred to the SHS
 - ❏ Patients' environmental exposures and family histories are recorded
 - ❏ Patient disease progression followed at supporting hospitals



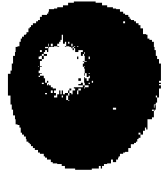
Uniqueness of Shanghai Study

- ✦ Study examines primary diagnostic and medical data in real time
- ✦ State-owned databases document worker exposure readings from some jobs/locations



Why Shanghai?

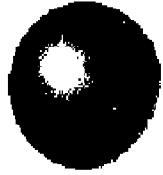
- ⊕ Benzene related health effects are #2 in reported chronic occupational health hazards in China in 2001 (*Source: Ministry of Public Health*)
- ⊕ Large range of exposure levels from a variety of occupational sources
- ⊕ Regulatory authorities interest in improving benzene exposure regulation and enforcement



Quality, Independent Science

- ⊕ All protocols reviewed and approved by external Institutional Review Boards (IRB's)
 - ❏ Govern use of human subjects
 - ❏ U.S. and China independently

- ⊕ Shanghai Health Study independent review panels
 - ❏ International Ethics Review Panel
 - 4 members – 1 each from China & Europe, and 2 US
 - ❏ International Scientific Review Panel
 - 12 members
 - 6 scientific disciplines
 - ❏ Involved during entire project

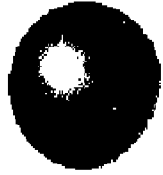


Benzene Health Research Consortium

Sponsoring Companies

- BP
- ChevronTexaco
- ConocoPhillips
- ExxonMobil
- Shell Chemical LP

- Marathon/Ashland providing additional support



Benzene Health Research Consortium

Organization

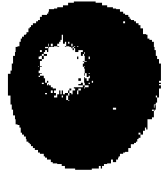
Oversight Committee



Technical/Budget Communication

Scientific Review Panel
Ethics Review Panel

API Administrative Support



Shanghai Health Study

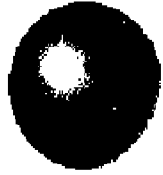
Study Participants

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
31 area Shanghai hospitals
Shanghai Municipal Center for Disease Prevention
Shanghai Hematology Society
Shanghai Pathology Institute for Public Health Supervision
Shanghai Public Health Bureau

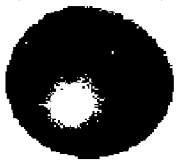
Internal Review Boards U of Colorado, Fudan University, AHS



Shanghai Health Study

Study Time Line

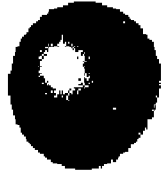
Aug 01	Consortium Formed
3/4Q01	Protocols Reviewed
2002	JCML Lab constructed, equipped at Fudan; technicians trained
3Q03	Began accruing cases
Aug 03	First Annual Meeting
4Q03	Opening Ceremony in Shanghai
Aug 04	Second Annual Meeting
Oct 04	International Benzene Symposium
Nov 05	Third Annual Meeting
2007/8	Report/Publications in scientific journals



Shanghai Health Study

Costs

❖ Budget	\$ 26M
❖ Funding	\$ 26M



Shanghai Health Study

Summary

- ⊕ Opportunity to obtain a better understanding of the mechanism of benzene induced disease in humans.
- ⊕ Potential significant impact on benzene risk assessment.
- ⊕ Highest Quality of Science:
 - employs state-of-the-art biological and epidemiological science
 - represents sound product stewardship
 - exemplifies best practices in research ethics
 - depends upon partnership of industry, governments, academia and public

Slide Notes

Slide 2:

NCI Study:

Benzene associated with AML and Non Hodgkin's Lymphoma (NHL) – first significant association with a non-AML cancer

No threshold observed (effects observed in lowest exposure group of 10 ppm or less)

Australian Health Watch

Australian Institute of Petroleum's (AIP) Health Watch Study: Case-control study published in 2001

Strong association with all leukemias, including chronic lymphocytic leukemia

No association with NHL or multiple myeloma

Low exposures (<1 – 2 ppm) with no apparent threshold

Significant methodological problems

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Slide 4:

Feasibility studies in Shanghai in 1999 documented

High exposure levels; good records

Sufficient numbers of cases of disease for valid study

Willing scientific collaborators in Shanghai

1.

Traditional epidemiology study to determine risk of AML, NHL among benzene exposed workers

Should identify other causal factors for NHL besides benzene exposure

Estimate 4 years to obtain 450 new AML and 450 new NHL cases

Improved Exposure Assessment based on historical and concurrent workplace monitoring and questionnaire

Slide Notes

2.

Prospective study on relationship of non-cancer bone marrow disease and benzene induced AML

Is benzene induced AML different from spontaneous AML?

Are there unique markers for benzene induced AML?

Questionnaire, interviews, review work histories; examine blood, breath, urine, evaluation of biomarkers of exposure

3.

Prospective study to establish quantitative relationship between exposure and effect

Do benzene exposures as low as 7 ppm (as in NCI study) cause blood effects?

Is there an association of blood effects and genetics

Do biomarkers of exposure accurately reflect workplace exposures?

Healthy workers exposed to varying levels of benzene will participate; extensive lab work including genetic tests will be conducted

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Slide 13:

General Toxicology and Biochemistry

Dr. Jerry M. Rice, (Chair), IARC

Dr. Helmut Greim, Technical University of Munich

Epidemiology Dr. Nancy Mueller (Vice Chair), Harvard School of Public Health

Dr. Harvey Checkoway, University of Washington

Statistics Dr. Howard Rockette, University of Pittsburgh

Industrial Hygiene

Dr. John Cherrie, Aberdeen University, Inst. Of Occ. Medicine

Dr. Robert F. Herrick, Harvard School of Public Health

Slide Notes

Hematology Dr. Richard Larson, University of Chicago Medical School

Dr. Mark Minden, University of Toronto

Genetic Toxicology

Dr. Li Guilan, Chinese Academy of Preventive Medicine

Dr. Richard Albertini, University of Vermont, College of Medicine

Ethics Review Panel

Dr. Baruch Brody (Chair), Baylor College of Medicine

Dr. XuZong-Liang, Fudan University