

The Shanghai Health Study

Patsy Clegg
Chair, Oversight Committee
Shell Chemicals, LP
May 2004

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; University of Colorado Health Sciences Center; Applied Health Sciences - an independent U.S. research firm; Chinese public health agencies; and Shanghai hospitals

Benefits to Industry

- Set science-based standards to protect workers and general population from benzene-induced disease
 - * Mobile source air toxics standards
 - * Water quality standards
 - * Site remediation clean-up standards
- Corporate responsibility and product stewardship

Shanghai Health Study Purpose

- To gain a quantifiable understanding of the relationship between benzene exposure and potential associated cancer risks

Path to developing the study:

- Pre-97: Benzene exposure associated with AML
- 97: NCI published conclusions from China study that:
 - Benzene can cause NHL
 - AML develops at exposures lower than previously known - no threshold observed
- 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
 - answer questions of disease progression and biomarkers

Benzene exposure and cancer

Conclusions from pre-1997 Epidemiology

- Only acute myelogenous leukemia (AML) associated with benzene
 - * No risk at exposures < 1 ppm
 - * Clear risk at exposures > 20 ppm
 - * Insufficient data at 1-20 ppm to assess risk

The Shanghai Health Study

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 to establish quantitative relationship between exposure and effect

Uniqueness of Shanghai Study

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

Uniqueness of Shanghai Study

- Study will be able to examine primary diagnostic and medical data in real time
- First-hand exposure reports are more reliable than second-hand or reconstructed information
- State-owned databases document worker histories

Uniqueness of Shanghai Study

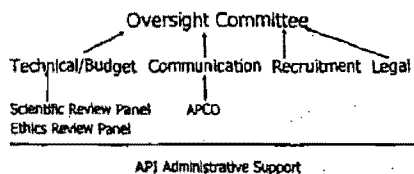
- Robust data set
 - State-maintained benzene exposure and health effects databases documented from 1970s
 - Benzene related health effects are #2 in reported chronic occupational health hazards in China in 2001 (Source: Ministry of Public Health)
 - Large range of exposure levels from a variety of occupational 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
 - International Scientific Review Panel
 - 12 members
 - 6 scientific disciplines
 - Involved during entire project

Redacted

Benzene Health Research Consortium Organization



Shanghai Health Study

Study Participants

Principal Investigators: Dr. Richard Luster, 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
26 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, AMS

Shanghai Health Study

Study Time Line

Aug 01	Consortium Formed
3/4Q01	Protocols Reviewed
2002	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
2007/8	Report

Shanghai Health Study

Costs

Redacted

Shanghai Health Study

Summary

- Opportunity to obtain a better understanding of the mechanism of benzene induced disease in humans.
- Significant impact on benzene risk assessment.
- Highest Quality of Science:
 - employ state-of-the-art biological and epidemiological science
 - represent sound product stewardship
 - exemplify best practices in research ethics
 - depend upon partnership of industry, governments, academia and public

The Shanghai Health Study

Patsy Clegg

Chair, Oversight Committee
Shell Chemicals, LP

May 2004

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; University of Colorado Health Sciences Center; Applied Health Sciences - an independent U.S. research firm; Chinese public health agencies; and Shanghai hospitals

Benefits to Industry

- Set science-based standards to protect workers and general population from benzene-induced disease
 - Mobile source air toxics standards
 - Water quality standards
 - Site remediation clean-up standards
- Corporate responsibility and product stewardship

Shanghai Health Study Purpose

- To gain a quantifiable understanding of the relationship between benzene exposure and potential associated cancer risks

Path to developing the study:

- Pre-97: Benzene exposure associated with AML
- 97: NCI published conclusions from China study that:
 - Benzene can cause NHL
 - AML develops at exposures lower than previously known - no threshold observed
- 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
 - answer questions of disease progression and biomarkers

Benzene exposure and cancer

Conclusions from pre-1997 Epidemiology

- Only acute myelogenous leukemia (AML) associated with benzene
 - No risk at exposures < 1 ppm
 - Clear risk at exposures > 20 ppm
 - Insufficient data at 1-20 ppm to assess risk

The Shanghai Health Study

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 to establish quantitative relationship between exposure and effect

Uniqueness of Shanghai Study

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

Uniqueness of Shanghai Study

- Study will be able to examine primary diagnostic and medical data in real time
- First-hand exposure reports are more reliable than second-hand or reconstructed information
- State-owned databases document worker histories

Uniqueness of Shanghai Study

- Robust data set
 - State-maintained benzene exposure and health effects databases documented from 1970s
 - 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

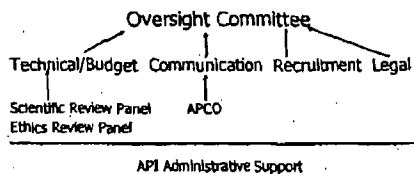
Quality, Independent Science

- 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
 - International Scientific Review Panel
 - 12 members
 - 6 scientific disciplines
 - Involved during entire project

Redacted

Benzene Health Research Consortium

Organization



Shanghai Health Study

Study Participants

Principal Investigators: Dr. Richard Jones, 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
26 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	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
2007/8	Report

Shanghai Health Study

Costs

Redacted

Shanghai Health Study

Summary

- Opportunity to obtain a better understanding of the mechanism of benzene induced disease in humans.
- Significant Impact on benzene risk assessment.
- Highest Quality of Science:
 - employ state-of-the-art biological and epidemiological science
 - represent sound product stewardship
 - exemplify best practices in research ethics
 - depend upon partnership of industry, governments, academia and public

The Shanghai Health Study

Patsy Clegg
Chair, Oversight Committee
Shell Chemicals, LP
May 2004

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; University of Colorado Health Sciences Center; Applied Health Sciences - an independent U.S. research firm; Chinese public health agencies; and Shanghai hospitals

Benefits to Industry

- Set science-based standards to protect workers and general population from benzene-induced disease
 - Mobile source air toxics standards
 - Water quality standards
 - Site remediation clean-up standards
- Corporate responsibility and product stewardship

Shanghai Health Study Purpose

- To gain a quantifiable understanding of the relationship between benzene exposure and potential associated cancer risks

Path to developing the study:

- Pre-97: Benzene exposure associated with AML
- 97: NCI published conclusions from China study that:
 - Benzene can cause NHL
 - AML develops at exposures lower than previously known - no threshold observed
- 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
 - answer questions of disease progression and biomarkers

Benzene exposure and cancer *Conclusions from pre-1997 Epidemiology*

- Only acute myelogenous leukemia (AML) associated with benzene
 - No risk at exposures < 1 ppm
 - Clear risk at exposures > 20 ppm
 - Insufficient data at 1-20 ppm to assess risk

The Shanghai Health Study

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 to establish quantitative relationship between exposure and effect

Uniqueness of Shanghai Study

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

Uniqueness of Shanghai Study

- Study will be able to examine primary diagnostic and medical data in real time
- First-hand exposure reports are more reliable than second-hand or reconstructed information
- State-owned databases document worker histories

Uniqueness of Shanghai Study

- **Robust data set**
 - State-maintained benzene exposure and health effects databases documented from 1970s
 - 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

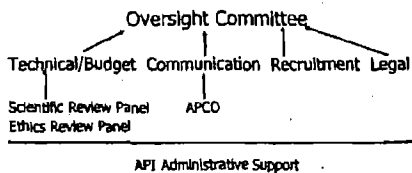
Quality, Independent Science

- 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
 - International Scientific Review Panel
 - 12 members
 - 6 scientific disciplines
 - Involved during entire project

Redacted

Benzene Health Research Consortium

Organization



Shanghai Health Study

Study Participants

Principal Investigators: Dr. Richard Isaac, U of Colorado Health Sciences Center
Dr. Otto Wong, Applied Health Sciences
Dr. Fu Hua, Fudan University

Collaborators: Excerpt Biomedical Sciences

Chinese Participants: Fudan University School of Medicine
26 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	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
2007/8	Report

Shanghai Health Study

Costs

Redacted

Shanghai Health Study

Summary

- Opportunity to obtain a better understanding of the mechanism of benzene induced disease in humans.
- Significant impact on benzene risk assessment.
- Highest Quality of Science:
 - employ state-of-the-art biological and epidemiological science
 - represent sound product stewardship
 - exemplify best practices in research ethics
 - depend upon partnership of industry, governments, academia and public

The Shanghai Health Study

Patsy Clegg
Chair, Oversight Committee
Shell Chemicals, LP
May 2004

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; University of Colorado Health Sciences Center; Applied Health Sciences - an independent U.S. research firm; Chinese public health agencies; and Shanghai hospitals

Benefits to Industry

- Set science-based standards to protect workers and general population from benzene-induced disease
 - Mobile source air toxics standards
 - Water quality standards
 - Site remediation clean-up standards
- Corporate responsibility and product stewardship

Shanghai Health Study Purpose

- To gain a quantifiable understanding of the relationship between benzene exposure and potential associated cancer risks

Path to developing the study:

- Pre-97: Benzene exposure associated with AML
- 97: NCI published conclusions from China study that:
 - Benzene can cause NHL
 - AML develops at exposures lower than previously known - no threshold observed
- 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
 - answer questions of disease progression and biomarkers

Benzene exposure and cancer

Conclusions from pre-1997 Epidemiology

- Only acute myelogenous leukemia (AML) associated with benzene
 - No risk at exposures < 1 ppm
 - Clear risk at exposures > 20 ppm
 - Insufficient data at 1-20 ppm to assess risk

The Shanghai Health Study

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 to establish quantitative relationship between exposure and effect

Uniqueness of Shanghai Study

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

Uniqueness of Shanghai Study

- Study will be able to examine primary diagnostic and medical data in real time
- First-hand exposure reports are more reliable than second-hand or reconstructed information
- State-owned databases document worker histories

Uniqueness of Shanghai Study

- **Robust data set**
 - State-maintained benzene exposure and health effects databases documented from 1970s
 - 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

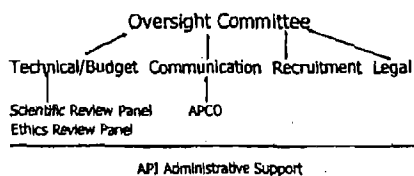
Quality, Independent Science

- 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
 - International Scientific Review Panel
 - 12 members
 - 6 scientific disciplines
 - Involved during entire project

Redacted

Benzene Health Research Consortium

Organization



Shanghai Health Study

Study Participants

Principal Investigators: Dr. Richard Jross, U of Colorado Health Sciences Center
Dr. Otto Wong, Applied Health Sciences
Dr. Fu Hua, Fudan University

Collaborators: Excerpta Biomedical Sciences

Chinese Participants: Fudan University School of Medicine
26 urban 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	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
2007/8	Report

Shanghai Health Study

Costs

Redacted

Shanghai Health Study

Summary

- Opportunity to obtain a better understanding of the mechanism of benzene induced disease in humans.
- Significant impact on benzene risk assessment.
- Highest Quality of Science:
 - employ state-of-the-art biological and epidemiological science
 - represent sound product stewardship
 - exemplify best practices in research ethics
 - depend upon partnership of industry, governments, academia and public

The Shanghai Health Study

Patsy Clegg

Chair, Oversight Committee
Shell Chemicals, LP

May 2004

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; University of Colorado Health Sciences Center; Applied Health Sciences - an independent U.S. research firm; Chinese public health agencies; and Shanghai hospitals

Benefits to Industry

- Set science-based standards to protect workers and general population from benzene-induced disease
 - Mobile source air toxics standards
 - Water quality standards
 - Site remediation clean-up standards
- Corporate responsibility and product stewardship

Shanghai Health Study Purpose

- To gain a quantifiable understanding of the relationship between benzene exposure and potential associated cancer risks

Path to developing the study:

- Pre-97: Benzene exposure associated with AML
- 97: NCI published conclusions from China study that:
 - Benzene can cause NHL
 - AML develops at exposures lower than previously known - no threshold observed
- 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
 - answer questions of disease progression and biomarkers

Benzene exposure and cancer

Conclusions from pre-1997 Epidemiology

- Only acute myelogenous leukemia (AML) associated with benzene
 - No risk at exposures < 1 ppm
 - Clear risk at exposures > 20 ppm
 - Insufficient data at 1-20 ppm to assess risk

The Shanghai Health Study

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 to establish quantitative relationship between exposure and effect

Uniqueness of Shanghai Study

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

Uniqueness of Shanghai Study

- Study will be able to examine primary diagnostic and medical data in real time
- First-hand exposure reports are more reliable than second-hand or reconstructed information
- State-owned databases document worker histories

Uniqueness of Shanghai Study

- Robust data set
 - State-maintained benzene exposure and health effects databases documented from 1970s
 - 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

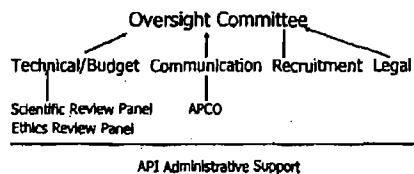
Quality, Independent Science

- 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
 - International Scientific Review Panel
 - 12 members
 - 6 scientific disciplines
 - Involved during entire project

Redacted

Benzene Health Research Consortium

Organization



Shanghai Health Study

Study Participants

Principal Investigators: Dr. Richard Irwin, 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
26 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	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
2007/8	Report

Shanghai Health Study

Costs

Redacted

Shanghai Health Study

Summary

- Opportunity to obtain a better understanding of the mechanism of benzene induced disease in humans.
- Significant impact on benzene risk assessment.
- Highest Quality of Science:
 - employ state-of-the-art biological and epidemiological science
 - represent sound product stewardship
 - exemplify best practices in research ethics
 - depend upon partnership of industry, governments, academia and public