

To: Lorraine Twerdok
Subject: RE: BHRC ACTION REQUESTED - BALLOT for OC CHAIR/Co-chair
Approve.

*Regards,
Patsy*

Patsy Clegg
Product Steward
Shell Chemical LP
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Internet: <http://www.shell.com/chemicals>

-----Original Message-----

From: Lorraine Twerdok [mailto:Twerdokl@api.org]
Sent: Friday, January 09, 2004 1:41 PM
To: Benzene OC listserve (E-mail)
Subject: BHRC ACTION REQUESTED - BALLOT for OC CHAIR/Co-chair
Importance: High

To BHRC Oversight Committee:

Don Burnett is rotating off as OC Chair, effective January 15, 2004. Patsy Clegg is willing to move from Co-Chair to Chair, and Brian Doll is willing to assume the Co-Chair position.

Please indicate by return email your vote (approve/reject) Patsy and Brian as Oversight Committee Chair and Co-Chair, respectively. Ballots are due next **Wednesday, January 14**.

Also, for your information, Lynn Russo and Patrick Beatty will continue on as Chair of the Communications and Technical Committees, respectively. And as approved in August, 2003, Stuart Cagen will serve as Vice Chair of the Technical Committee and Chair the Technical Committee Budget Workgroup.

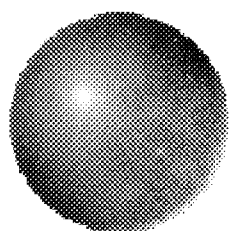
Thank you for your prompt response to this email.

*Regards,
Lorraine*

Lorraine E. Twerdok, Ph.D., DABT
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Regulatory and Scientific Affairs
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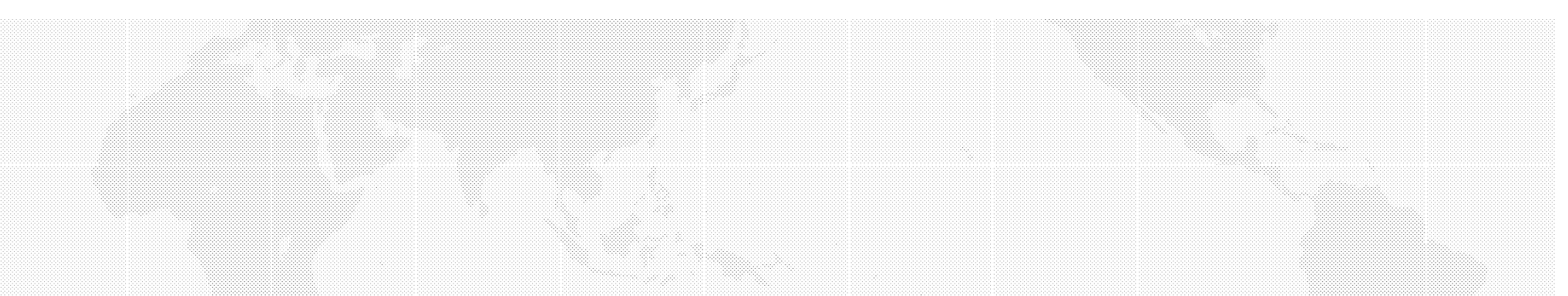
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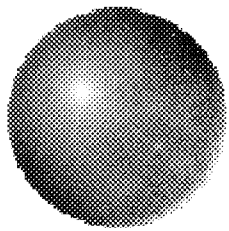
The Shanghai Health Study

Benzene Health Research Consortium

www.shanghaihealthstudy.org

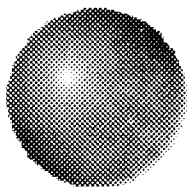


Presentation Topics



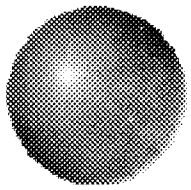
- ⊗ Shanghai Health Study Overview
- ⊗ Shanghai Solutions
- ⊗ Benzene Basics
- ⊗ Current Benzene Science
- ⊗ Shanghai Health Study Elements
- ⊗ Shanghai Health Study Sponsors
- ⊗ Shanghai Health Study Funding Structure
- ⊗ Terms, Sources and Resources

Final 11/22/02



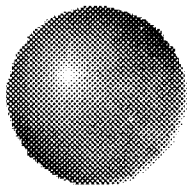
What is the Shanghai Health Study?

- A long-term clinical study to investigate the potential cause and development of lymphohematopoietic diseases (diseases of the lymphoid organs, blood and bone marrow)
- A project of Fudan University Medical Center; Colorado Health Sciences Center, University of Colorado; Applied Health Sciences - an independent U.S. research firm; Chinese public health agencies; and Shanghai hospitals



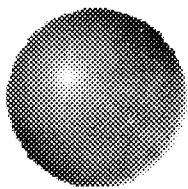
Shanghai Health Study Purpose

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



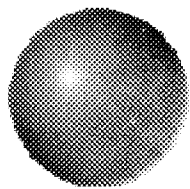
Benzene Is . . .

- ❖ A chemical found primarily in solvents, glues and petroleum fuels
- ❖ A recognized human carcinogen
 - ❑ Acute Myelogenous Leukemia (AML)
- ❖ Tightly regulated although worldwide standards vary
- ❖ What is currently not known:
 - ❑ benzene's impact on a molecular level;
 - ❑ if a safe level of exposure exists (threshold effect);
 - ❑ whether and how associated cancers or other related diseases may be caused; and
 - ❑ the role genetic susceptibility may play in adding to existing knowledge



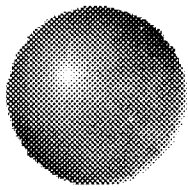
Benzene Toxicity

- ◆ The effects of exposure to any hazardous substance depend on:
 - dose,
 - duration,
 - how exposure occurs,
 - personal traits and habits,
 - genetic susceptibility
- ◆ Co-exposure to other chemicals can also influence toxicity



Why is Understanding Benzene Important?

- ⊗ Benzene exposure is universal
- ⊗ Advancing current scientific understanding of benzene exposure would be a significant contribution to health and worker safety
- ⊗ Understanding health effects of low-level benzene exposures would improve benzene risk assessments



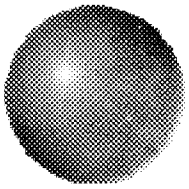
Why Shanghai?

❖ Unique Study Environment

- ❑ Databases documenting exposure
- ❑ Exposure across industries
- ❑ Range of exposure levels

❖ Committed Collaboration

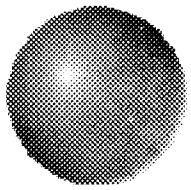
- ❑ Chinese government
- ❑ University and hospital based researchers
- ❑ Community hospitals
- ❑ Shanghai Municipal Center for Disease Control and Prevention
- ❑ Institute for Public Health Supervision



Unparalleled Collaboration

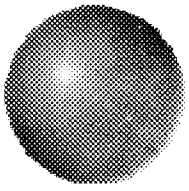
• “This study is an enormous collaborative effort, unlike anything American and Chinese researchers have ever done.”

- Dr. Richard Irons, PhD, SHS principal investigator, professor and director of the University of Colorado’s Molecular Toxicology and Environmental Health Sciences Program



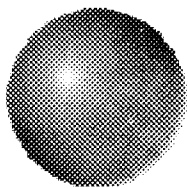
Shanghai Health Study Background

- Most environmental and occupational standards for benzene are based on mathematical extrapolations of cancer risk from high-level exposures to environmental concentrations
- These extrapolations are based on almost no knowledge of how benzene functions at a molecular level in humans



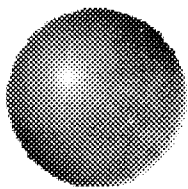
Slides: Histology/Biology

- Optional insert: slide examples of histological tissues and biological tissues



Difficulties in Past Benzene Research

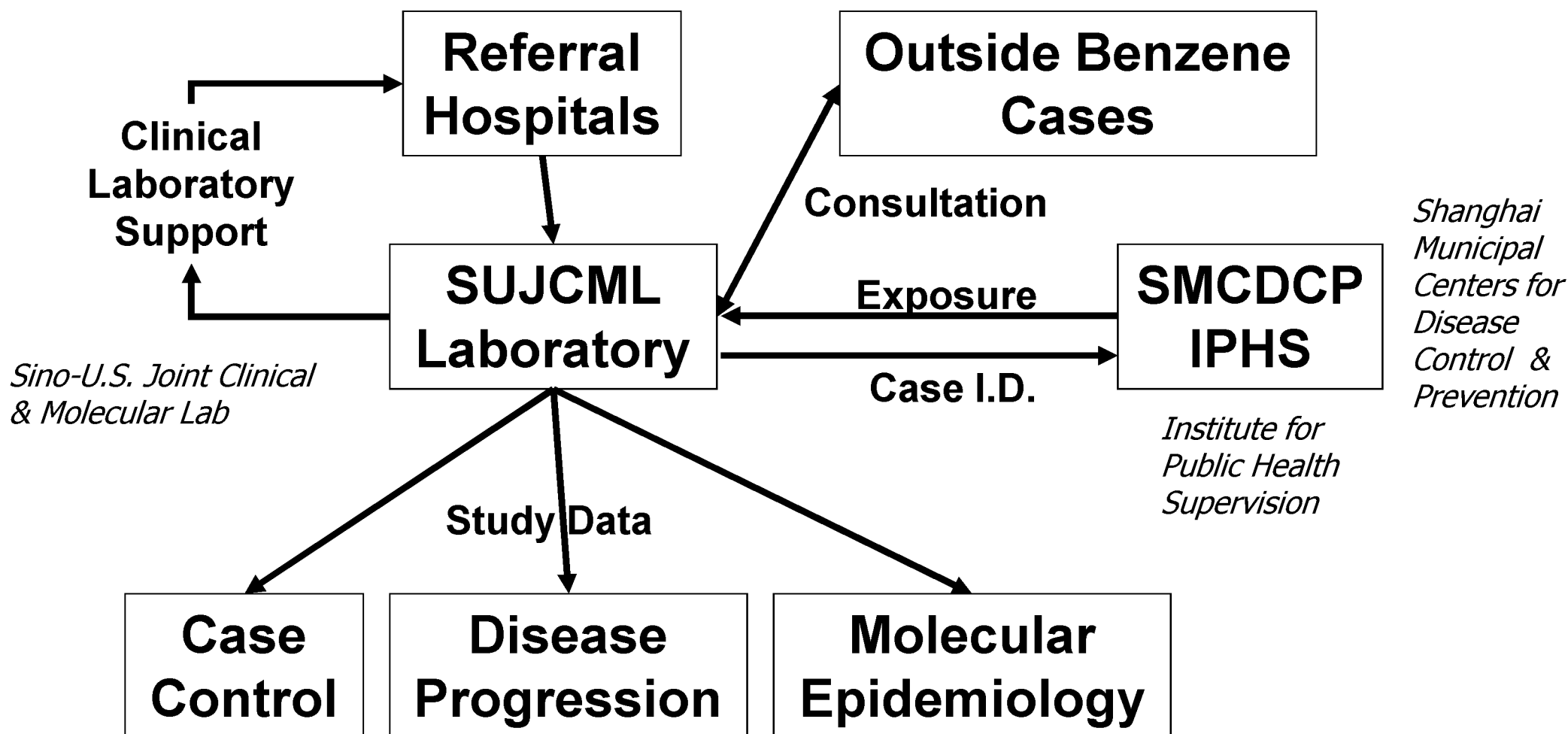
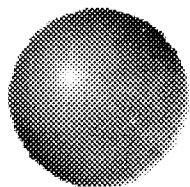
- ⊗ Animal models do not replicate human benzene-related diseases
- ⊗ Retrospective research
 - ▣ Review case files of people who have died
 - ▣ Rely on inexact diagnoses
 - ▣ Accuracy of reconstructed exposure data
 - ▣ Guess at lifestyle and dietary habits
- ⊗ Data difficult to isolate
 - ▣ Exposure limits; cultural/political issues

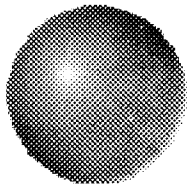


How is the SHS Distinct?

❖ Prospective research

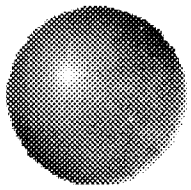
- ❖ Patients at participating hospitals suspected of having a lymphoid, blood or bone marrow disease will be referred to the SHS
- ❖ Patients' diets, environmental exposures and family histories will be recorded
- ❖ Patient disease progression followed at supporting hospitals





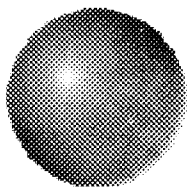
How is the SHS Distinct?

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



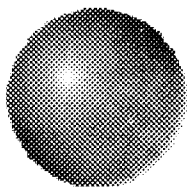
Shanghai Health Study Background

- The SHS is designed to provide mechanistic data on AML development in humans
- A more reliable basis for the extrapolation of leukemia risk associated with low-level benzene exposure can be made with that information



Shanghai Solutions

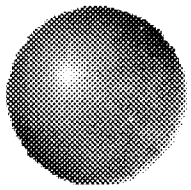
- ❖ Unique Study Environment
- ❖ Unparalleled Collaboration
- ❖ Shanghai Health Study Genesis
- ❖ Rare Opportunity
- ❖ Shanghai Health Study Partners
- ❖ Shanghai Health Study Hospital Partners
- ❖ Sino-U.S. Joint Clinical & Molecular Lab



Unique Study Environment: Shanghai

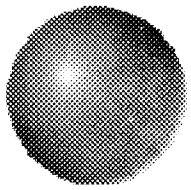
● Robust data set

- 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



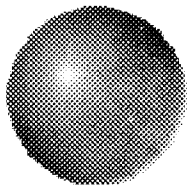
Unique Study Environment: Shanghai

- ⊗ China interested in scientific basis for improved worker-safety regulations
 - ▣ Chinese occupational standards based on measurable human health effects
- ⊗ Chinese Occupational Diseases Protection Law (*effective May 1, 2002*)
 - ▣ Increases worker protections
 - ▣ Specifies company mandates for workers afflicted with health problems due to occupational exposures
 - ▣ Benzene receiving additional scrutiny



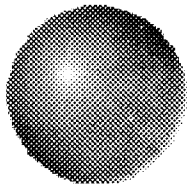
Unique Study Environment: Shanghai

- ❖ High interest in collaborating on research
 - ❖ Technology transfers
 - ❖ International health standards
 - ❖ State-of-the-art lab/ equipment
 - ❖ Shanghai hematology/pathology communities support and expertise
 - ❖ Strong research program supports China's regulatory understanding and objectives



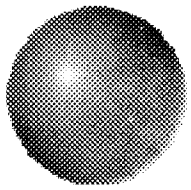
Unique Study Environment: Shanghai

- ⊗ Fudan University Medical Center
 - ⊠ Research partnership
- ⊗ Community participation
 - ⊠ 16 hospitals will refer patients to the SHS
 - ⊠ Shanghai Municipal Center for Disease Prevention and Control
 - ⊠ Shanghai Institute for Public Health and Supervision



Unparalleled Collaboration

- Insert quote from Fu Hua or Fudan University Official



SHS Genesis

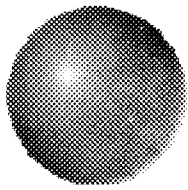
● NCI/CAPM study

- Retrospective study published 1997
- Raised new questions on effects of low-level benzene exposure

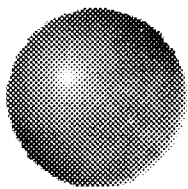
● 1999 Shanghai feasibility assessed

- Respected scientific collaborators
- Well-documented occupational exposure levels across variety of industries
- Detailed health and historical records
- Sufficient incidences of disease
- Conclusion: full study feasible

● Three distinct, highly integrated studies designed

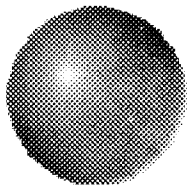


- Insert quote from Dr. Wong re:
opportunity to conduct rare research
in China



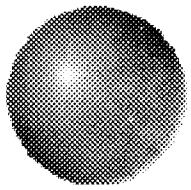
Rare Opportunity

- Unique data set
- Technological advances
- Earlier, consistent detection and diagnosis of leukemias and related diseases in Shanghai
- Identification of more sensitive benzene exposure biological markers



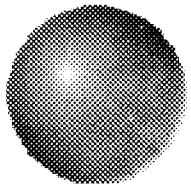
Shanghai Partners

- ❖ Fudan University Medical Center
- ❖ Institute for Public Health Supervision
Shanghai Public Health Bureau
- ❖ Shanghai Hematology Society
- ❖ Shanghai Pathology Society
- ❖ Shanghai Municipal Centers for Disease
Control and Prevention



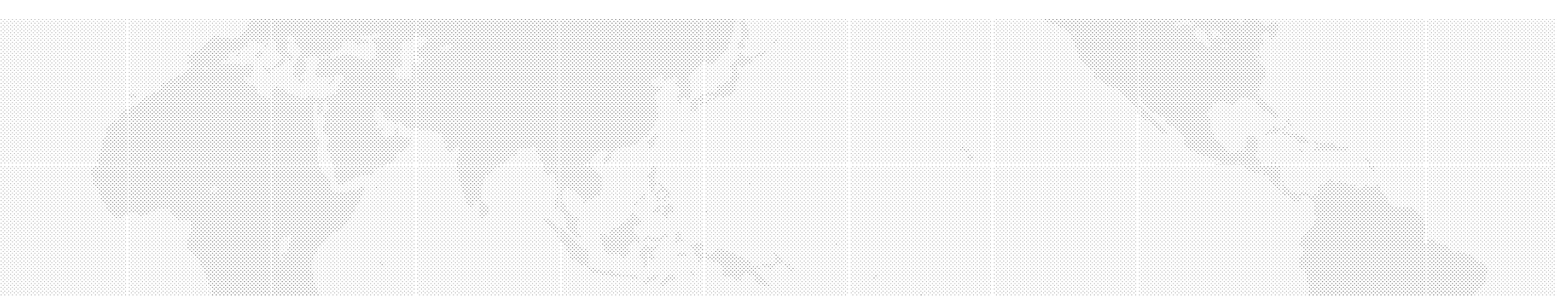
SHS Hospital Partners

- Changhai Hospital
- Changning Central District Hospital
- Changzheng Hospital
- First Municipal Hospital
- Fifth Municipal Hospital
- Sixth Municipal Hospital
- Ninth Municipal Hospital
- Huadong Hospital
- Huangpu Central District Hospital
- Huashan Hospital
- Renji Hospital
- Shuguang Hospital
- Tielu Hospital
- Tongji Hospital
- Xinhua Hospital
- Zhongshan Hospital

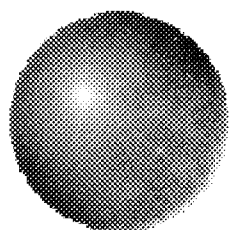


Sino-U.S. Joint Clinical and Molecular Laboratory

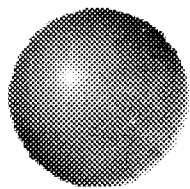
- ◆ Insert pictures of laboratory under construction and when complete
- ◆ Virtual lab tour?



Benzene Basics

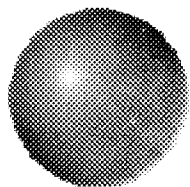


- ⊕ What is Benzene
- ⊕ Benzene Uses



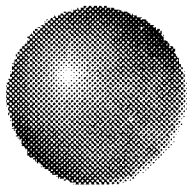
What is Benzene?

- ⊗ A colorless, volatile, flammable liquid with a sweet aromatic odor;
- ⊗ A natural component of many substances including crude oil;
- ⊗ A by-product of combustion;
- ⊗ A chemical building block; and
- ⊗ One of top-20 most-produced U.S. chemicals



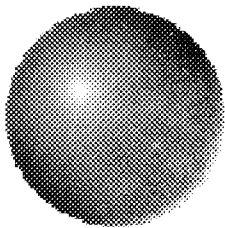
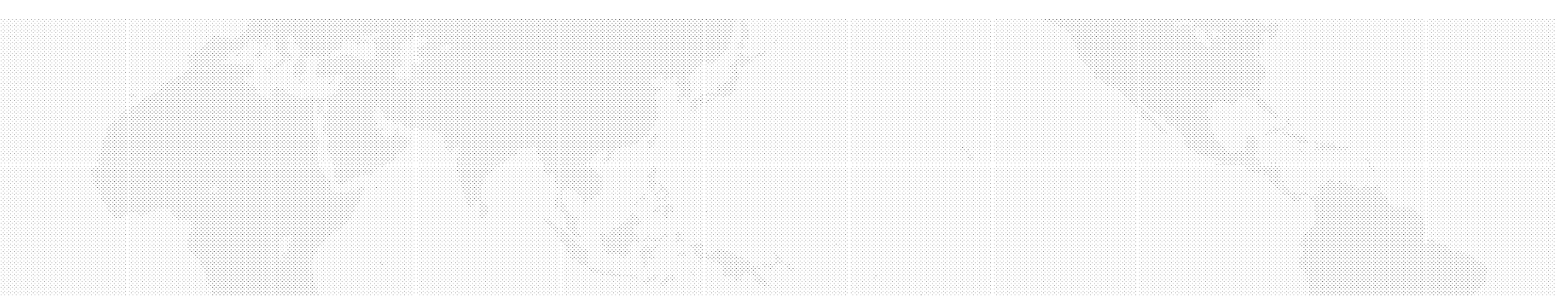
Benzene Uses

- ✿ Benzene is a basic petrochemical building block, widely used in the manufacture of products such as:
 - ✻ Dyes and laundry detergents
 - ✻ Lubricants
 - ✻ Nylon and synthetic fibers (carpet, clothing)
 - ✻ Pharmaceuticals
 - ✻ Pesticides
 - ✻ Plastics and resins
 - ✻ Some types of rubbers (tires)



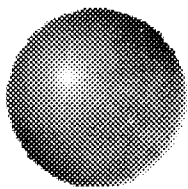
Benzene Uses

- ❖ Element of crude oil; found in small amounts in petroleum products
- ❖ As a chemical building block, is transformed in the manufacturing process
- ❖ Eliminated as an unconverted additive to solvents and adhesives



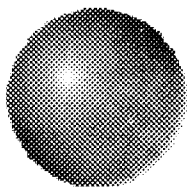
Existing Benzene Knowledge

- ⊕ Conclusions pre-1997
- ⊕ U.S. Regulatory Interpretation
- ⊕ Recent Epidemiological Studies
- ⊕ Challenges
- ⊕ Observations on Existing Science



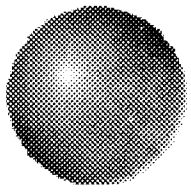
Epidemiology Conclusions pre-1997

- ✦ Acute Myelogenous Leukemia (AML) associated with benzene
 - ▣ No risk at exposures < 1ppm
 - ▣ Clear risk at exposures > 20 ppm
 - ▣ Insufficient data at 1-20 ppm to 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



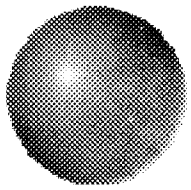
U.S. Regulatory Interpretation

- ⊗ Regulatory decisions based on no-threshold assumption
- ⊗ This assumption does not fit the science with respect to benzene



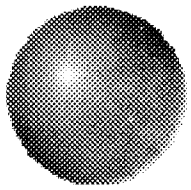
Challenges

- ⊕ Accounting for multiple exposures
- ⊕ Addressing confounding factors
- ⊕ Quality control
- ⊕ Accuracy of diagnosis
- ⊕ Analysis of results



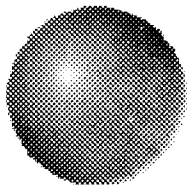
Recent Epidemiological Studies

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



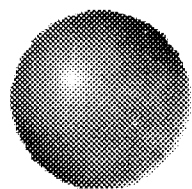
Recent Epidemiological Studies

- ❖ Australian Institute of Petroleum's (AIP) Health Watch Study – case-control study released in 2001
 - ❖ Association with all leukemias, including chronic lymphocytic leukemia
 - ❖ No association with NHL or multiple myeloma



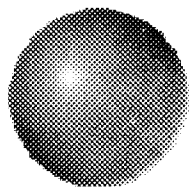
Observations on Current Science

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



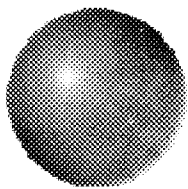
SHS Elements

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



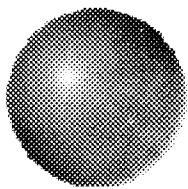
Specific Study Goals

- 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



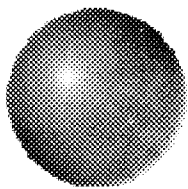
Study #1 - Case Control Study

- ❖ Traditional epidemiology study to determine risk of AML, and potential NHL among benzene exposed workers
- ❖ Data collection allow analysis of other causal factors for NHL besides potential benzene exposure
- ❖ Estimate 4 to 5 years to obtain 450 new AML and 450 new NHL cases
- ❖ Improved exposure assessment based on historical and concurrent workplace monitoring and questionnaire



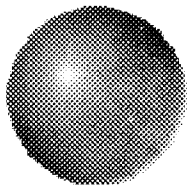
Study #2 - Disease Progression

- 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



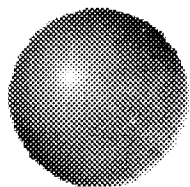
Study #3 – Molecular Epidemiology

- Prospective study to establish quantitative relationship between exposure and effect
 - Do benzene exposures as low as 5-7 ppm (AIP & NCI study) 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



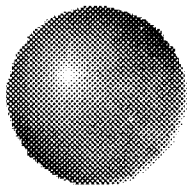
Quality Science

- ❖ 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 panels
 - ❑ International Independent Ethics Expert Panel
 - ❑ International Independent Scientific Expert Panel
 - 12 members
 - 6 scientific disciplines
- ❖ Expert panels will participate during entire course of studies



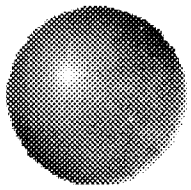
Scientific Review Panels

General Toxicology and Biochemistry	Dr. Jerry M. Rice, (Chair), IARC; Dr. Helmut Greim, Technical U. of Munich
Epidemiology	Dr. Nancy Mueller (Vice Chair), Harvard U., Public Health; Dr. Harvey Checkoway, WA U.
Statistics	Dr. Howard Rockette, U. of Pittsburgh
Industrial Hygiene	Dr. John Cherrie, Aberdeen U., Inst. Of Occ. Medicine; Dr. Robert F. Herrick, Harvard U., Public Health
Hematology	Dr. Richard Larson, U. of Chicago Medical School; Dr. Mark Minden, U. of Toronto
Genetic Toxicology	Dr. Li Guilan, Chinese Academy of Preventive Medicine; Dr. Richard Albertini, U. of VT, College of Medicine
Ethics Review Panel	Dr. Baruch Brody (Chair), Baylor College of Medicine; Dr. Xu Zong-Liang, Fudan University



Current SHS Status

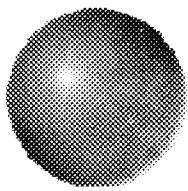
- ❁ State-of-the-art laboratory constructed on Fudan University campus
 - ❁ Sustainable technology transfer an important project design component
 - ❁ Equipment imported from U.S.
 - ❁ Built according to international standards
 - ❁ Lab will support the project, Shanghai medical community and remain at Fudan
- ❁ Technology transfers
 - ❁ Chinese staff receiving training at University of Colorado
 - ❁ U.S. researchers collaborate with Chinese colleagues



Scientific and Ethical Review Status

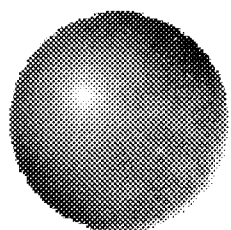
Disease Progression/Molecular Epidemiology

- ❖ Fudan University IRB – final approval Nov 01
- ❖ External International Scientific Review Panel – final approval Jan 02
- ❖ External Ethics Review Panel – final approval Feb 02
- ❖ University of CO IRB – final approval May 02
- ❖ Applied Health Sciences – review pending

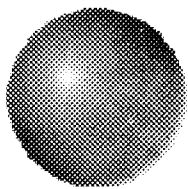


SHS Projected Timeline

- ❖ Questionnaire development, pilot testing in progress, 2002
- ❖ Key laboratory personnel trained, 2002
- ❖ Laboratory complete, early 2003
- ❖ Case recruitment begins – 1st quarter, 2003
 - ❑ 1600 benzene exposed workers, 400 controls
 - ❑ Time necessary to identify qualified patients
 - ❑ Length of study may be extended if required
- ❖ Laboratory opening, spring 2003
- ❖ Research, analysis expected 2003-2007
- ❖ Results published upon project completion

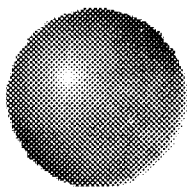


SHS Sponsors



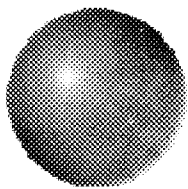
Who is Sponsoring the SHS?

- ❖ A consortium of petroleum and chemical companies concerned about understanding the human health effects of benzene
 - ❑ British Petroleum, ChevronTexaco, ConocoPhillips, ExxonMobil, Shell
 - ❑ Other members being recruited
 - ❑ American Petroleum Institute, project administrator
- ❖ Individual company product stewardship and corporate responsibility programs



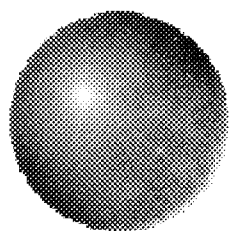
Why Industry Sponsors?

- ⊕ SHS goal to provide an accurate understanding of how benzene works on a molecular level in humans
 - Advanced understanding of benzene-induced disease could lead to development of effective disease prevention strategies
 - Would allow a more finely calibrated assessment of potential health effects
 - Provide best protection for workers and public



Why Industry Sponsors?

- ❁ Worldwide, benzene occupational exposure regulatory standards vary widely
 - ▣ Examples: 0.5ppm in Malaysia; 10ppm in Japan; China in the middle range
 - ▣ American Conference of Governmental Industrial Hygienists recommends 0.5ppm
- ❁ Industry has long sponsored benzene research

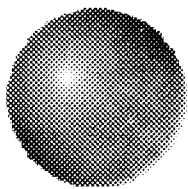


SHS Funding Structure

Final 11/22/02

54

SHELL-MCCLURG-067481

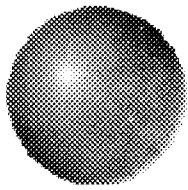


SHS Funding Structure

- ❖ \$22.8 million program total for all costs over 5 years
 - \$16.5 million confirmed as of October 2002
 - Current funding through October Q3 03
- ❖ Costs projected to be highest during first yrs.

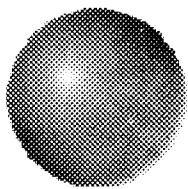
❖ Payment schedule

■ August 2001	15%
■ January 2002	15%
■ August 2002	25%
■ <u>August 2003</u>	<u>15%</u>
■ <i>August 2004</i>	<i>15%</i>
■ <i>August 2005</i>	<i>15%</i>



SHS Funding Structure

- ❖ Funding shares determined by size and sector
- ❖ Formula used to assign 1 to 3 shares
 - Refiners: 1 to 3 shares based on U.S. capacity
 - Chemical companies: 2 shares
 - Other companies: 1 share
- ❖ One share currently equals \$1.5 million



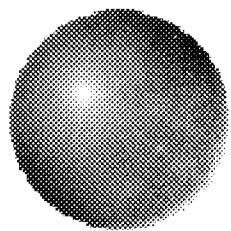
SHS Funding Structure

⊗ Direct costs

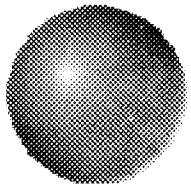
- ⊠ Data collection and analysis with procedures to protect privacy;
- ⊠ Procedures and training for data collection in participating clinics;
- ⊠ Constructing, training, staffing state-of-the-art hematology laboratory;
- ⊠ Laboratory operations for research and clinical tests; and
- ⊠ Operations for 5 years estimated to identify study cases

⊗ Administrative costs

- ⊠ Internal and external communications and coordination;
- ⊠ API project administration, travel; off-site meetings

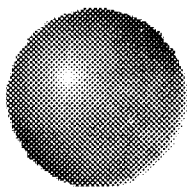


Terms, Sources and Resources



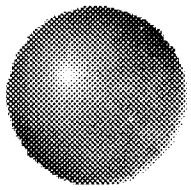
Terminology

- ⊕ AA
- ⊕ AML
- ⊕ Biomarker
- ⊕ Epidemiology
- ⊕ Histology
- ⊕ NHL



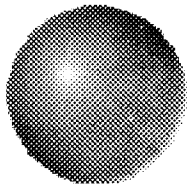
Acronyms

- API – American Petroleum Institute
- AIP – Australia Institute of Petroleum
- IRB – Institutional Review Board
- CAPM – Chinese Academy of Preventive Medicine
- IPHS – Institute for Public Health Supervision (China)
- NCI – National Cancer Institute (U.S.)
- SUJCML – Sino-U.S. Joint Clinical and Molecular Lab
- SMCDPC – Shanghai Municipal Center for Disease Control and Prevention
- USEPA – U.S. Environmental Protection Agency



Sources

- American Council of Government Industrial Hygienists
- Agency for Toxic Substances and Disease Registry ToxFAQs, U.S. Department of Health and Human Services
- American Petroleum Institute
- International Agency for Research on Cancer
- United States Environmental Protection Agency
- University of Colorado Cancer Center, Denver, CO



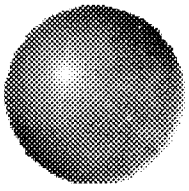
For More Information

❖ Template: Add your and your team's contact information here.

❖ Lorraine Twerdok, BHRC Administrator

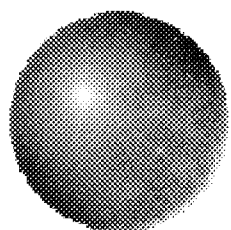
❖ 202.682.8319

❖ Twerdokl@api.org



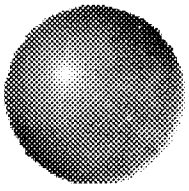
For More Information

- ✦ Patrick Beatty, Chair, Technical Committee
- ✦ Don Burnett, Chair, Oversight Committee
- ✦ Bill Frick
- ✦ Lorraine Twerdok, BHRC Administrator



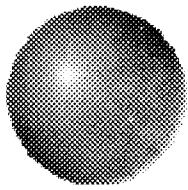
The Shanghai Health Study

Lorraine Twerdok
American Petroleum Institute
twerdokl@api.org



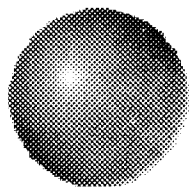
Conclusions from pre-1997 Epidemiology

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



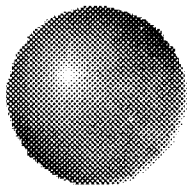
Regulatory Interpretation

- ⊕ Regulatory risk assessment default of linear, no threshold model does not fit the science
- ⊕ Current regulatory decisions imply recognition of a threshold or a no observed adverse effect level (NOAEL)



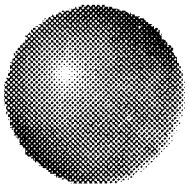
Recent Epidemiological Results

- National Cancer Institute Shanghai Study – published in 1997
 - Benzene associated with AML and Non Hodgkin's Lymphoma (NHL) – first association with a non-AML cancer
 - No threshold observed (effects observed in lowest exposure group of 10 ppm or less)
- NCI Exposure Methods Criticized in published literature



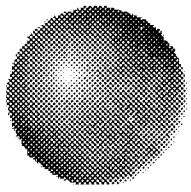
Recent Epidemiological Results

- ❖ 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



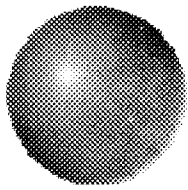
Observations on Current Science

- ❖ No definitive epidemiological evidence to support or refute a threshold
- ❖ NCI and AIP studies conflict with earlier studies by associating benzene exposure with AML and non-AML cancers
- ❖ Effects described at lower doses than previously seen; no apparent threshold



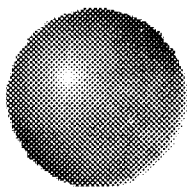
Genesis of Shanghai Health Study

- ⊗ 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
- ⊗ Three closely related studies were designed



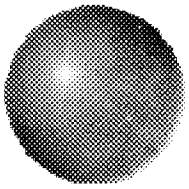
Study #1 - Case Control Study

- ❖ 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



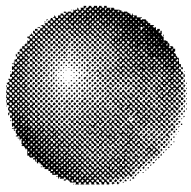
Study #2 - Disease Progression

- ❖ Prospective study on relationship of non-cancer bone marrow disease and benzene induced AML
 - ❖ Is benzene induced AML different from spontaneous AML?
 - ❖ Are there unique markers for benzene induced AML?
- ❖ Questionnaire, interviews, review work histories; examine blood, breath, urine, evaluation of biomarkers of exposure



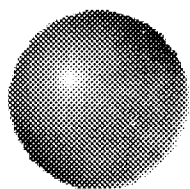
Study #3 – Molecular Epidemiology Study

- ⊗ 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



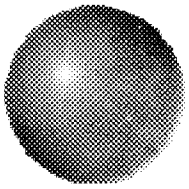
Highest Quality of Science

- ❖ All protocols reviewed and approved by:
 - Use of Human Subjects Committees (IRB's) in US and China
 - International Independent Ethics Expert Panel
 - International Independent Scientific Expert Panel
 - 12 members
 - 6 scientific disciplines
- ❖ Expert Panels will participate during entire course of studies



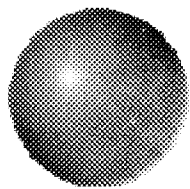
Scientific Review Panels

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
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



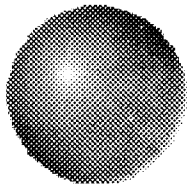
Current Status of Program

- ❖ Consortium of 5 companies have committed \$16.5 million dollars of a \$22.5 million budget for estimated 5 year program
 - BP, ChevronTexaco, Conoco, ExxonMobil, Shell
 - Other members being recruited
- ❖ State-of-the-art science facility is under development in Shanghai
- ❖ Questionnaire development and pilot testing in progress
- ❖ Case recruitment – 1st quarter of 2003



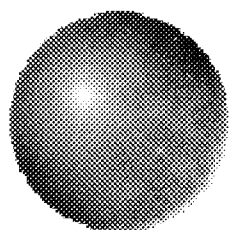
In Summary . . .

- These studies are an opportunity to obtain a better understanding of the mechanism of benzene induced disease in humans.
- Completion of these studies should have a significant impact on benzene risk assessment
- These studies:
 - 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



For More Information

- ✿ Patrick Beatty
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- ✿ Stuart Cagen
szcagen@shell.com
- ✿ Lorraine Twerdok
twerdokl@api.org
- ✿ Bill Frick
frick@api.org



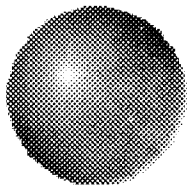
The Shanghai Health Study

Patsy Clegg

Chair, Oversight Committee

Shell Chemicals LP

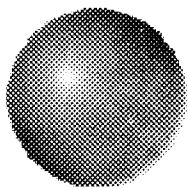
June 2005



What is the Shanghai Health Study?

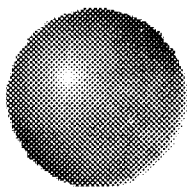
- ◆ A long-term clinical study to investigate the potential causes and development of lympho-hematopoietic diseases (diseases of the lymphoid organs, blood and bone marrow) as related to benzene

- ◆ 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

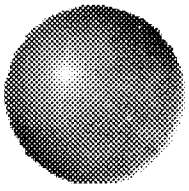
Traditional, prospective epidemiology study to determine risk of AML, NHL among benzene exposed workers
- 450 AML and 450 NHL patients into study

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

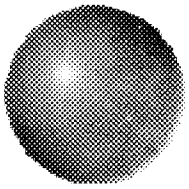
Traditional, prospective epidemiology study to determine risk of AML, NHL among benzene exposed workers

- 450 AML and 450 NHL patients into study

As of YE04:

☐ Disease recruitment on track

[This is much too detailed for this audience, and are non-vetted numbers -- suggest something like –
“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 – 30-200 ppm, 6-20 years

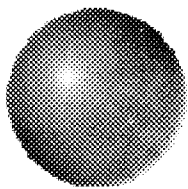
- Characterized as BIMDS (benzene-induced myelodysplastic syndrome)

- MDS subtype profile was established across 100 consecutive MDS cases

- provided a unique profile for this genetic pool and geographic region

- both BIMDS and MDS-subtyping will appear as manuscripts

[Suggestion -- eliminate concentrations/numbers, since this is unpublished data (100 is incorrect anyway). Reference to BIMDS is OK. The bottom line from this is mechanistic: “Suggests that immune parameters have a much larger influence than originally thought” (which is better than the alternative genetic parameters).]



The Shanghai Health Study

3. Molecular Epidemiology Study - Update

Prospective study seeking to establish quantitative relationship between exposure and effect

ME Phase I

- 400 medical records from 48 factories had been reviewed (of 1800 total medical records from 84 factories)

ME Phase 2A

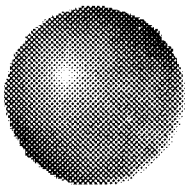
- Analyses performed on blood/urine from 231 high-exposure workers

ME Phase 2B

- Worker recruitment issues remain... only 3 bone marrow samples obtained

[Numbers from phase 1 are incorrect (84 factories/1800 med records???) , rest is theoretically OK.

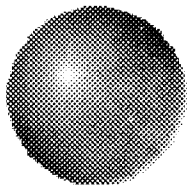
-- “have successfully recruited several factories and records for over 1000 cases have been abstracted to dat



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' diets, environmental exposures and family histories are recorded
 - Patient disease progression followed at supporting hospitals

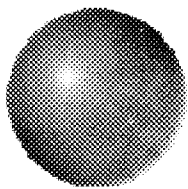
[Leave out “DIETS”]



Uniqueness of Shanghai Study

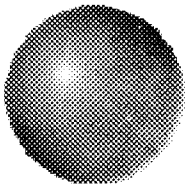
- Study examines primary diagnostic and medical data in real time
- First-hand exposure reports are more reliable than second-hand or reconstructed information
- State-owned databases document worker histories exposure readings from some jobs/locations

[We are NOT going into every factory of patients' to get "first hand" exposure reports. Nor can the IPHS database be used for every patient. We DO have to re-construct exposure, especially for CC and ME-1 studies. The 'state-owned' databases don't document worker histories, they document exposure readings for some jobs/locations.]



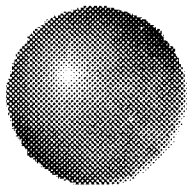
Why Shanghai?

- ❖ 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
 - 3 members – 1 each from China, Europe, and US
 - ❑ International Scientific Review Panel
 - 12 members
 - 6 scientific disciplines
 - ❑ Involved during entire project
- [Should read "4 members – 1 each from China, Europe, 2 from US"]

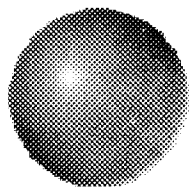


Benzene Health Research Consortium

Sponsoring Companies

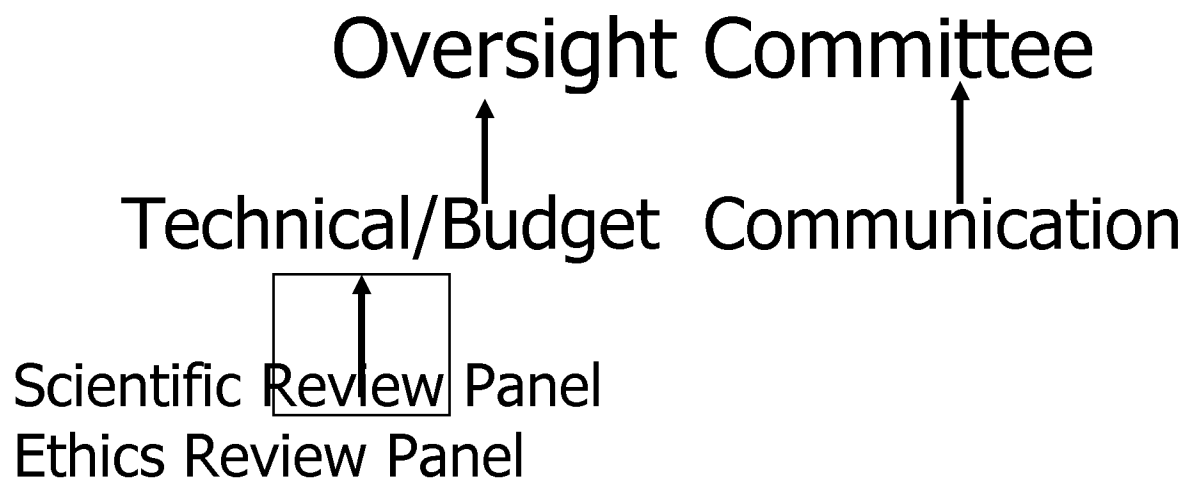
- BP
- ChevronTexaco
- ConocoPhillips
- ExxonMobil
- Shell Chemical LP

- Marathon/Ashland providing additional support



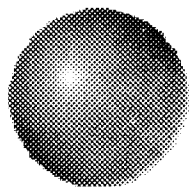
Benzene Health Research Consortium

Organization



API Administrative Support

[Suggest leaving out the arrow for SRP/ERP...they are independent]



Shanghai Health Study

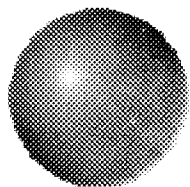
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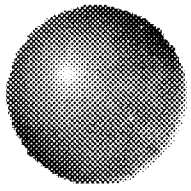
Internal Review Boards U of Colorado, Fudan University, AHS



Shanghai Health Study

Study Time Line

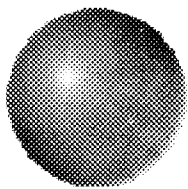
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4Q03	Opening Ceremony in Shanghai
Aug 04	Second Annual Meeting
Oct 04	International Benzene Symposium
Nov 05	Third Annual Meeting
2007/8	Report/Publications in scientific journals



Shanghai Health Study

Costs

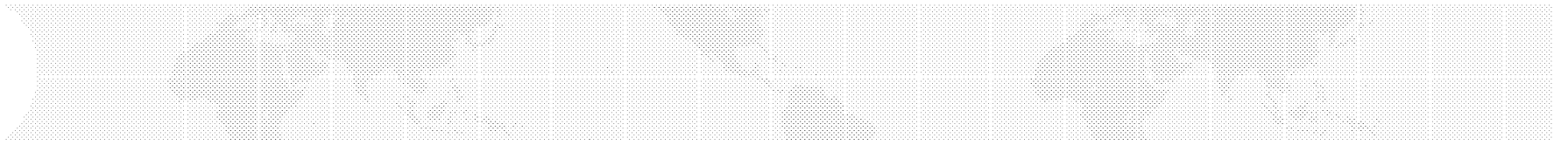
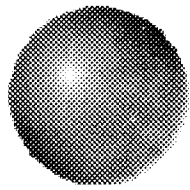
❖	Budget	\$ 26M
❖	Funding	\$ 26M

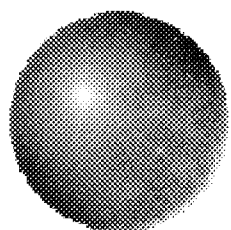


Shanghai Health Study

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





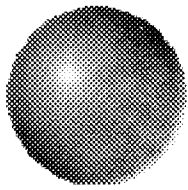
The Shanghai Health Study

Patsy Clegg

Chair, Oversight Committee

Shell Chemicals LP

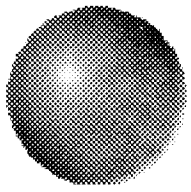
July 2005



What is the Shanghai Health Study?

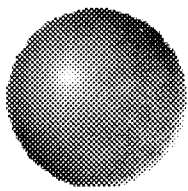
- ◆ A long-term clinical study to investigate the potential causes and development of lympho-hematopoietic diseases (diseases of the lymphoid organs, blood and bone marrow) as related to benzene

- ◆ 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



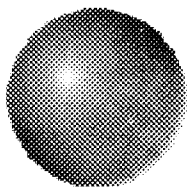
Shanghai Health Study Purpose

- ✦ 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:
 - 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

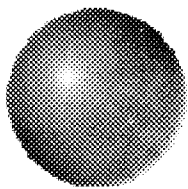
Traditional, prospective epidemiology study to determine risk of AML, NHL among benzene exposed workers
- 450 AML and 450 NHL patients into study

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

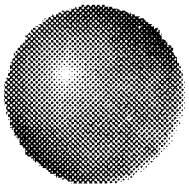
1. Case Control Study - Update

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

- 450 AML and 450 NHL patients into study

As of YE04:

- 437 AML cases had been accrued
- 155 NHL cases had been accrued
 - Expect 300-325 thru 2005; 450-500 thru 2006
- 2 controls per case were also processed through JCML lab analysis

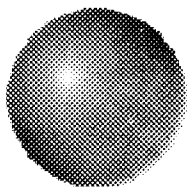


The Shanghai Health Study

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 – 30-200 ppm, 6-20 years
 - Characterized as BIMDS (benzene-induced myelodysplastic syndrome)
 - MDS subtype profile was established across 100 consecutive MDS cases
 - provided a unique profile for this genetic pool and geographic region
 - 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

ME Phase I

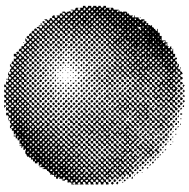
- 400 medical records from 48 factories had been reviewed (of 1800 total medical records from 84 factories)

ME Phase 2A

- Analyses performed on blood/urine from 231 high-exposure workers

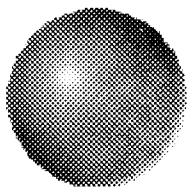
ME Phase 2B

- Worker recruitment issues remain... only 3 bone marrow samples obtained



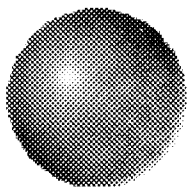
Uniqueness of Shanghai Study

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



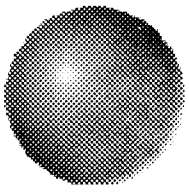
Uniqueness of Shanghai Study

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



Why Shanghai?

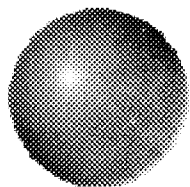
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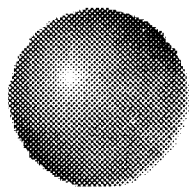
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Benzene Health Research Consortium

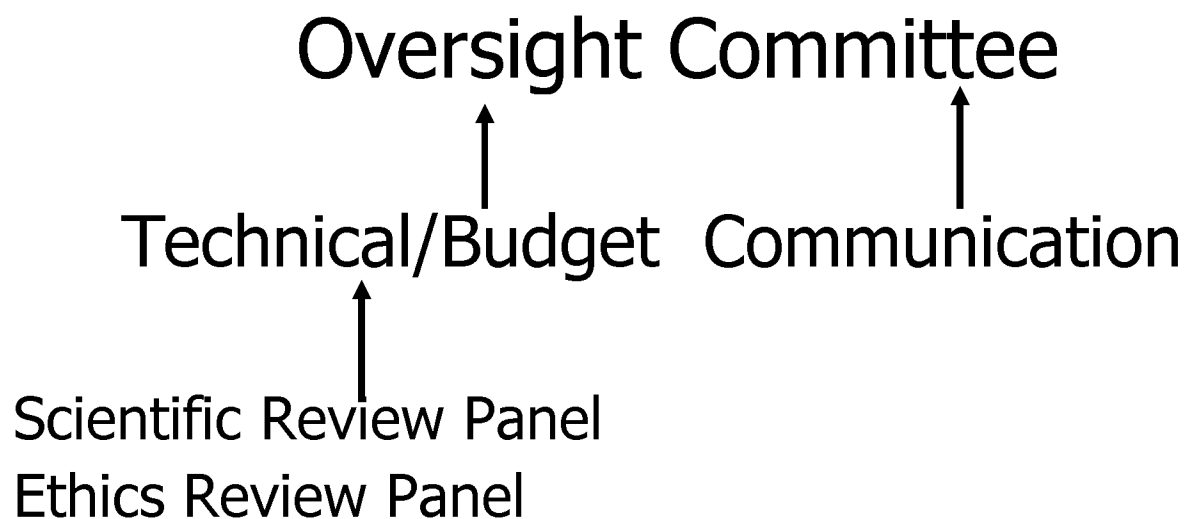
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 - Shell Chemical LP
-
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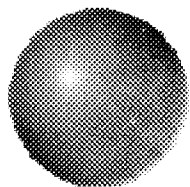


Benzene Health Research Consortium

Organization



API Administrative Support



Shanghai Health Study

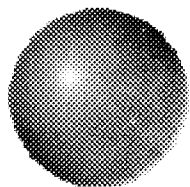
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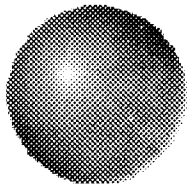
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Shanghai Health Study

Study Time Line

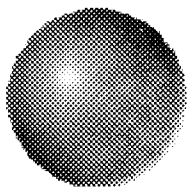
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Shanghai Health Study

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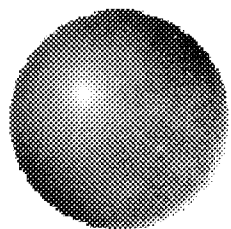
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Shanghai Health Study

Summary

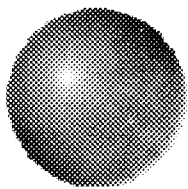
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The Shanghai Health Study

Patsy Clegg

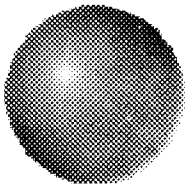
October 2002



The Shanghai Health Study

❖ Path to developing the study:

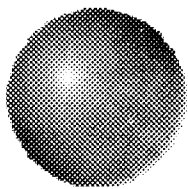
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- 01: Benzene Health Study Consortium formed to:
 - **do a study to test conclusions**
 - **answer questions of disease progression and biomarkers**



Benzene exposure and cancer

Conclusions from pre-1997 Epidemiology

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



The Shanghai Health Study

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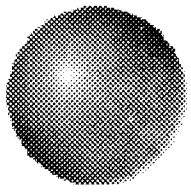
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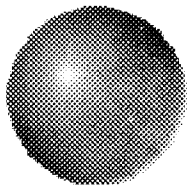
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Benzene Health Research Consortium

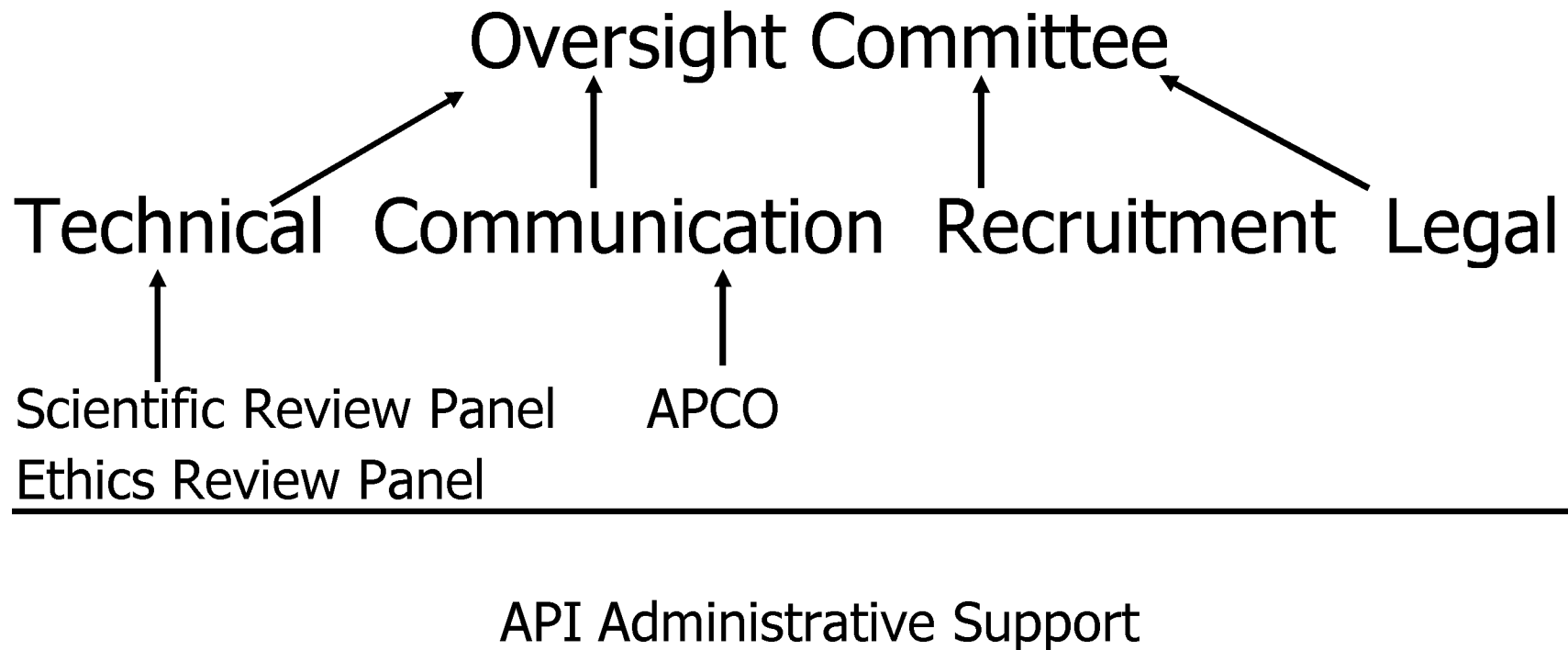
Sponsoring Companies

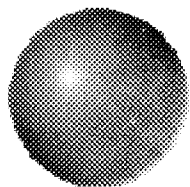
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Benzene Health Research Consortium

Organization





Shanghai Health Study

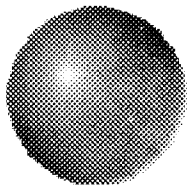
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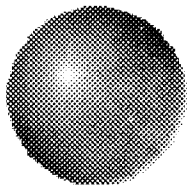
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Shanghai Health Study

Study Time Line

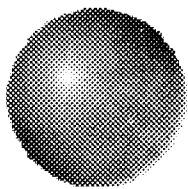
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2002	Lab Constructed and Equipped at Fudan
1Q03	Begin accepting cases
2Q03	Opening Ceremony in Shanghai
Aug 03	First Annual Meeting
2007	Report



Shanghai Health Study

Costs

- ❖ Budget \$22.5M
- ❖ Funding \$16.5M
- ❖ Recruitment Plan to gain additional support



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

Shanghai Health Study Overview

Purpose: To gain an accurate understanding of the true relationship between benzene exposure and the risk of certain hematopoietic diseases. This study is an important element in the product stewardship programs of participating companies. It can also 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.

A unique set of circumstances exists at this point in time in Shanghai to conduct meaningful benzene research. These include a database of occupational exposures in a different regulatory environment, and willing and qualified co-investigators influential in local scientific medical, and regulatory establishments. Therefore, questions that have plagued benzene health risk assessment for decades appear to be answerable in Shanghai.

The Studies: The program involves three inter-related studies:

- 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 possible “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 workers.

The investigators are leading experts in their fields, coming from such well-known institutions as the University of Colorado Health Sciences Center and Fudan University Medical Center. The combined studies apply cutting-edge, 21st century technologies in ways that will not only advance our understanding of benzene-induced disease, but may also identify potential prevention strategies benzene-induced disease in individuals.

Benefits: Information gained from this project will have a direct 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 the highest product stewardship goals and in oversight of their risk management programs.

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 developing sound benzene risk assessments. To that end, a Scientific Review Panel made up of leading experts from a number of fields relevant to these studies has reviewed and endorsed the research protocols. Additionally, the protocols have been reviewed by Use of Human Subjects Committees (IRB) both in the US and China.
- Ethical - To address the ethical issues, the study protocols have all undergone a thorough analysis to ensure that they meet international standards for research involving humans, including that the subjects and participating communities benefit from having participated in

Shanghai Health Study Overview

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** – A key to this program's success is local partnerships. Collaborators on these studies include researchers from the Medical School at Fudan University, the Institute for Public Health Supervision, and the Shanghai Municipal Centers for Disease Control and Prevention (the latter two are responsible for occupational exposure monitoring and enforcement in Shanghai).

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.

For More Information: Please contact any one of the following individuals.

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Myron Harrison	ExxonMobil	myron.c.Harrison@exxonmobil.com	+ 1 972-444-1673
Chris Roythorne	BP	roythorc@bp.com	+ 44 (0)20 7496 4126
Lorraine Twerdok	API	twerdokl@api.org	+1 202-682-8344