Shanghai Health Study

Update to API HESGC

Patsy Clegg

Chair, Oversight Committee

November 20, 2008

Shanghai Health Study Update

The purpose of the Shanghai Health Study is to gain a more refined understanding of the relationship between benzene exposure and potentially associated human health effects.

Shanghai Health Study Update

- 3 Studies
  - AML and NHL prospective case study
  - Disease Progression study
  - Molecular Epidemiology study

- Studies done at Fudan University in Shanghai
  - Laboratory donated to Fudan
  - Chinese scientists participated in study

Shanghai Health Study Update

- Study Case Accrual Complete
  - >500 AML cases (acute myelogenous leukemia)
  - >500 NHL cases (non-Hodgkins lymphoma)
  - Protocols set a goal of 500 cases for each
- Data Analysis in progress
- Publications have appeared in scientific literature
- Anticipate publications on all 3 studies in 2009

Shanghai Health Study Update

- Investigators
  - Richard Irons, Principal Investigator, Cinpathogen
  - Otto Wong, Applied Health Sciences
  - Fu Hua, Fudan University
  - You-Xin Liang, Fudan University
  - Rob Schnatter, EMBSI

Shanghai Health Study Update

- Scientific and Ethics Review Panels
  - Provide expertise and review to investigators
- Quality Assurance company hired to do QA/QC
- API oversight provided by General Committee on Special Programs

Shanghai Health Study Update

- Highlights
  - WHO classification of tumors applied
  - Nutritional anemias identified
  - Benzene Induced Dysplasia – indicates benzene may have a unique signature
    - TSCA 8(e) filed
  - Lab transferred to Fudan University School of Medicine
  - Cinpathogen, a private company, replaced University of Colorado as lead institution

Shanghai Health Study Update

Path Forward

- 2008
  - Case accrual completed
  - Data analysis
- 2009
  - Publications
  - International Benzene Symposium in Munich
  - Benzene Health Research Consortium will disband

Benzene Health Research Consortium

Sponsoring Companies

- BP
- Chevron
- ConocoPhillips
- ExxonMobil
- Shell Chemical LP

- Marathon/Ashland providing additional support

Shanghai Health Study

Costs

- Budget $ 35M
- Funding $ 35M

Shanghai Health Study

Summary

- Case accruals met protocol goals
- Budget adequate to complete study
- Lab at Fudan may continue to provide services to Shanghai community
- Publications expected in 2009
- Study will be reported at International Benzene Symposium in Munich in 2009
- Sponsors consortium will disband at the end of 2009

Shanghai Health Study

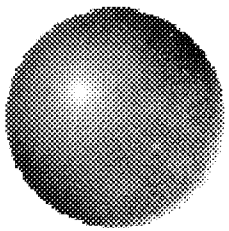
API HESGC Update

November 20 2008

Presented by

Patsy Clegg, Chair Oversight Committee

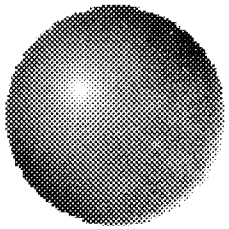
Benzene Health Research Consortium



The Shanghai Health Study

Benzene Health Research Consortium

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

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

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 constituent of crude oil and a chemical building block
- A recognized human carcinogen:
  - Acute Myelogenous Leukemia (AML)
- Tightly regulated although worldwide standards vary
- What is not currently known:
  - benzene's impact on a molecular level;
  - the "threshold" exposure level;
  - whether and how associated cancers or other related diseases may be caused; and
  - the role of genetic susceptibility

Benzene Toxicity

- The effects of exposure to any hazardous substance depend on:
  - dose,
  - duration,
  - other exposures,
  - 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 advance benzene science

Why Shanghai?

- Unique Study Environment
  - Databases documenting exposure
  - Exposure across industries
  - Range of exposure levels
- Committed Collaborators
  - 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

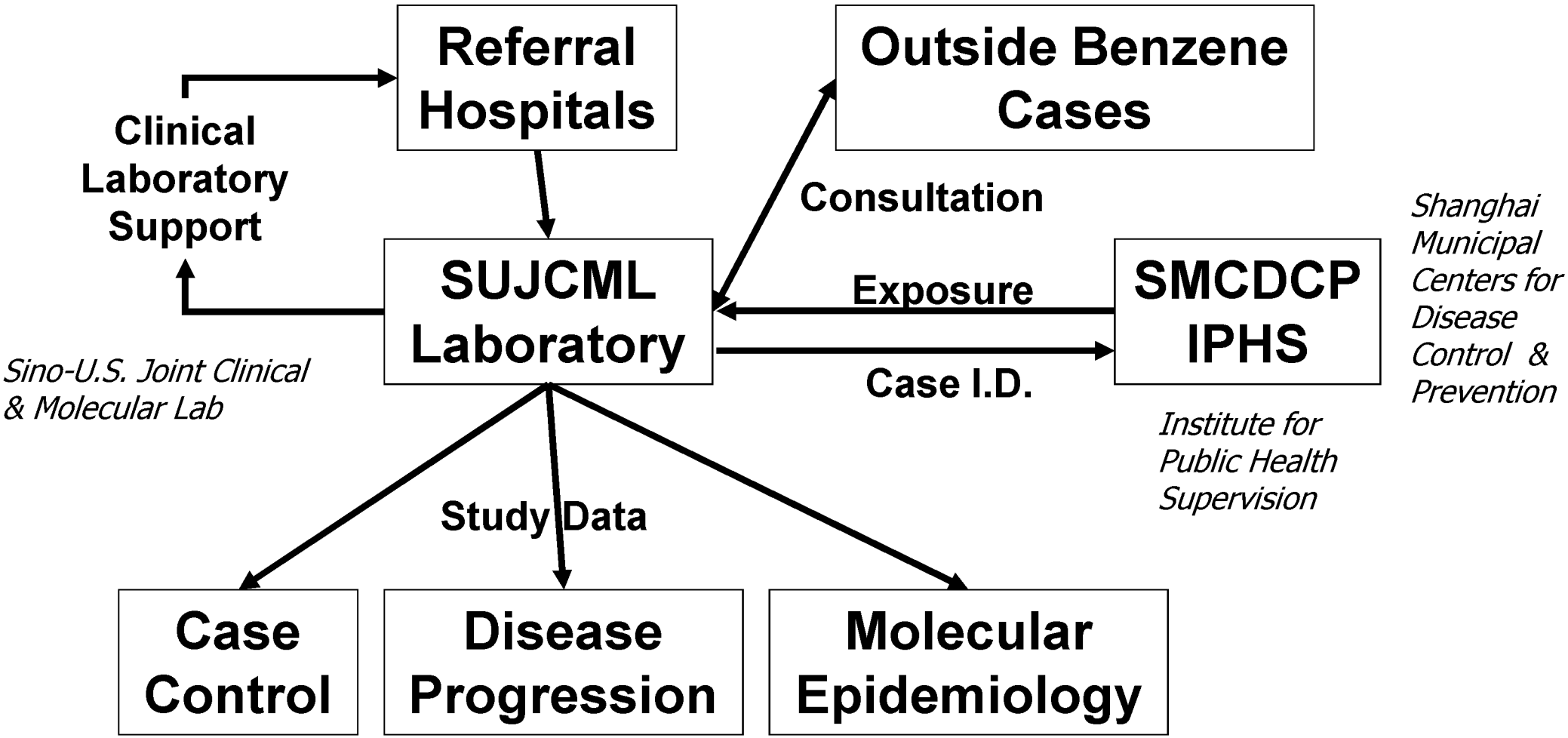
Difficulties in Past Benzene Research

- 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

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

Shanghai Health Study



How is the SHS Distinct?

- 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

Shanghai Health Study Purpose

- Designed to provide mechanistic data on AML development in humans
- Goal to identify a more reliable basis for the extrapolation of leukemia risk associated with low-level benzene exposure

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 role regarding worker health problems resulting from 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 with a leading research university
- 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 in Shanghai
  - Retrospective study published 1997
  - Raised new questions on effects of low-level benzene exposure
- Assessed feasibility of building on Shanghai experience
  - 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
- Early, consistent detection and diagnosis of leukemias and related diseases in Shanghai
- Identification of more sensitive benzene exposure biological markers
- Convergence of company and local Shanghai research interests

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

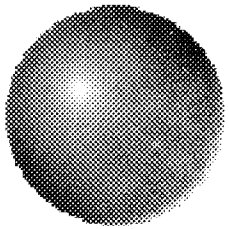
SHS Hospital Partners

- 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

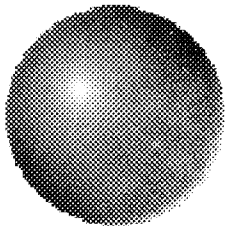
Benzene Uses

- 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
- More research needed to assess threshold assumption

Research Challenges

- Accounting for multiple exposures
- Addressing confounding factors
- Exposure estimates
- Accuracy of medical diagnosis
- Analysis of results (case numbers, exposure range, etc.)

Recent Epidemiological Studies

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

Recent Epidemiological Studies

- Australian Institute of Petroleum's (AIP) Health Watch Study – case-control study released in 2001
  - Association with all leukemias, including chronic lymphocytic leukemia
  - 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 potentially NHL, among benzene exposed workers
- Data collected will allow analysis of other causal factors for NHL
- Estimate 4 to 5 years to obtain 450 AML and 450 NHL patients into study
- Improved exposure assessment based on historical and concurrent workplace monitoring and questionnaire

Study #2 - Disease Progression

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

Study #3 – Molecular Epidemiology

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

Quality Science

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

Scientific Review Panels

General Toxicology and Biochemistry	Dr. Jerry M. Rice, (Chair), IARC (Retired) 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 Dr. Juhana Idanpaan-Heikkila, World Health Organization

Current SHS Status

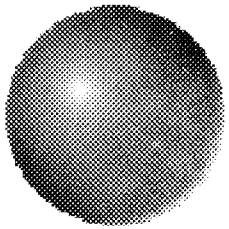
- State-of-the-art laboratory constructed on Fudan University campus
  - Sustainable technology transfer an important project design component
  - Built according to international standards
  - Lab will support the project, Shanghai medical community and remain at Fudan
- Technology transfers
  - Chinese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

Scientific and Ethical Review Status

- 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 – final approval 02

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?

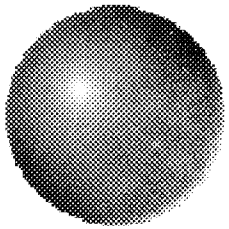
- A consortium of petroleum and chemical companies concerned about understanding the human health effects of benzene
  - British Petroleum, ChevronTexaco, ConocoPhillips, ExxonMobil, Shell
  - Other members being recruited
  - American Petroleum Institute, project administrator
- Individual company product 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
  - 0.5ppm in Malaysia; 1.0ppm in U.S.; 10ppm in Japan
  - American Conference of Governmental Industrial Hygienists recommends 0.5ppm
- Industry has long sponsored benzene research



SHS Funding Structure

SHS Funding Structure

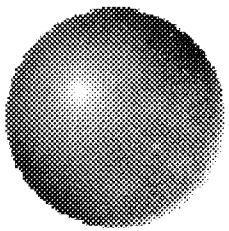
- $22.8 million program total for all costs over 5 years
  - $16.5 million confirmed as of October 2002
  - Current funding through October Q3 03
- Costs projected to be highest during first yrs.
- Payment schedule
  - August 2001 15%
  - January 2002 15%
  - August 2002 25%
  - August 2003 15%
  - *August 2004 15%*
  - *August 2005 15%*

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



Conclusions

Conclusions

- PRESENTER: SELECT AUDIENCE
  - General
  - Recruitment – Funding
  - Recruitment – Technical

Conclusions

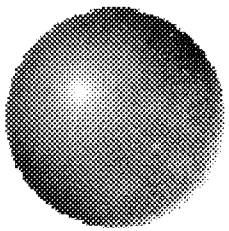
- Study will advance benzene science
- Sponsors funding study
  - Product stewardship
  - Corporate social responsibility goals
- Anticipate results published 2007/8
- Results will add to accepted body of scientific research on benzene
  - Referenced by government, industry decision-makers

Additional Sponsors Needed

- Responsibility to understand the health impacts of your products
- Commitment to worker health, safety
- Need for most advanced science possible

Technical Committee Membership

- Review study progress
- Opportunity to comment on analyses
- Annual meetings with investigators, sponsors



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
- SMCDCP – 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
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For More Information

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  - burnetdm@bp.com
- Bill Frick
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- Lorraine Twerdok, BHRC Administrator
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DRAFT AGENDA
DOWNSTREAM COMMITTEE
American Petroleum Institute
Wednesday, May 12, 2004 – 8:00 a.m. – Noon CT— Houston, TX

Continental Breakfast 7:30 a.m.

8:00 a.m.	**Introductory Remarks**	**Gary Heminger** Chair, Downstream Committee
8:05 a.m.	**Presentation by a Member Company on Initiatives to Improve Environmental and Safety Performance**	**TBD**
8:30 a.m.	**National Energy Bill (Attachment 1)** • Status and strategies for the future **Action: Provide guidance on further advocacy efforts**	**Patricia Richards** Chair, Transportation Fuels Committee
9:00 a.m.	**NAAQS (Attachment 2)** • Review EPA's final rule implementing the 8-hour ozone standard • Results of April 23 NAAQS strategy discussions among API committees of jurisdiction **Action: Provide guidance on advocacy goals and objectives**	**TBD**
9:45 a.m.	**Fuels Committee Activities (Attachment 3)** • Review EPA's non-road diesel rule • Northeast states initiatives: low sulfur heating oil, regional fuels • NAAQS implementation issues for fuels • Auto's Top Tier Gasoline Program **Action: Provide guidance on strategies to address the above**	**Mike Leister** Chair, Fuels Committee
10:15 a.m.	**API Health Effects Subscription Research Programs (Attachment 4)** • Overview of API Programs • Status of Shanghai Health Study (China Benzene) o Potential business impacts o Use in advocacy	**Ed Murphy** Downstream Group Director **Patsy Clegg** Chair, Benzene Health Research Consortium Oversight Committee
11:00 a.m.	**API Involvement in International Activities (Attachment 5)** • World Petroleum Congress • IPIECA (global climate, corporate reporting, transparency, corporate social responsibility) • UN Partnership on Clean Fuels and Vehicles	**TBD**
11:30 a.m.	**Update on Strategic Communications Steering Committee (Attachment 6)** • Next phase: defining an envisioned future	**Pamela Beall** Marathon Ashland
11:35 a.m.	**Marketing Committee Activities Update (Attachment 7)** • Gasoline supply and communications activities, underground storage tank legislation, SPCC litigation	**Mary Ellen Peters** Chair, Marketing Committee
11:45 a.m.	**Other Business (Attachment 8)** • Review 2005 Budget Time Line and 2005 Major Issues	**Ed Murphy**
Noon	**Adjournment**	**Gary Heminger**