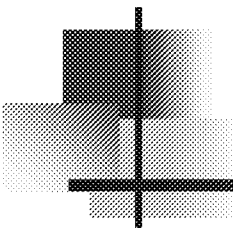


Case-control Study of AML and NHL in Shanghai



Principal Investigators:

Otto Wong, Sc.D.

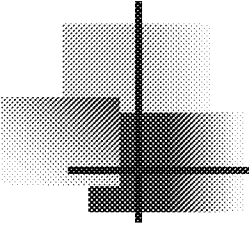
Applied Health Sciences, San Mateo, California, USA
Tulane University, New Orleans, Louisiana, USA
Chinese University of Hong Kong, Hong Kong, China

Fu Hua, M.B., Ph.D.

Fudan University School of Public Health, Shanghai, China

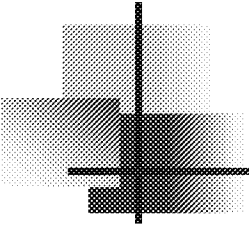
18 August 2004

Asilomar Conference Center, Monterey, California, USA



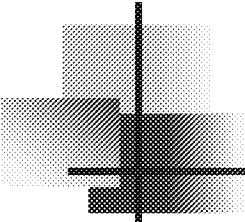
Shanghai Health Study

- The AML-NHL case-control study is one of the three research projects of the Shanghai Health Study.
- Clinical diagnosis is provided by the Joint Sino-US Clinical & Molecular Laboratory (under the direction of Dr. Richard Irons).
- Exposure assessment is carried out by Fudan's Exposure Assessment Team (under the direction of Mr. Thomas Armstrong).



Study Design

- Hospital-based case-control study in metropolitan Shanghai, China.
- Two diseases under investigation:
 - Acute myeloid leukemia (AML), and
 - Non-Hodgkin's lymphoma (NHL).
- Prospective patient enrollment starting in June 2003 (reporting in the first 2-3 months might have been sporadic and incomplete).



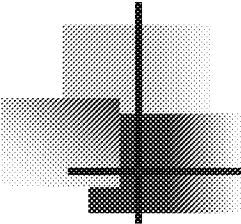
Study Design

- For each AML or NHL case, up to 2 individually matched controls.
- Demographic, occupational, lifestyle and medical information obtained through the use of face-to-face questionnaire interviews.
- Individual exposure profiles for each study subjects, with emphasis on benzene and other potential confounding exposures.

Study Base

Participating Hospitals

- 29 participating hospitals in the study.
- Participating hospitals located throughout the city.
- Three types of hospitals included in the study:
 - Municipal hospitals,
 - District hospitals, and
 - Occupational hospitals.



Participating Hospitals

(1) Municipal Hospitals

No.	Chinese name	English name
1	华山医院 ^a	Huashan Hospital
2	肿瘤医院 ^a	Tumour Hospital
3	沪铁中心医院 ^c	Shanghai Railway Centre Hospital
4	市六医院 ^d	Shanghai Municipal No.6 Hospital
5	仁济医院 ^b	Renji Hospital
6	长征医院 ^e	Changzheng Hospital
7	曙光医院 ^f	Shuguang hospital
8	华东医院 ^a	Huadong Hospital

Participating Hospitals

(1) Municipal Hospitals

No.	Chinese name	English name
9	长海医院 ^e	Changhai Hospital
10	中山医院 ^a	Zhongshan Hospital
11	同济医院(甘泉医院) ^c	Tongji Hospital
12	市九医院 ^b	Shanghai Municipal No.9 Hospital
13	市一医院 ^d	Shanghai Municipal No.1 Hospital
14	瑞金医院 ^b	Ruijin Hospital
15	新华医院 ^b	Xinhua Hospital
16	龙华医院 ^f	Longhua Hospital

Participating Hospitals

(2) District Hospitals

No.	Chinese name	English name
17	静安区中心医院	Jinan District Hospital
18	杨浦区中心医院	Yangpu District Hospital
19	闸北区中心医院	Zhabei District Hospital
20	奉贤区中心医院	Fengxian District Hospital
21	松江区中心医院	Songjiang District Hospital
22	黄浦区中心医院	Huang-pu District Hospital
23	市东医院	Shidong Hospital
24	嘉定区中心医院	Jiading District Hospital
25	长宁区中心医院	Changning District Hospital
26	第五人民医院 ^a	No. 5 Hospital
27	普陀区中心医院	Putuo District Hospital

Participating Hospitals

(3) Occupational Hospitals

No.	Chinese name	English name
28	化工职业病防治医院	Chemical & Occupational Disease Hospital
29	上海职业病医院	Shanghai Occupational Disease Hospital

Affiliated universities:

a: Fudan University

b: Shanghai No. 2 Medical University

c: Tongji University

d: Jiaotong University

e: No. 2 Military Medical University

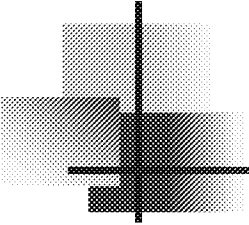
f: Shanghai Traditional Chinese Medical University



Cases

Definition

- Acute myeloid leukemia (AML) and non-Hodgkin's lymphoma (NHL) patients aged 18 or older.
- For NHL, both the broader WHO definition and the traditional ICD9 definition are used.
- Preliminary diagnoses provided by participating hospitals.
- Preliminary diagnoses to be confirmed by the Joint Sino-US Clinical & Molecular Laboratory (JCML) at Fudan University.
- Only JCML-confirmed cases are included in the study.

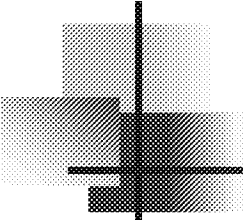


Individually Matched Controls

Matching Criteria (original)

- Same hospital as the case.
- Same gender as the case.
- Similar in age (± 5 years).
- Same inpatient/outpatient status (many NHL patients are outpatients).
- Lymphatic and hematopoietic diseases excluded.
- Closest admission time.

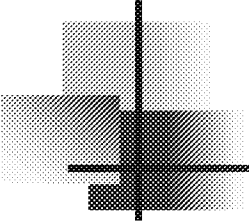
Note: Age can be relaxed to ± 10 years, if suitable controls (± 5 years) cannot be found.



Identification of Cases and Controls

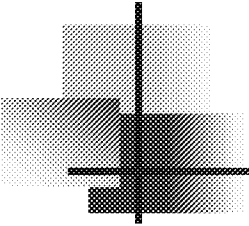
Clinical Coordinators

- Identification of cases and controls at each hospital is the responsibility of the clinical coordinators at the hospital.
- For AML, the clinical coordinators are hematologists at the participating hospitals, under the supervision of Prof. LIN Guowei of Huashan Hospital.
- For NHL, the clinical coordinators are pathologists at the participating hospitals, under the supervision of Dr. ZHU Xiongzeng of Tumor Hospital.



Interview of Cases and Controls

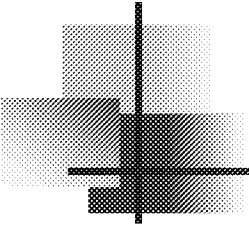
- Newly diagnosed cases and matched controls are identified by clinical coordinators at each participating hospitals.
- Questionnaire interviewers at Fudan are notified of new cases and controls.
- Face-to-face interviews at the hospital (by the bedside) are to take place within one week.
- Interviews are conducted by trained questionnaire takers, under the supervision of Dr. Chen Xiaobao.



Interview of Cases and Controls

Each patient receives:

- A verbal description of the investigation,
- Disclosure of the identities of sponsors and investigators of the study.
- Reassurance of voluntary participation,
- Reassurance of the release of statistical data only, and
- Reassurance of confidentiality of personal information.

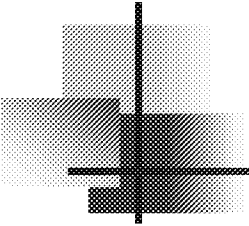


Interview of Cases and Controls

If the patient agrees to participate, he or she is asked to sign the appropriate consent forms.

Each patient will receive financial compensation of ¥240 RMB (240 yuans, or approximately US\$30) for the interview.

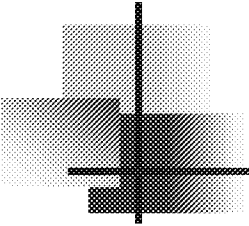
A 17-page (primary) questionnaire in Chinese is then administered verbally by the interviewers (average: 30 to 45 minutes per interview).



Primary Questionnaire

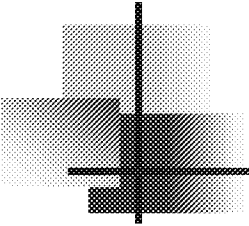
The 17-page primary questionnaire contains the following sections:

- Demographics,
- Family history,
- Medical history,
- Medication history (both Western & Chinese traditional),
- Employment and exposure histories, and
- Non-occupational exposures (tobacco, alcohol, hobbies & farming).



Secondary Questionnaires

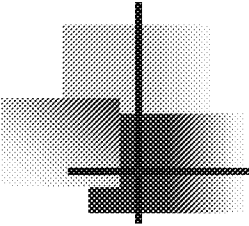
- Certain occupations of interest will trigger secondary questionnaires that are more detailed and industry- or occupation-specific (ranging from 4 to 9 pages).
- 64 occupations of interests have been identified.
Examples: shoe worker, leather worker, painter, mechanic, farmer, mechanic, mechanist, electrician, assembly worker, health care worker, textile worker, laborer, manager & supervisor.



Secondary Questionnaires

A typical secondary questionnaire contains the following information:

- Industry and occupational title,
- Description of tasks,
- Substances handled,
- Frequency and duration of exposure,
- Workplace environment, and
- Use of personal protection equipment.



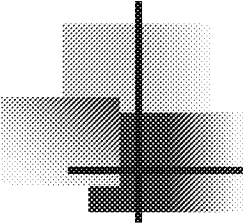
Questionnaires

Verification & Data Entry

Before data entry, each questionnaire is checked for completeness and clarity by Dr. Chen.

Verified questionnaires are then copied and stored in locked file cabinets in a separate building.

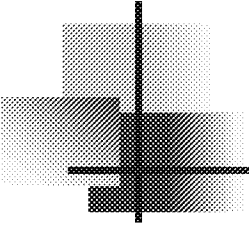
Copies of questionnaires are sent to the data entry team.



Questionnaires Data Entry

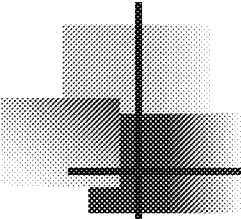
Questionnaire data entry:

- Double data entry by two independent data entry persons,
- Results compared, and
- Discrepancies reviewed and resolved by data entry supervisor.



Exposure Assessment

- Verified questionnaires are processed for exposure assessment.
- Only the employment and exposure sections of the questionnaire are provided to the Exposure Assessment Team (blinded as to case/control status).

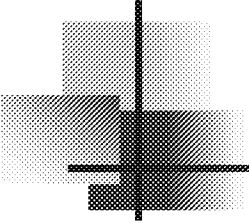


Exposure Assessment

Exposure classification of study subjects is assigned by the Exposure Assessment Committee (blinded as to case/control status).

The Exposure Assessment Committee consists of:

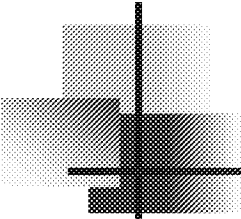
- Dr. YANG Shixin, a retired occupational physician from IPHS who is familiar with many factories in Shanghai,
- Professor JIN Xipeng at Fudan University who has published extensively on benzene, and
- Mr. HE Yonghua, Exposure Assessment Coordinator.



Exposure Assessment

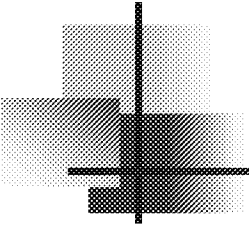
Primary sources of exposure information:

- Shanghai Municipal Institute of Public Health Supervision (IPHS) database (computerized),
- Exposure data at district IPHS (not computerized).
- Monitoring data maintained at factories,
- Facility histories (raw materials, engineering changes) maintained at factories,
- New *ad hoc* monitoring data to be collected, and
- Exposure information in Chinese journals.



Exposure Assessment

Source	Data potentially available
Municipal IPHS	Subject's factory, surrogate factories, same industry
District IPHS	Subject's factory, surrogate factories
<i>Ad hoc</i> IH measurements	Subject's factory, surrogate factories
Literature	Same industry, similar occupation



Exposure Assessment

IPHS Database

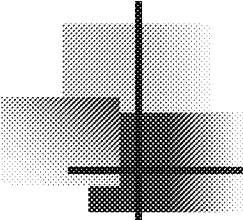
IPHS database:

- Data dated back to the 1950s,
- Some 50,000+ exposure measurements of benzene taken at factories in Shanghai,
- Occupational codes and industrial codes have been standardized to the classifications used in the 1982 national census, and
- Records in computerized form (FoxPro).

Exposure Assessment

IPHS Database

A - Microsoft Visual FoxPro												
文件(F) 编辑(E) 显示(V) 工具(T) 程序(P) 表(A) 窗口(W) 帮助(H)												
Inducode	Haracode	Locatit1	Occurcode	Numb	Conc1	Conc2	Conc3	Conc4	Conc5	Conc6	Fjad	
439	0715	喷漆	901b	4	3.70	12.90	9.00	22.30	0.00	0.00	11.98	
442	0715	胶木车间指示灯小组	869	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
407	0715	车间空气	901b	2	0.00	153.00	0.00	0.00	0.00	0.00	76.50	
407	0715	喷漆呼吸带	901b	4	4.00	17.00	0.00	12.00	0.00	0.00	8.25	
407	0715	喷化操作带	901b	3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
423	0715	喷漆工人呼吸带	901b	4	0.00	31.93	6.84	41.81	0.00	0.00	20.15	
423	0715	喷漆工人呼吸带	901b	4	6.84	3.80	3.80	4.56	0.00	0.00	4.75	
291	0715	印学工人呼吸带	916	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
291	0715	静喷呼吸带	901b	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
422	0715	喷漆呼吸带	901b	2	2.00	4.00	0.00	0.00	0.00	0.00	3.00	
419	0715	照相修版呼吸带	822	3	75.00	1.00	14.00	0.00	0.00	0.00	30.00	
291	0715	调漆呼吸带	901a	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
291	0715	印字呼吸带	823	4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
407	0715	喷漆呼吸带	901b	4	11.00	14.00	11.00	11.00	0.00	0.00	11.75	
428	0715		0	6	0.00	0.00	1.60	2.10	0.00	0.00	0.62	
422	0715	苯其他其他	863	4	6.30	6.10	19.00	11.00	0.00	0.00	10.60	
341	0715	浸胶刮浆	741	3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
341	0715	橡胶制浆	741	6	130.00	170.00	150.00	71.00	18.00	24.00	93.83	
422	0715	家具涂饰	803	4	12.00	16.00	13.00	15.00	0.00	0.00	14.00	
342	0715	刷胶	762	6	0.00	0.00	0.00	0.00	0.00	8.00	1.33	
428	0715	喷涂	726	6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
252	0715	皮革制品制造其他工种	762	6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
408	0715	电喷涂	726	6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
408	0715	电喷涂	726	6	70.00	18.00	7.70	8.10	4.40	5.70	18.98	
408	0715	电喷涂	726	6	110.00	39.00	34.00	25.00	11.00	18.00	39.50	
252	0715	皮革制品制造其他工种	762	6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	



Exposure Assessment

IPHS Database

IPHS exposure records include the following items:

- Date of sampling,
- Industrial code,
- Occupational code,
- Hazard code (0715 for benzene),
- Name and address code of the factory,
- Sampling location at the factory, and
- Individual and average measurements of benzene.

IPHS Exposure Records

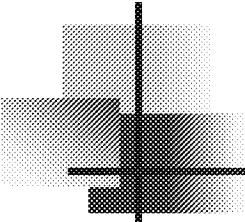
An Example (Rubber Products Factory)

Date	1959-05-06
Industry code	341 橡胶制品制造业 (rubber products, including tires, hoses, shoes & bags)
Occupational code	739 其他化工工人 (other petrochemical workers)
Hazard code	0715 苯 (benzene)
Name & address code of factory	大成橡胶厂 (Daicheng Rubber Products Factory) 310109
Sampling location	刮浆车间工人操作地带 (glue application area)
Measurements (mg/m ³)	130.00, 600.00 Average=365.00

IPHS Exposure Records

An Example (Shoe Factory)

Date	1986-12-26
Industry code	341 橡胶制品制造业 rubber products, including tires, hoses, shoes & bags)
Occupational code	741c 橡胶粘合工人(glue application workers)
Hazard code	0715 苯 (benzene)
Name & address code of factory	花木冈乐运动鞋厂 (Huamuganle Athletic Shoe Factory) 310115
Sampling location	粘胶工人呼吸带 (breathing zone of glue application workers)
Measurements (mg/m ³)	391.28, 391.28, 330.39, 330.39 Average=360.84



Reports in Chinese Medical Journals

Generally, two types of articles in Chinese medical journals reporting benzene exposure information:

- Industrial hygiene surveys, and
- Benzene poisoning cases.

Reports in Chinese Medical Journals

An Example (Coal Tar Plant)

Wang et al., 1999

“Control of benzene exposure and health effects
at Jinan Steel & Iron Company’s Coal Tar Plant”

- *Chin J Ind Med* 1999;12(3):179.
- Authors: Wang LC, Wei YZ, Lin ZX.
- Affiliation: Jinan Steel & Iron Company.
- Text in Chinese.

Reports in Chinese Medical Journals

An Example (Coal Tar Plant)

Wang et al., 1999

- Benzene refining unit at Jinan Steel & Iron Company's Coal Tar Plant (济南钢铁公司焦化厂).
- Comparison of benzene measurements by work area and year.
- Major renovations (primarily ventilation) since 1980.

Reports in Chinese Medical Journals

An Example (Coal Tar Plant)

Wang et al., 1999

Benzene measurements (mg/m³) at refining unit

Work area	1973	1979	1983	1995
Distillation 蒸馏工	18.1	31.1	9.33	1.80
Washing 洗涤工	104.2	157.2	17.75	5.20
Finished products 成品工	156.0	531.1	26.96	2.90
Chemical analysis 化验工	233.0	316.4	15.44	1.95

Reports in Chinese Medical Journals

An Example (Bag Workshops)

Zhao et al., 2003

"Analysis on the benzene poisoning event about Gaobeidian's bag industry in 2002" (authors' translated title)

- *Chin Occup Med* 2003;30(3):32-34.
- Authors: Zhao CX, Luo R, Li JG.
- Affiliation: Hebei Provincial Center for Disease Prevention and Control .
- Text in Chinese, with an English abstract.

Reports in Chinese Medical Journals

An Example (Bag Workshops)

Zhao et al., 2003

- Health survey of leather bag processing workers in 2001-2002 in Gaobeidian City, Hebei (河北 高碑店市).
- 6482 workers (4906 females & 1576 males).
- 33 cases of benzene poisoning (including 31 serious cases: 23 AA, 5 pancytopenia, 2 MDS & 1 AML); prevalence rate=0.51%.
- 9 deaths; fatality rate=17.6%.
- 27 females & 6 males.
- Age: 16-22, average=17.

Reports in Chinese Medical Journals

An Example (Bag Workshops)

Zhao et al., 2003

- Workshops were converted rooms in residential houses; 30-80 m²; inadequate or no ventilation.
- Of the 20+ adhesives used, 7 with benzene content >30%.
- Employees worked, ate and slept there.
- 12-17 working hours a day; no days off.
- Benzene concentrations up to 2040 mg/m³.
- Toluene up to 949 mg/m³.
- n-hexane up to 85800 mg/m³.

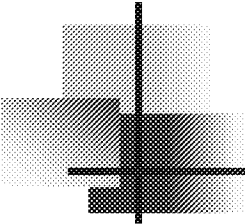
Typical Makeshift Workshops

Shoe & Hand Bag Workers



A young woman applying glue from an open container to a small hand bag with a brush.

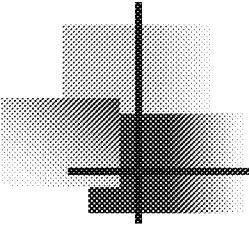
Note the location of the exhaust vent.



Chinese Medical Literature

Sources:

- Shanghai Municipal Library (all years available),
- Fudan University Medical School (2000-present),
- Chinese Scientific & Medical Journal Indices (1980-present) 中国学术期刊数据库.

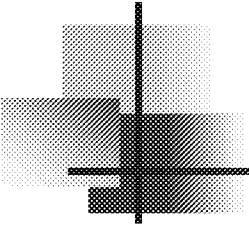


Chinese Medical Literature

Key words used in identifying potential journals, conference proceedings, books, & agency reports:

- Public health,
- Occupational health/medicine,
- Preventive medicine,
- Industrial health/medicine,
- Occupational diseases, and
- Occupational poisoning.

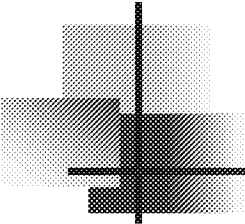
43 journals plus 40 other documents



Chinese Medical Literature

The title and/or the abstract of every article of the selected journals or report is searched for the following keywords: benzene, gasoline, glue, and paint.

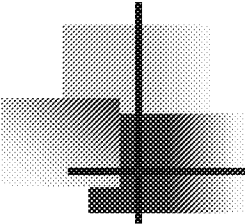
If one or more keywords are found, the entire article is copied at the library and brought back to our offices.



Chinese Medical Literature

The copied articles are then read and the following items are entered into an Excel spreadsheet:

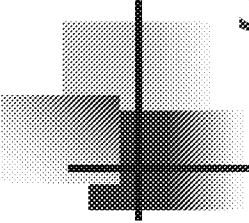
- Industry,
- Occupational title,
- Task description,
- Date,
- Benzene exposure levels,
- Description of physical environment, and
- Diagnosis.



Chinese Medical Literature

The Excel spreadsheet contains:

- ◆ All post-1980 articles or reports,
- ◆ Nearly 1000 line items, and
- ◆ Each line contains one set of benzene measurement (representing a sampling location or job title, with one to several benzene measurements).



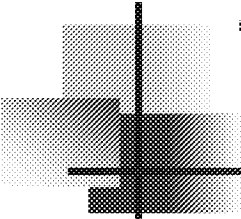
Study Status Summary

Enrollment of AML and NHL cases

Enrollment of patients started in June (AML) or August/September (NHL) 2003.

The delay was due to the late completion of JCML and SARS in 2003.

Patient enrollment in the first 2-3 months might have been sporadic and incomplete at some hospitals.

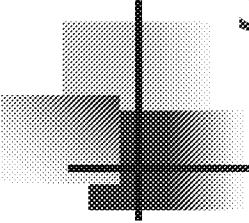


Study Status Summary

Number of AML and NHL cases

Number of JCML-confirmed cases projected for the 12 months ending on 4 September 2004 and by end of 2006:

Diagnostic category	Original estimate 12 months	Current projection 12 months	Expected cumulative by Dec. 2006
AML	120	150+	500-600
NHL (WHO)	200	139+	385-450
NHL (ICD9)	120	108+	300-350

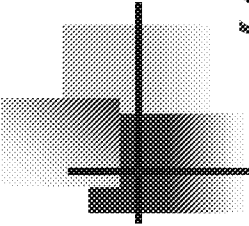


Study Status Summary

Selection of Cases and Controls

So far, no cases or controls refused to participate in the study.

We have been able to select two controls for every case.

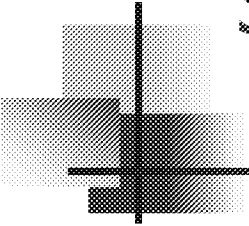


Study Status Summary

Controls Inappropriately Selected

In February 2004, a review of the questionnaires of cases and controls revealed:

- Quite a few outpatient NHL controls at Tumor Hospital lived at the same address or in the same neighborhood (n=21, 51% of all controls at Tumor Hospital), and
- Several outpatient NHL controls at No. 6 Hospital were health care workers, i.e., nurses or physicians (n=6, 50% of all controls at No. 6 Hospital).

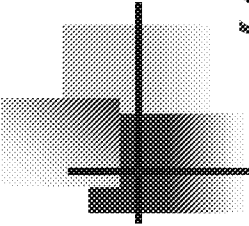


Study Status Summary

Controls Inappropriately Selected

Further investigation revealed:

- These “recruited” controls were relatives, neighbors or co-workers of the clinical coordinators at the two hospitals.
- These controls were not “real” patients at the hospitals, and their diagnoses were non-specific, such as upset stomach or minor respiratory symptoms.
- These controls registered at the hospitals as outpatients (registration fee of ¥10) so that they could participate in the study and receive study participation fee of ¥240.

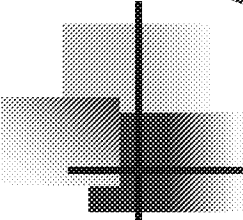


Study Status Summary

Controls Inappropriately Selected

Corrective and preventive measures implemented:

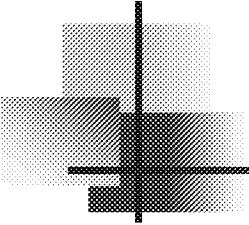
- Talked to the clinical coordinators involved.
- As of May 2004, require all controls be selected from inpatients, regardless of the status of the cases.
- Replaced the inappropriate controls.
- Closely monitor the selection of controls.
- Review distribution of controls by diagnosis, address, or occupation.



Study Status Summary

Total Number of Questionnaires (All Studies)

Total number of completed questionnaires	~ 1750
Number of questionnaires entered	~ 1300
Number of questionnaires verified	~ 1250
Number of subjects assessed for exposure	~ 1200

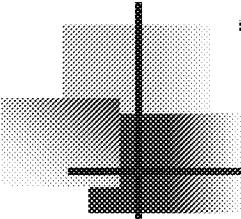


Study Status Summary

Occupations/Industries of Benzene-exposed Subjects

Most frequent occupations/industries of benzene-exposed subjects:

- Shoe workers,
- Painters,
- Mechanics or mechanists, and
- Printers.



Study Status Summary

Benzene-exposed Subjects

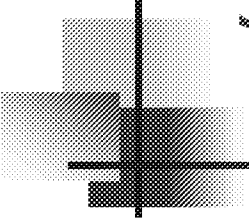
Earliest exposure	1941
Occupation with highest exposure	Brush painter, spray painter
Highest maximum exposure	1300 mg/m ³
Highest minimum exposure	200 mg/m ³
Highest typical exposure	690 mg/m ³
Longest exposure	40 years

Study Status Summary

Occupations/Industries of Subjects Exposed to Other Substances

Most frequent occupations/industries of subjects exposed to other substances:

- ◆ Farmers,
- ◆ Textile workers,
- ◆ Teachers,
- ◆ Engineers,
- ◆ Drivers,
- ◆ Cooks, chefs,
- ◆ Military personnel.



Study Status Summary

Exposure Assessment

The Exposure Assessment Team noted the following:

- Completeness and accuracy of the Shanghai Municipal IPHS database (reported by local/district IPHS).
- Timely access to IPHS database.
- Scheduling factory visits through IPHS.
- Limited usefulness of data from the literature.