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**CASE-CONTROL STUDIES OF ACUTE MYELOID LEUKEMIA (AML) AND
NON-HODGKIN'S LYMPHOMA (NHL) IN SHANGHAI**

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Benzene studies: chronology

Pre-1970s	Case reports: clinical description, but no risk estimates Aksoy: shoe makers in Turkey
1978	Ott: Dow Chemical workers in Michigan
1986	Bond: Update of the Dow study
1983	Decouflé: Conoco plant in Baltimore (a former refinery)
1987	Wong: 7 chemical plants in the US
1980s & 1990s	Cohort studies of petroleum workers in the US and UK
1995	Wong & Raabe: Meta-analysis by cell type (n = 208,000)
1977	Infante: Pliofilm workers in Ohio
1981, 1987	Rinsky: First update of the Pliofilm study (total leukemia)
1994	Paxton: Second update of the Pliofilm study (total leukemia)
1995	Wong: Second update of the Pliofilm study (AML, exposure-response)
2000	Wong and Raabe: Meta-analysis of NHL (n = 308,000)

Studies of Chinese workers

Original epidemiologic study by the Chinese Academy of Preventive Medicine (CAPM)

- Yin et al., 1986; Epidemiologic study [in Chinese]
- Yin et al., 1987; Exposure survey
- Yin et al., 1987; Epidemiologic cohort study (28,460 exposed workers)
- Li and Yin, 1988; Case-control study of leukemia
- Yin et al., 1989; Epidemiologic cohort study

Expanded epidemiologic study by CAPM and US NCI

- Yin et al., 1994; General methods and resources of epidemiologic study
- Dosemeci et al., 1994; Exposure assessment
- Yin et al., 1996; Overall epidemiologic results (74,828 exposed workers)
- Hayes et al., 1997; Dose-response analyses in epidemiologic study

Clinical investigations by CAPM and US NCI

- Travis et al., 1994; Clinical discussion of 82 cases
- Rothman et al., 1996; Hematotoxicity of 44 exposed workers
- Rothman et al., 1998; Benzene metabolites of 38 exposed workers

Studies of Chinese workers

Comparison of the CAPM and CAPM-NCI study attributes

Study attribute	Original CAPM study	Expanded CAPM-NCI study
Number of workers: exposed	28460	74828
unexposed	28257	35805
Follow-up period	1972-1981	1972-1987
Person-years: exposed	178556	782497
unexposed	199201	419523
Number of facilities: benzene control	233 exposed factories 83 unexposed factories	672 exposed factories 40 unexposed factories + 69 unexposed units
Major industries with benzene exposure (exposed group)	Painting, paint producing, rubber, glue, shoemaking, leather, & organic synthesis.	Food, textile, leather products, wood and furniture, paper products, stationery, printing, agricultural chemical, organic chemical, other chemical, pharmaceutical, rubber and plastic, petroleum products, glass products, metallurgy, fabricated metal, electrical equipment, transportation equipment, precision machinery, other manufacturing, & construction.
Industries with no benzene exposure (unexposed group)	Machine production, textile, & cloth factories.	Not reported.
Exposure assessment	Exposure levels of leukemia cases were reported. No overall exposure assessment was done.	An overall exposure assessment was done for the entire cohort.
Number of deaths: exposed	474	1369
unexposed	277	598
Major diseases analyzed	Leukemia (all cell types). No exposure-response analyses done.	Lymphohematopoietic malignancies & other hematologic disorders. Exposure-response analyses on selected diseases.
Major findings reported	Increased risk of leukemia (primarily ANLL).	Increased risk of all lymphohematopoietic malignancies, malignant lymphoma, leukemia (particularly ANLL), agranulocytosis, aplastic anemia, & myelodysplastic syndrome.

Studies of Chinese workers

CAPM-NCI study (1972-1987) (Yin et al., 1996)

Major findings:

Diagnosis	Exposed workers	Unexposed workers	Relative Risk	95% CI
Lymphohematopoietic cancers	63	13	2.6	1.5-5.0
Non-Hodgkin's Lymphoma	17	3	3.5	1.2-14.9
Multiple myeloma	1	1	0.4	0.1-10.7
All leukemias	42	9	2.6	1.3-5.7
AML	23	4	3.1	1.2-10.7
CML	9	2	2.6	0.7-16.9
ALL	5	1	2.8	0.5-54.5

Studies of Chinese workers

CAPM-NCI study (1972-1987) (Hayes et al., 1997)

Overall analyses:

Cancer	Cases in exposed workers	Cases in unexposed workers	Relative Risk	95% CI
AML	21	4	3.0	1.0-8.9
NHL	16	3	3.0	0.9-10.5

Exposure-response analyses:

Diagnosis	Unexposed workers	<40 ppm-years	40-99 ppm-years	100+ ppm-years	p-value trend
Non-Hodgkin's Lymphoma					
Number	3	6	1	9	
Relative Risk	1.0	3.3	1.1	3.5	0.02
95% CI	--	0.8-13.1	0.1-11.1	0.9-13.2	
Acute Myeloid Leukemia					
Number	4	5	5	11	
Relative Risk	1.0	1.9	4.3	3.6	0.06
95% CI	--	0.5-7.0	1.1-16.0	1.10-11.6	

Comparison of leukemia results in studies of workers exposed to benzene

Study variable	Pliofilm US	CAPM-NCI China	Petroleum US & UK
Author, year	Wong 1995	Yin 1996	Wong & Raabe 1995
Cohort: exposed workers follow-up person-years comparison group	1,212 1950-1987 40,345 general population	74,828 1972-1987 782,497 35,805 unexposed workers	250,000+ 1937-1995 5,000,000+ general population
RR (n): leukemia AML	3.60 (14) 5.03 (6)	2.6 (42) 3.1 (23)	1.02 (498) 0.96 (148)
Bz measurements: range & high levels	1974 mean: 8-260 ppm max: 355 ppm	1979-1981 95%: 0.02-266 ppm 1.3% > 314 ppm	1973-1982 89% < 1 ppm 10%: 1-10 ppm
Industries or occupations	Pliofilm (rubber hydrochloride) manufacturing	Paint, varnish, shoe, insecticide, chemical, rubber, pharmaceutical, printing, plastic	Refining (majority), distribution, & pipeline
Potential concomitant exposures	A few cases previously worked in tire building	Other solvents, other chemicals, insecticides, drugs, etc.	Other petroleum products

Benzene exposure and leukemia: Summary

Exposure to benzene increases the risk of AML.

Question: What is the threshold for benzene-related AML?

**Based on US (NIOSH) data: 200-500 ppm-years (or 4 to 12 ppm for a 40-year work life)
(Wong, *Occup Environ Med*, 1995)**

**Based on Chinese data: 40 ppm-years?
Exposure levels underestimated (see critique by Wong, *Regul Toxicol Pharmacol*, 2000)**

Benzene exposure and NHL

Cohort studies of chemical workers exposed to benzene in the US

Author (year)	Cohort	Benzene levels	Observed deaths	Expected deaths	SMR (95% CI)
Wong 1987	7676	TWA > 50 ppm peaks > 100 ppm	7	5.12	1.37 (0.55-2.82)
Rinsky 1987; Wong 1998	1165	TWA up to 260 ppm, peaks up to 680 ppm	3	3.28	0.91 (0.19-2.66)
Ott 1976; Bond 1986	594	TWA > 25 ppm peaks up to 937 ppm	2	1.70	1.17 (0.14-4.22)
Decouflé 1982	259	not reported	0	not reported	0
Total	9694		12	10.10	1.18 (0.60-2.05)

**NHL in a multi-national cohort of more than 308,000 petroleum workers
by country and by industrial division**

Country	Division	Observed deaths	Expected deaths	SMR	95% CI
US	Refinery	317	330.79	0.96	0.86-1.07
Non-US	Refinery	91	81.41	1.12	0.90-1.37
Global	Distribution	64	99.38	0.64	0.50-0.82
Global	Crude Oil	34	50.10	0.68	0.47-0.95
Global	ALL	506	561.68	0.90	0.82-0.98

Source: Wong and Raabe, *Journal of Occupational and Environmental Medicine*, 2000

Case-control studies of non-Hodgkin's lymphoma and benzene exposure

Authors (year)	Location	No. of cases	Exposure as stated	Odds ratios (confidence interval)
Schumacher and Delzell (1988)	North Carolina, US	501	Benzene	0.77 (95% CI 0.56-1.07) for whites 0.94 (95% CI 0.47-1.87) for blacks
Ott et al. (1989)	West Virginia, US	52	Benzene	1.0 (95% CI not reported)
Scherr et al. (1992)	Boston, US	303	Benzene	1.2 (95% CI 0.5-2.6)
Blair et al. (1993)	Iowa and Minnesota, US	622	Benzene	1.1 (95% CI 0.9-1.4)
Siemiatycki et al. (1991)	Montreal, Canada	215	Benzene	0.7 (90% CI 0.5-1.0) for any exposure 0.8 (90% CI 0.4-1.7) for substantial exposure
Franceschi et al. (1989)	Northeast Italy	208	Benzene & solvents	1.14 (95% CI 0.57-2.28)
Cartwright et al. (1988) & Bernard et (1984)	Yorkshire, UK	158	Benzene	0.49 (95% CI 0.21-2.00)

Source: Wong and Raabe, *Journal of Occupational and Environmental Medicine*, 2000

Chinese Academy of Preventive Medicine-US National Cancer Institute
CAPM-NCI study (Hayes et al., 1997)

Occupation	Mean exposure	Person-years	NHL cases	Relative risk
All occupations	22.5 ppm	698,000	16	3.0
Coatings/paints	21.5 ppm	350,000	4	1.6
Rubber	53.5 ppm	34,000	1	4.0
Chemical	24.8 ppm	88,000	5	7.8
Shoe	21.8 ppm	68,000	1	1.6
Other/mixed	17.4 ppm	158,000	5	4.1

"Chemical" included "organic, insecticide, & benzene production" (Dosemeci et al., 1994).

Numerous studies have found an association between agricultural chemicals and NHL.

Comparison of NHL results

Study	Country	NHL cases	Risk ratios
Cohort studies of US benzene workers	US	12	Meta-SMR = 1.18
Cohort studies of petroleum workers	US, UK, Canada, Australia, Finland, Italy	506	Meta-SMR = 0.90
Case-control studies	US, Canada, Italy, UK	2059	Range of RR: 0.49-1.2
Cohort study of workers in different industries	China	16	RR = 3.0 overall RR = 7.8 "chemical" RR = 4.1 "mixed"

Benzene exposure and NHL: Summary

Does exposure to benzene increase the risk of NHL?

Why are the results from the Chinese study not consistent with other studies?

Occupational Epidemiologic Studies in China

Difficulties in conducting historical cohort studies in China:

- No systematic follow-up similar to that in the US (e.g., SSA, NDI).
- Follow-up depends on a variety of sources (employers, families, co-workers, treating physicians), which may vary in quality and reporting completeness.
- Unavailability of detailed national mortality rates of AML/NHL for comparison.
- Comparison may have to rely on *ad hoc* "unexposed" workers.
- Rates derived from *ad hoc* comparison groups are unstable.
- Since rates of AML and NHL are low in China, cohorts (exposed and unexposed) have to be extremely large.

PROPOSAL

Hospital-based case-control studies of AML and NHL in Shanghai

Objectives:

- 1. To determine the risk of developing AML or NHL (and major subtypes) among workers exposed to benzene in Shanghai.**
- 2. To quantify the exposure-response relations between exposure to benzene and AML or NHL among these workers.**
- 3. To determine other risk factors (e.g., occupational exposures other than benzene) of AML or NHL among these workers.**

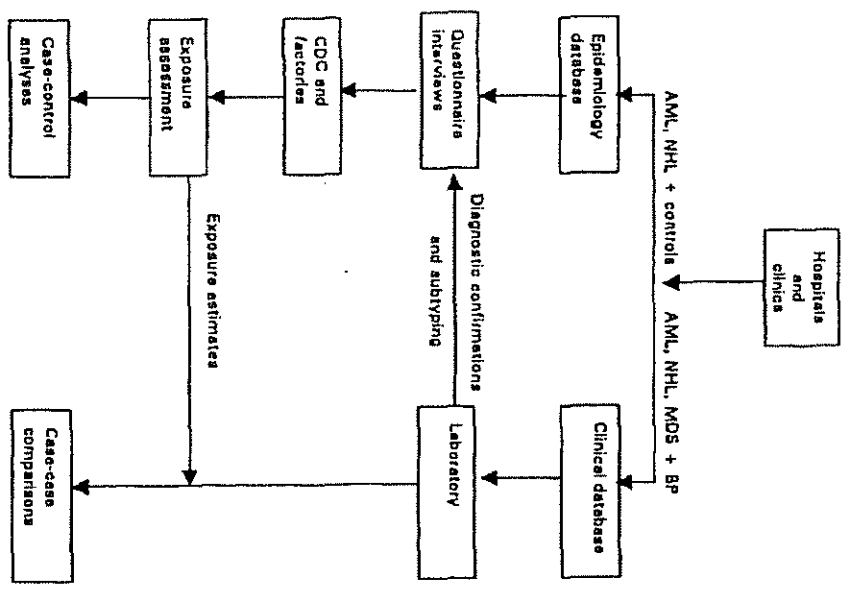
Reasons for choosing Shanghai

1. The largest data contributor in the CAPM-NCI cohort study.
2. One of the sites of the CAPM case-control study.
3. Site for the CAPM-NCI clinical investigation.
4. Large population (13-14 million).
5. Major medical establishments (universities, hospitals, tumor registry).
6. Experienced local investigators.
7. A variety of industries in the area.
8. A wide range of benzene exposure levels.
9. Documented employment histories from employers through Shanghai CDC.
10. Availability of historical measurements of benzene exposure at workplaces.

Information on risk factors

- **Demographic, lifestyle, medical histories and occupational information will be obtained from medical records and by questionnaire.**
- **For those identified to have been exposed to benzene, detailed benzene exposure histories will be obtained from employers through Shanghai CDC.**
- **Exposure levels and other relevant information (such as engineering controls) will be obtained from employers and Shanghai CDC (limited data before 1970).**
- **Based on employment histories and exposure data, an exposure profile will be developed for each exposed study subject.**
- **In addition to benzene, attempts will be made to obtain information on a number of selected other occupational exposures.**

Information flow chart



Feasibility investigations

First feasibility investigation (October and November, 1998)

- Procedure for access to patient records was developed.
- Number of AML and NHL patients per year estimated.
- A test sample of 6 AML cases and 24 patient controls was selected.
- The questionnaire used in the Montreal study (by Siemiatycki) was translated and tested in the sample. Suggestions were made for future revision.
- Exposure data at Shanghai CDC was reviewed.

Second feasibility investigation (August, 1999)

- Visits to factories confirmed high exposure levels at some work sites.
- Review of exposure data at Shanghai CDC.

Data Access

Cooperation and data access have been obtained from:

- Shanghai Medical University (and all affiliated hospitals)
- Shanghai Tumor Registry
- Shanghai Hematology Association
- Shanghai Municipal Center for Disease Control and Prevention (SCDC)

A joint research agreement between Shanghai Medical University and Applied Health Sciences has been signed, and a copy has been filed with the Office of International Exchange Programs at SMU.

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Summary

- Optimal study design: hospital-based case-control studies in Shanghai.
- Study size: 500 AML cases, 500 NHL cases and 1500 controls.
- AML or NHL cases can be enrolled over 3 to 4 years (approximately 150 cases per year) on prospective basis.
- The investigation will take approximately 5 years to complete.
- Occupational exposure information from 1970s onward will be relatively complete.
- Occupational exposure information prior to 1970 will likely be limited.
- Study subject cooperation will be high, given that data collection will be non-invasive.
- Data access has been obtained from all major organizations.
- Joint research agreement between Shanghai Medical University and Applied Health Sciences has been signed, and a copy has been filed with the Office of International Exchange Programs at SMU.