National Cancer Institute

National Cancer Advisory Board

Occupational Exposure to Benzene and Risk of Leukemia and Lymphoma

Nathaniel Rothman, MD, MPH, MHS

Occupational & Environmental Epidemiology Branch
Division of Cancer Epidemiology and Genetics
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Occupational Exposure to Benzene

- Benzene (high level exposure) causes –
  - acute myelogenous leukemia
  - hematotoxicity
  - possibly non-Hodgkin lymphoma (NHL)
- Several million workers exposed to benzene in developed and developing countries
- >20 billion pounds/year manufactured in the US
- Essentially entire population is exposed to low benzene levels from gasoline, ETS
- Ongoing debate about risk at low levels of exposure

China CDC-NCI Cohort Study

Cohort Study evaluates benzene and cancer risk

Collaboration established in 1986 and continues to the present

Rationale for Study in China:

Large study population
Access to large, stable factories
Wide range of benzene exposure levels
Excellent local infrastructure support

- **12 study sites in China**

Initial Findings from Benzene Cohort Study of 110,633 workers in China

Risks of AML and myelodysplastic syndrome (MDS) were elevated in workers exposed to < 10 ppm benzene

Increased risk of non-Hodgkin lymphoma

Increased risk of lung cancer

Cohort is now being further analyzed to follow-up these findings

Hayes et al., 1997, J. Natl. Cancer Inst.

Benzene Occupational Exposure Limits in China Lowered Due to NCI-China CDC Study

Years	Standard (8-hour time-weighted average)
1979–2002	13 ppm
2002-present	2 ppm

U.S. Occupational Standard

1 ppm benzene as an 8-hour time-weighted average

Persistent Questions About Benzene's Health Effects

What is the health risk from occupational exposure to 1 ppm benzene?

What is the health risk from environmental exposure to benzene?

Does benzene cause cancers besides AML such as NHL?

What are benzene's mechanisms of action and what is the role of genetic susceptibility?

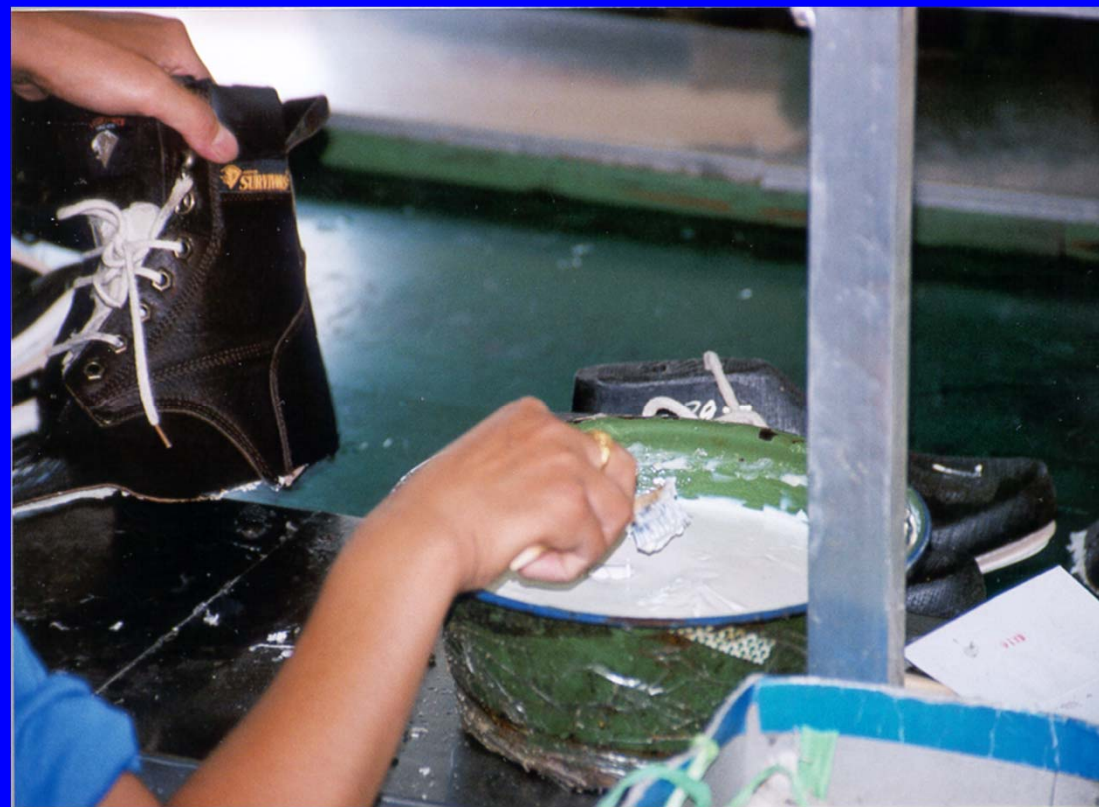
Molecular Epidemiology Study in Tianjin, China

Goal: to evaluate biologic effects in workers exposed to < 1 ppm benzene

Evaluate hematologic changes and chromosomal aberrations in healthy workers exposed to < 1 ppm benzene

Benzene Study in Tianjin, 2000-2001

- 250 healthy shoe manufacturing workers from two factories with benzene exposure
- 140 healthy age- and sex-matched unexposed controls in clothes factories

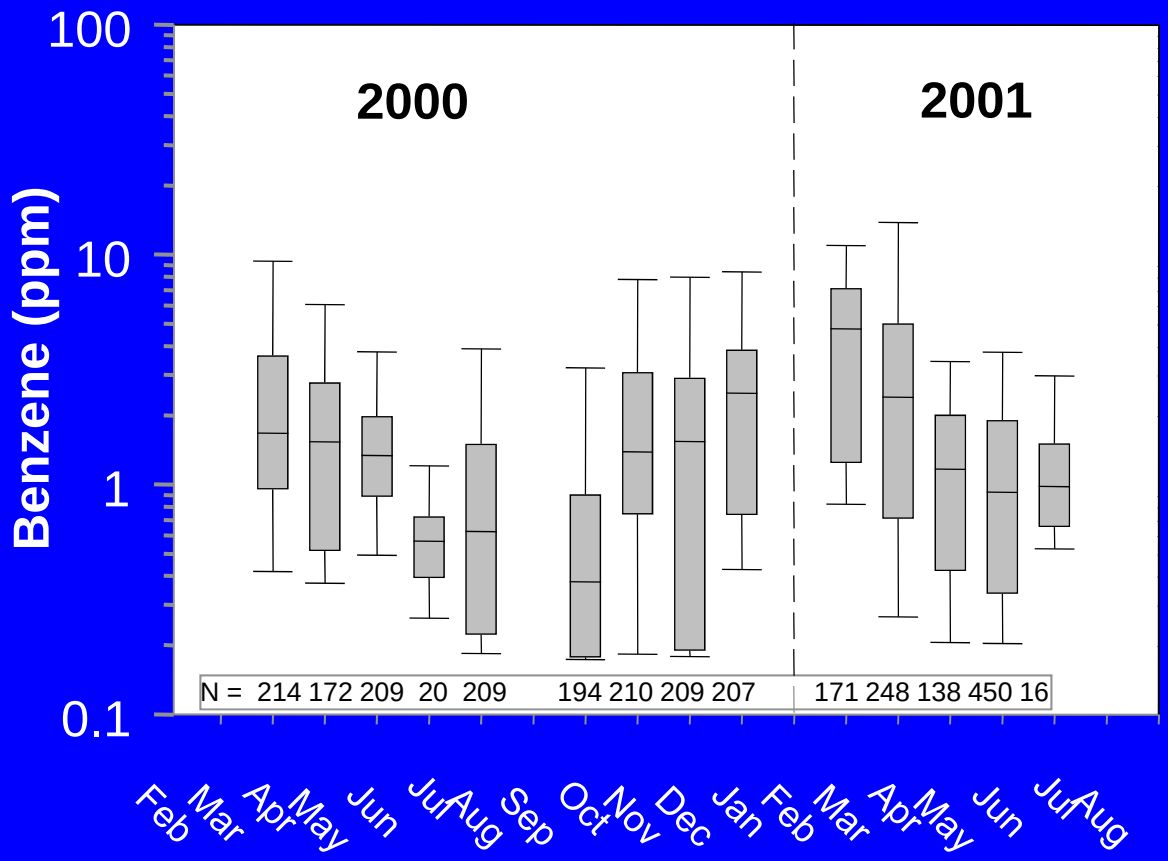


Benzene Exposure Assessment

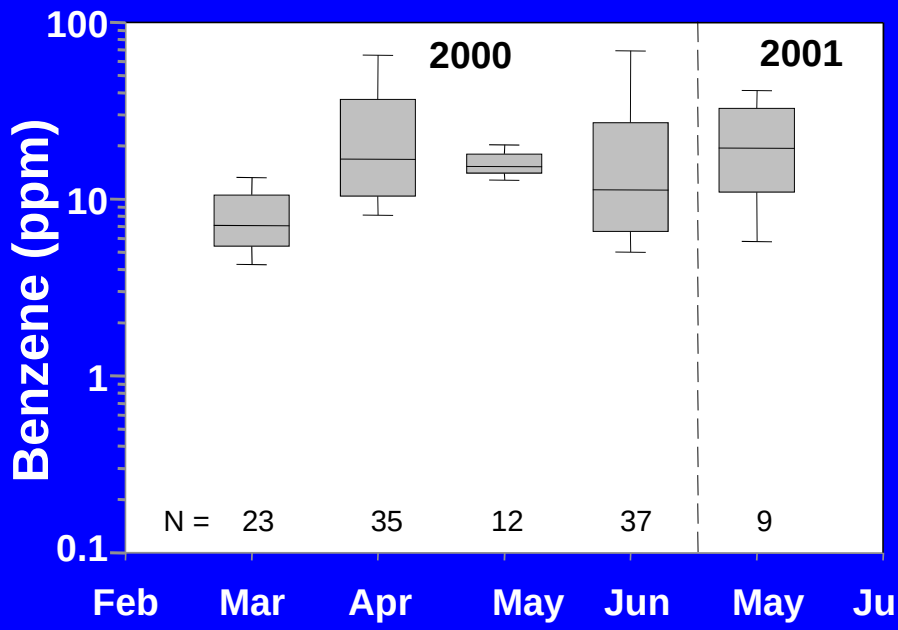
- Detailed exposure assessment to identify a low-exposed group of workers (2000-2001)
- Exposure to benzene measured by 3M badges in workplace and home over 16 months (~ 4,000 measurements)
- Benzene measured in post-workshift urine samples strongly correlated with benzene air levels

Data from Monthly Benzene Monitoring

Factory B (n=213)



Factory A (n=37)



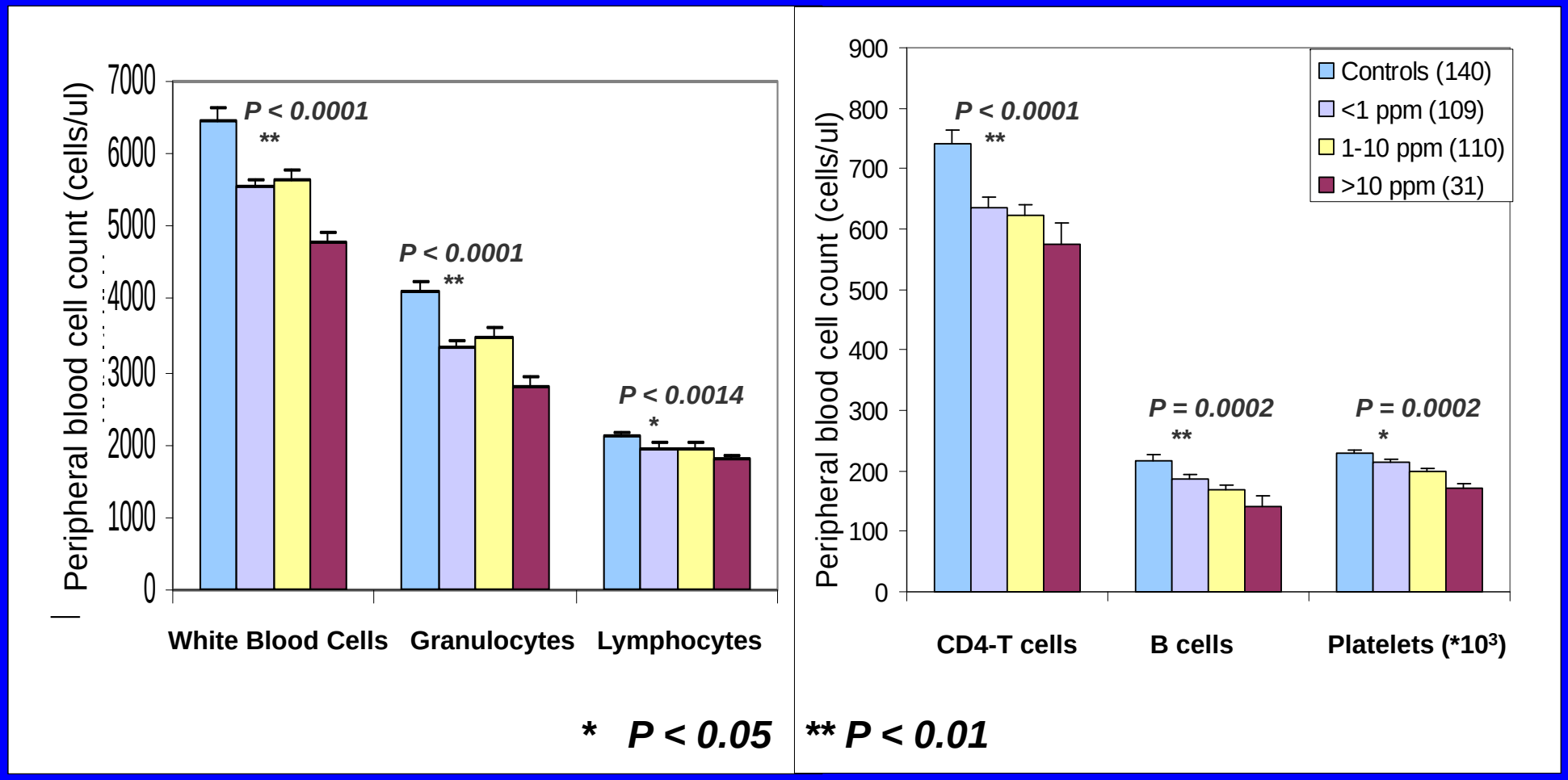
Clinical Phase of Study

- Interview
- Physical exam
- Biological sample collection

Demographic Characteristics of Study Subjects

	Controls	<1 ppm	1-10 ppm	>10 ppm
	n=140	n=109	n=110	n=31
Gender	n (%)	n (%)	n (%)	n (%)
Male	52 (37)	37 (34)	39 (35)	10 (32)
Female	88 (63)	72 (66)	71 (65)	21 (68)
Recent infection				
Yes	16 (11)	10 (9)	5 (5)	3 (10)
No	124 (89)	99 (91)	105 (95)	28 (90)
Current smoking				
Yes	39 (28)	20 (18)	25 (23)	7 (23)
No	101 (72)	89 (82)	85 (77)	24 (77)
Age	30.34 ± 8.69	28.42 ± 7.84	29.27 ± 8.20	34.81 ± 8.09

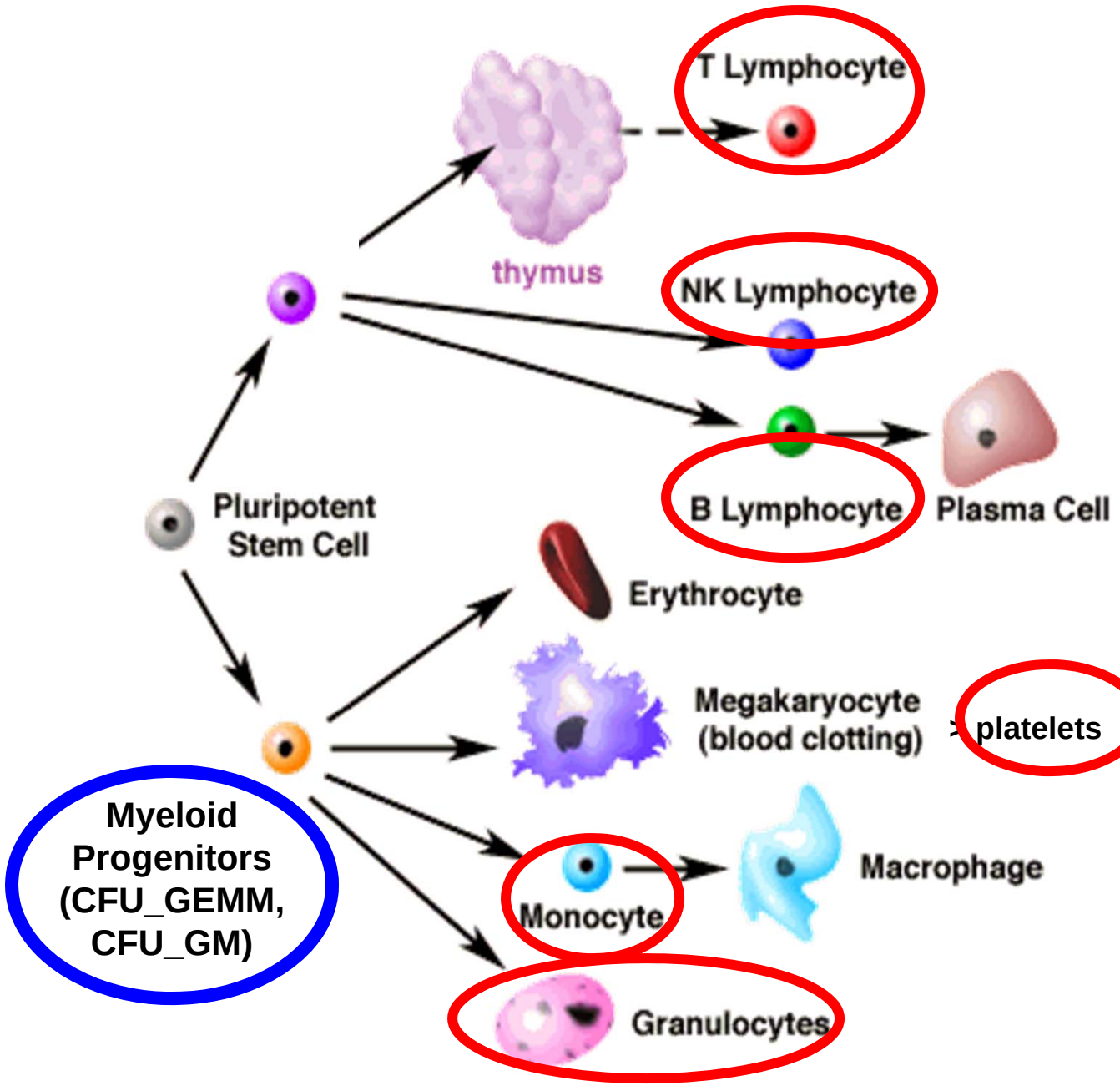
All Major Peripheral Blood Cells Decreased in Workers Exposed to < 1 ppm Benzene



Lan et al., 2004 Science

Benzene → blood cell types→ depressed bone marrow stem or progenitor cells.

Bone marrow progenitor cells present in peripheral blood at 1-10 / 100,000 mature cells, in a dynamic equilibrium with the stem cell pools in the bone marrow



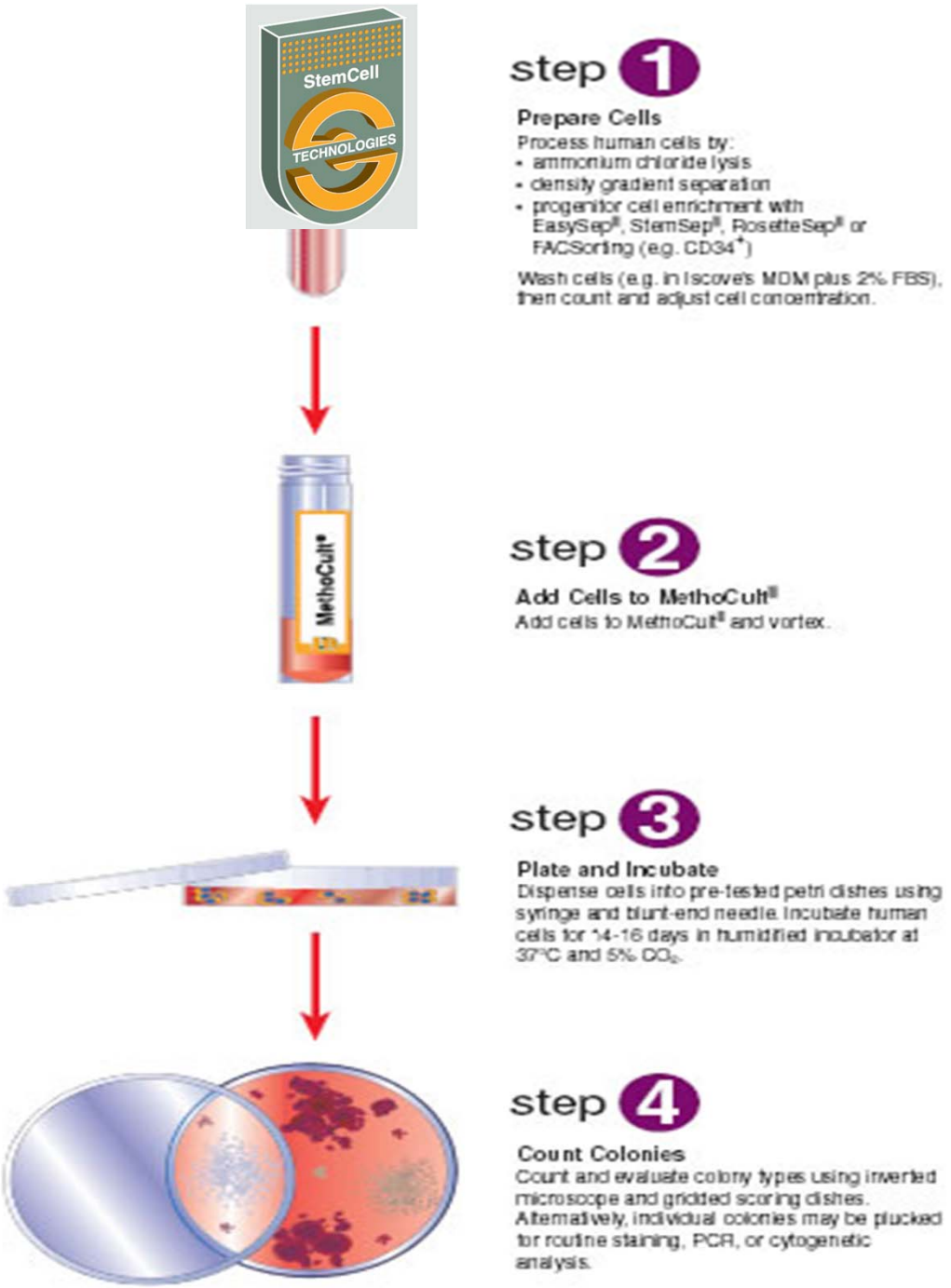
Colony-forming assay:

Cultured hematopoietic progenitor cells from peripheral blood to measure their proliferative potential

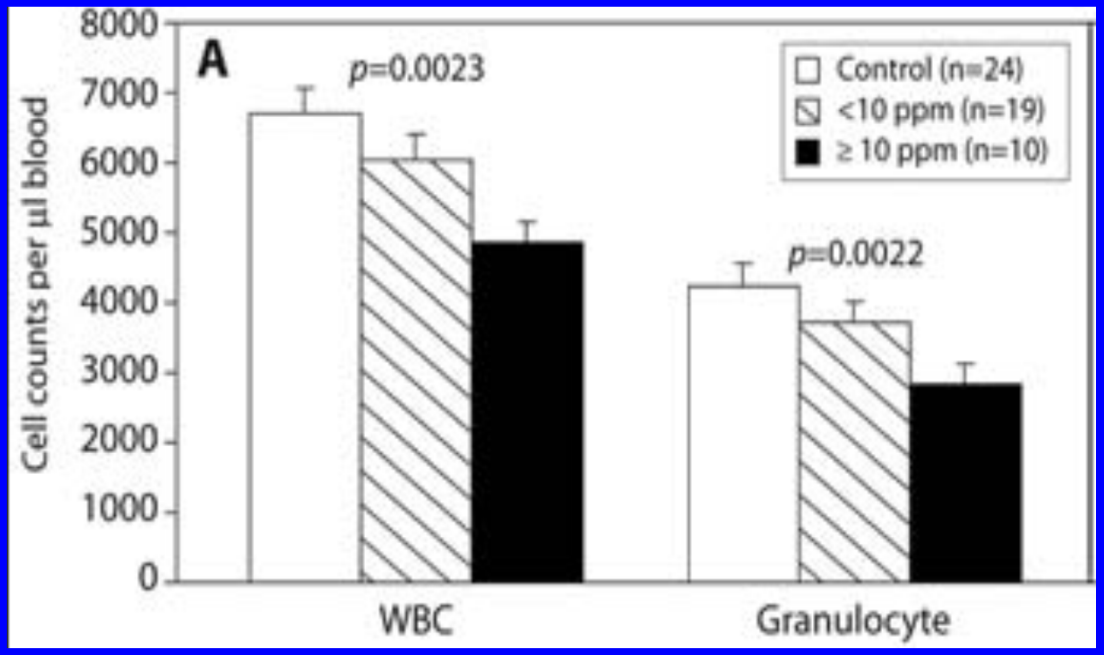
Applied to a subgroup of 29 study subjects exposed to a wide range of benzene, 24 controls

Peripheral blood mononuclear cells isolated by Ficoll separation

Progenitor cells were cultured in methylcellulose media

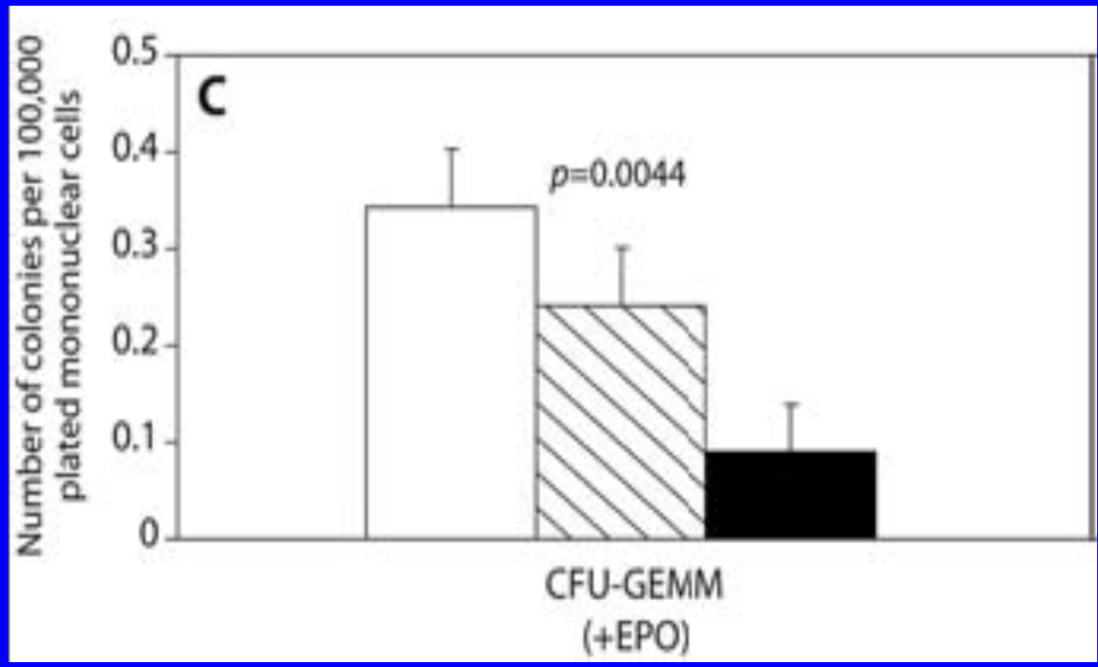


Effect of Benzene Exposure on WBCs, Granulocytes and Progenitor Cells (CFU-GEMM - colony-forming unit-granulocyte, erythroid, macrophage, megakaryocyte)

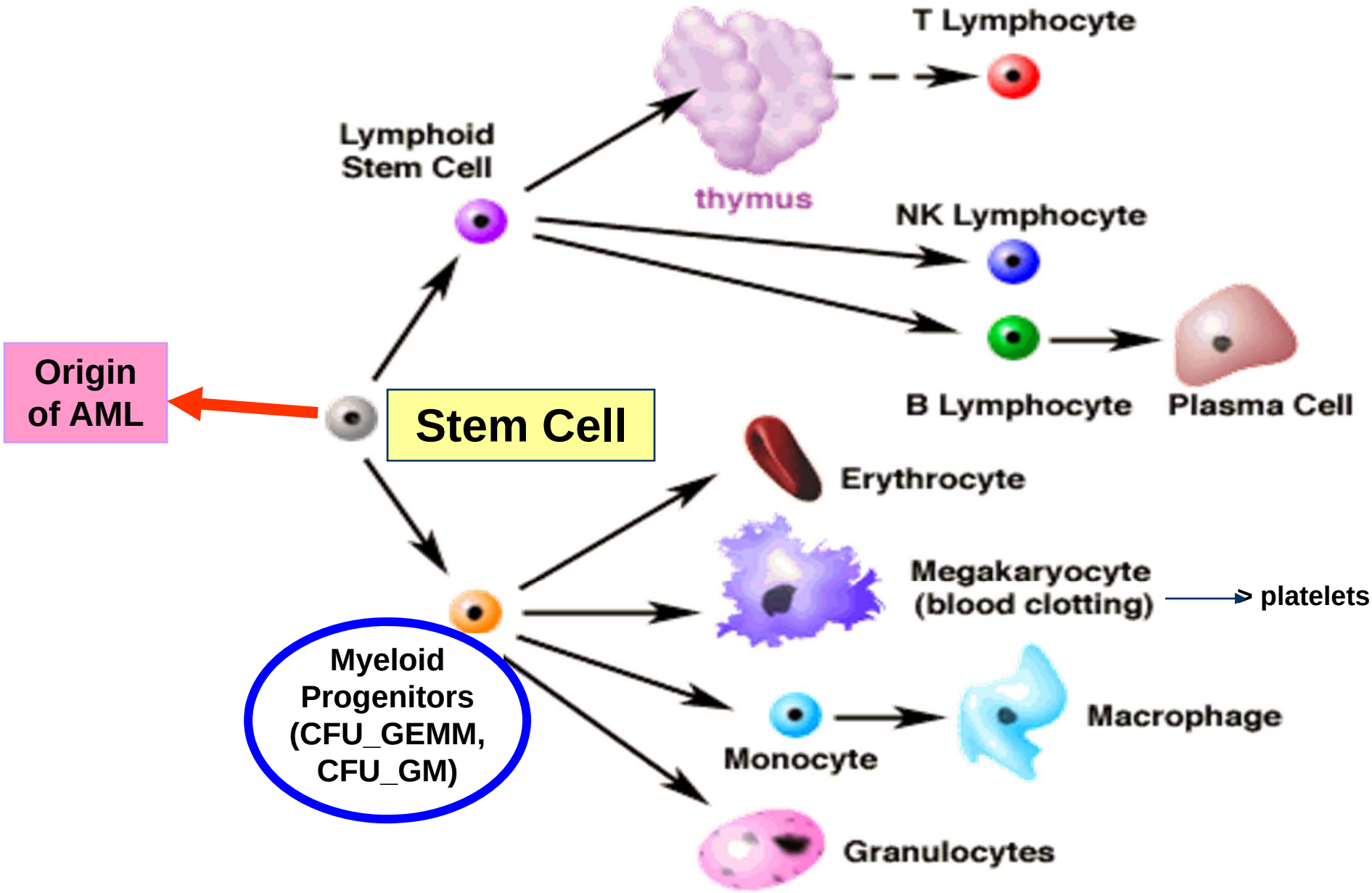


Progenitor cells were more sensitive than mature cells to benzene exposure

Suggests that mature cell counts may underestimate benzene's hematotoxic effects

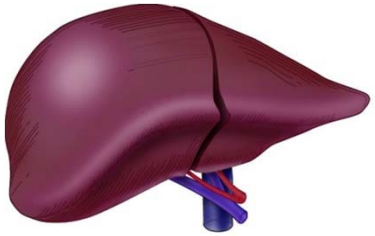


Lan et al., 2004 Science


T Lymphocyte
Lymphoid Stem Cell
thymus
NK Lymphocyte
B Lymphocyte
Plasma Cell
Origin of AML
Stem Cell
Erythrocyte
Megakaryocyte (blood clotting)
platelets
Myeloid Progenitors (CFU_GEMM, CFU_GM)
Monocyte
Macrophage
Granulocytes

Genetic Susceptibility for Benzene Toxicity

Liver



Benzene

↓

Phenol — **CYP2E1**

↓

Hydroquinone

↓

Bone Marrow

Hydroquinone

NQO1 ↑ ↓ **MPO**

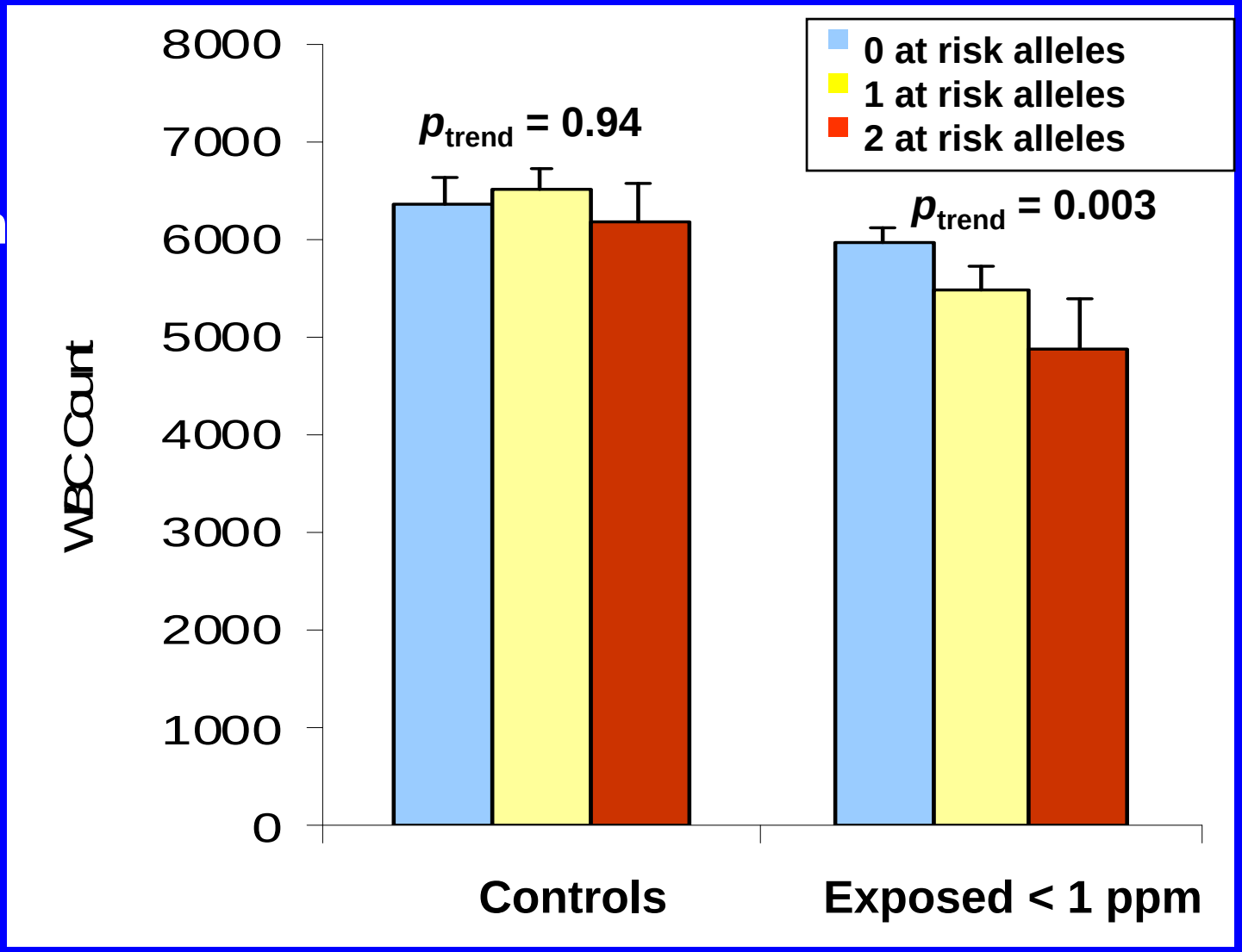
Benzoquinone

↓

TOXICITY

Combined *MPO-463G>A* and *NQO1465C>T* at Risk Genotypes Associated with Lower WBC Count at < 1 ppm Benzene

Test for interaction
$p = 0.03$



Lan et al., 2004 Science

What Are the Implications of a Lowered WBC Count in Workers Exposed to Benzene?

We observed subtle hematologic effects in this population

Unclear if there are any *immediate* clinical consequences

Hematotoxicity May Be Associated with *Future Risk* of Hematologic Malignancies

- **Benzene poisoning -- compensable condition in China**
- **Definition:**
  - **having a WBC count < 4000/ul over several months**
  - **a history of benzene exposure**
- **Previous studies: benzene poisoning → with greater risk of developing a hematologic malignancy or a related disorder**

Yin et al., 1987, Br. J. Ind. Med; Rothman et al., 1997, Cancer Res.

Benzene Hematotoxicity (WBC < 4,000/ul) and Risk of Hematologic Malignancy Among Benzene-exposed Workers in Shanghai

Benzene Hematotoxicity	# Subjects	# Cases	Person-Yrs	RR (95% C.I.)
No	11,074	7	122,62	1.0
Yes	103	3	848	42.3 (10.7-167.0)[1]

[1] Adjusted for age, sex, benzene exposure

Rothman et al., 1997, Cancer Res.

Risk of Having a White Blood Cell Count < 4000 Cells/ul by Benzene Exposure in Previous Month in Tianjin

	WBC < 4000/μl		OR (95% CI)*
Exposure	Yes (%)	No (%)	
Controls	5 (3.6)	135 (96.4)	1.0
<1 ppm	11 (9.6)	104 (90.4)	3.1 (1.1-9.5)
1- 10 ppm	12 (10.0)	112 (90.3)	3.2 (1.1-9.5)
>10 ppm	7 (18.4)	31 (81.6)	6.2 (1.8-22.3)
			P trend = 0.0016

* Adjusted for age, sex, current smoking status and recent infections

Conclusions

Exposure to < 1 ppm benzene associated with decrease in WBCs, granulocytes, lymphocytes, CD4+ cells, CD4/CD8 ratio, B cells, and platelets

Genetically defined subgroups with greater sensitivity to benzene probably exist, and this is currently being followed up with a genome-wide scan

Raises additional concerns about health effects of benzene at current occupational standards in the US and China

Occupational Exposure to Benzene and Risk of Leukemia and Lymphoma

- New evidence linking benzene to lymphoma
- Refinement of effects at low exposure levels
- Molecular epidemiology revealing mechanisms

Impact of Research Findings

- U.S. EPA decision: lower benzene content of gasoline (Federal Register, February 9, 2007)
- A U.S. National Research Council review group on regulation of selected chemicals in submarines recommended lowering the 90 day benzene exposure limit from 1.0 ppm to 0.2 ppm (National Academies, 2008)

Impact of Research Findings

A recent WHO IARC working group (Volume 100F) concluded in October 2009 that there is now additional limited evidence that benzene causes:

- **Acute Lymphocytic Leukemia**
- **Chronic Lymphocytic Leukemia**
- **Non-Hodgkin Lymphoma**
- **Multiple Myeloma**

Impact of Research Findings

Research approach serves as a model for studying the biologic plausibility that other occupational exposures cause leukemia (e.g., formaldehyde)

Collaborators

China CDC: Gulan Li, Songnian Yin

Investigators from CDCs in China:
Shanghai, Tianjin, Chengdu, Chongqing, Harbin, Shenyang, Jinzhou, Luoyang, Zhengzhou, Guangzhou, Nanchang, Kaifeng

U.S. NCI: Qing Lan, Martha Linet, Roel Vermeulen, Stephen Chanock, Richard Hayes, Min Shen, Blanche Alter, Charles Rabkin, Bill Kopp, Mustafa Dosemeci, Bill Blot

UC Berkeley: Martyn Smith, Luoping Zhang, Stephen Rappaport