National Cancer Institute

National Cancer Advisory Board

Formaldehyde Exposure and Risk of Nasopharyngeal Cancer and Leukemia

Laura Beane Freeman, Ph.D.

Occupational and Environmental Epidemiology Branch
Division of Cancer Epidemiology and Genetics

December 2, 2009

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Formaldehyde: An Important Chemical

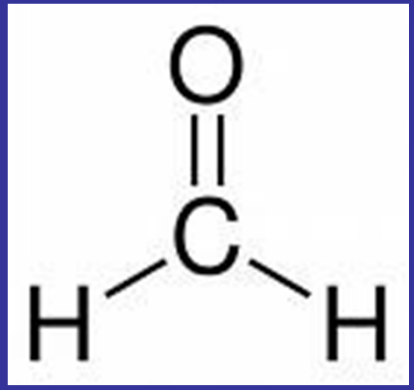
- Ubiquitous in the atmosphere and life forms
- >5% of yearly U.S. GDP
- 2.1 million U.S. workers exposed (1995)
  - Fixatives and disinfectants
  - Wood products, resins, molded plastics, crease-resistant fabrics, paper products
- Environmental exposures
  - Off-gassing from home furnishings, automobile engines, cigarette smoke, incomplete fuel combustion

U.S. Occupational Standard

0.75 ppm for 8-hr time weighted average

2.0 ppm for short-term exposure limit

Background: Evidence for Carcinogenicity



- Genotoxic
- Causes DNA-protein cross-links at site of contact
- Inhaled formaldehyde causes nasal tumors in rats

Formaldehyde Research: 3 Exposure Scenarios

- NCI Cohort of Industrial Workers
- Study of Funeral Industry Workers
- Molecular Epidemiology Study

Formaldehyde and Nasopharyngeal Cancer

NCI Cohort of Industrial Workers

Blair, et al. JNCI 1986

NCI Industrial Cohort Study

- Mortality study of 25,619 workers in 10 plants
  - Employed prior to 1966
  - Work histories through 1980
- Time-dependent exposure metrics
- 13,951 deaths as of 2004
- 42 years of median follow-up

NCI Industrial Cohort Study: Nasopharyngeal Cancer

- 8 exposed cases
  - All cases in highest peak exposure category:
    - RR=1.83, p-trend=0.044

Hauptmann, et al., Amer J Epidemiol, 2004

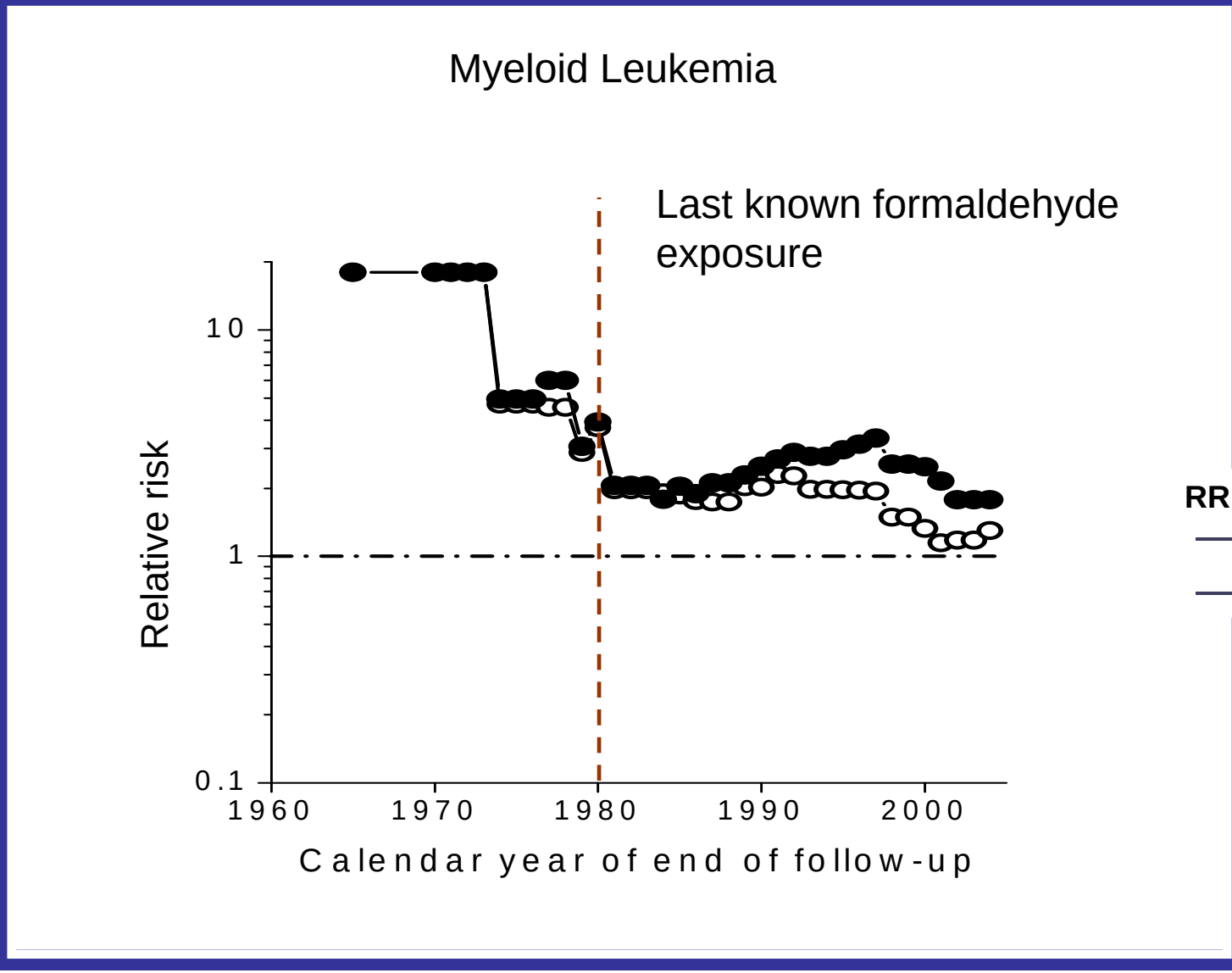
Formaldehyde and Leukemia

Relative Risks by Peak Formaldehyde Exposure (ppm)

	0	>0-<2.0	2.0-<4.0	≥4.0	
	RR	RR	RR	RR	p-trend*
Lymphohemato.	1.07	1.0	1.17	1.37*	0.02
Leukemia	0.59	1.0	0.98	1.42	>0.50
Lymphatic leukemia	0.27	1.0	0.81	1.15	>0.50
Myeloid leukemia	0.82	1.0	1.30	1.78	0.13

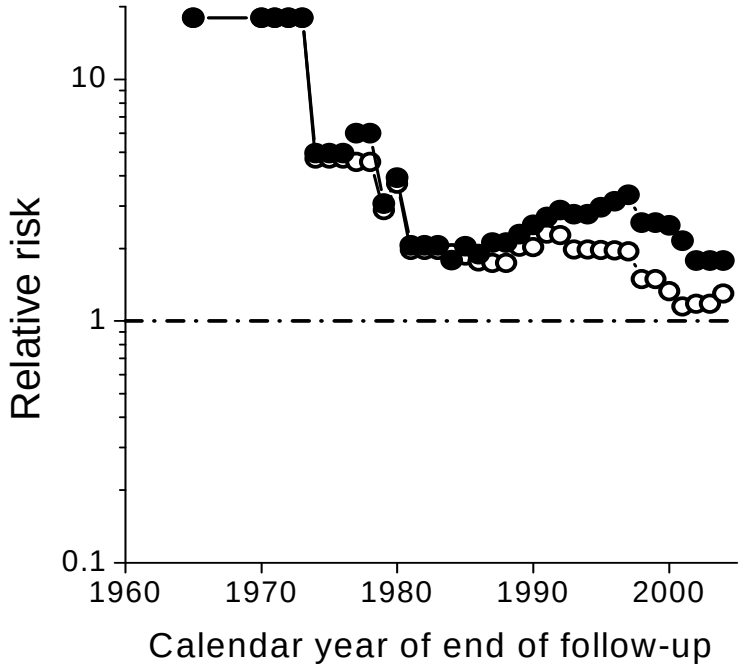
Beane Freeman, et al., JNCI. 2009; 101: 751-761.

RR for Medium and High Peak Formaldehyde Exposure Categories

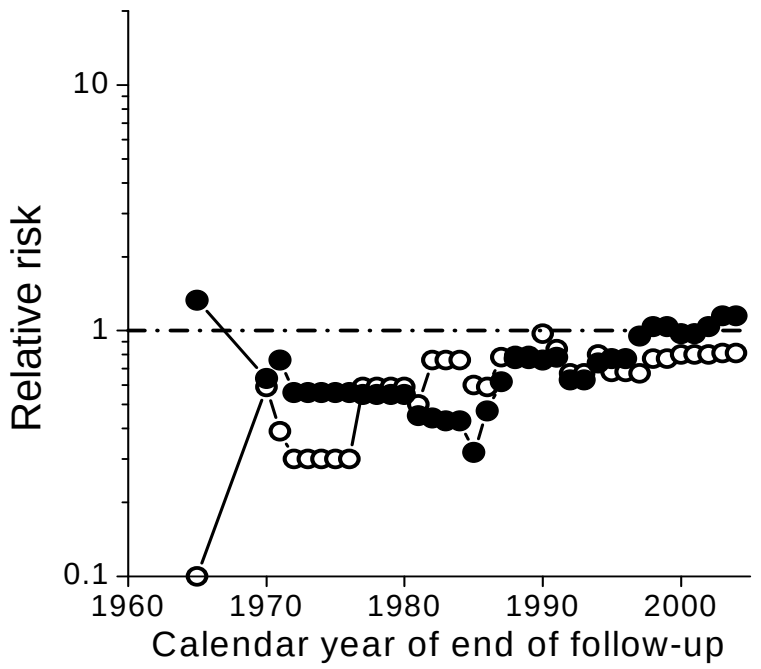


RR for Medium and High Peak Formaldehyde Exposure Categories

Myeloid Leukemia



Lymphatic Leukemia



RR for Peak

Medium

High

Study of Funeral Industry Workers

Study of Funeral Industry Workers

- 6,808 deaths among 13,994 inactive/deceased funeral directors/embalmers
- Identified through professional associations and licensing boards
- 268 deaths from lymphohematopoietic malignancies, 34 from myeloid leukemia
- 286 controls: deaths due to natural causes, matched by study source, sex, dates of birth and death

Study of Funeral Industry Workers: Exposure Assessment

- 1,278 interviews with next of kin and co-workers
- Work history, including embalming characteristics
- Exposure study
  - 25 embalmings under controlled conditions
    - Ventilation
    - Solution strength
    - Type of case (intact or autopsy)
  - Continuous measurement of formaldehyde concentration in breathing zone

Study of Funeral Industry Workers: Results

- 3-fold increased risk of myeloid leukemia for
  - Longest duration of embalming
  - Most embalmings performed
  - Highest cumulative exposure
- First study to relate cancer risk to work practices in funeral industry

Hauptmann, et al. JNCI, 2009

Molecular Epidemiology Study

Molecular Epidemiology Study

- Is formaldehyde-->leukemia plausible?
- Formaldehyde is highly reactive
- Almost completely deposited in the upper respiratory tract

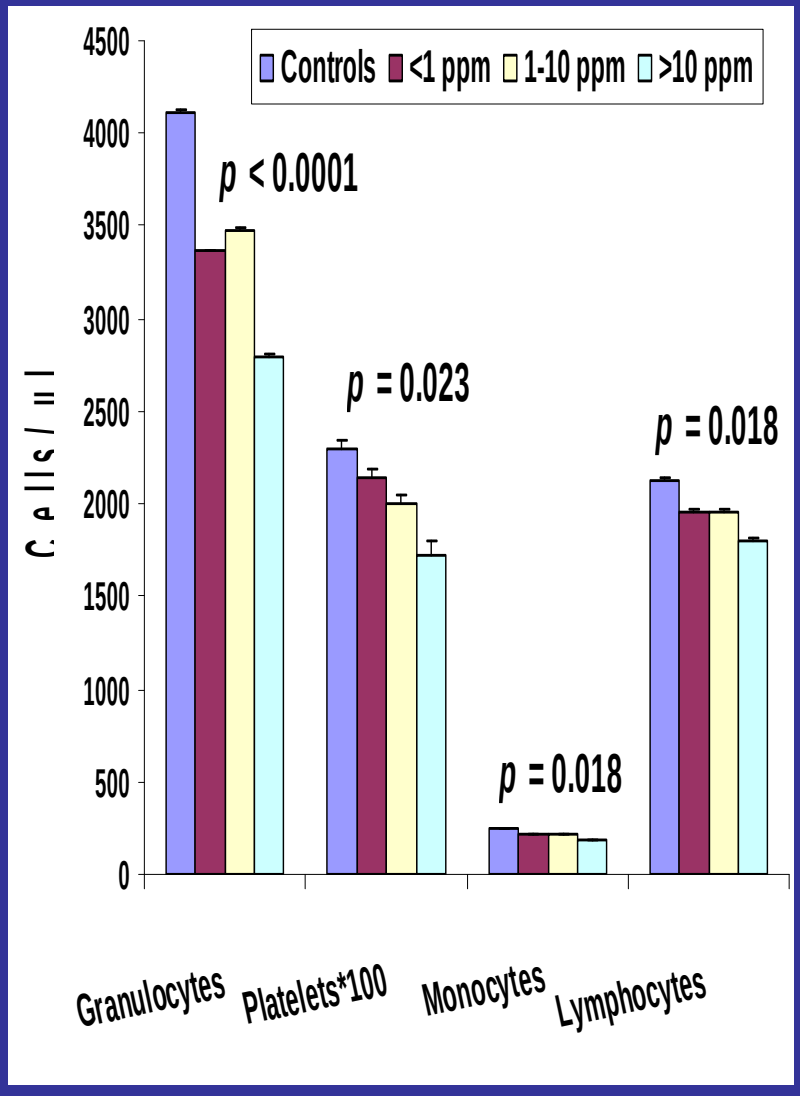
Molecular Epidemiology Study of Formaldehyde in Guangdong, China*

- Designed to evaluate whether formaldehyde can cause toxic effects on the bone marrow
- 43 workers in two plastic dish manufacturing plants currently exposed to formaldehyde (1-2 ppm)
- 51 healthy age- and sex-matched unexposed controls in three control factories

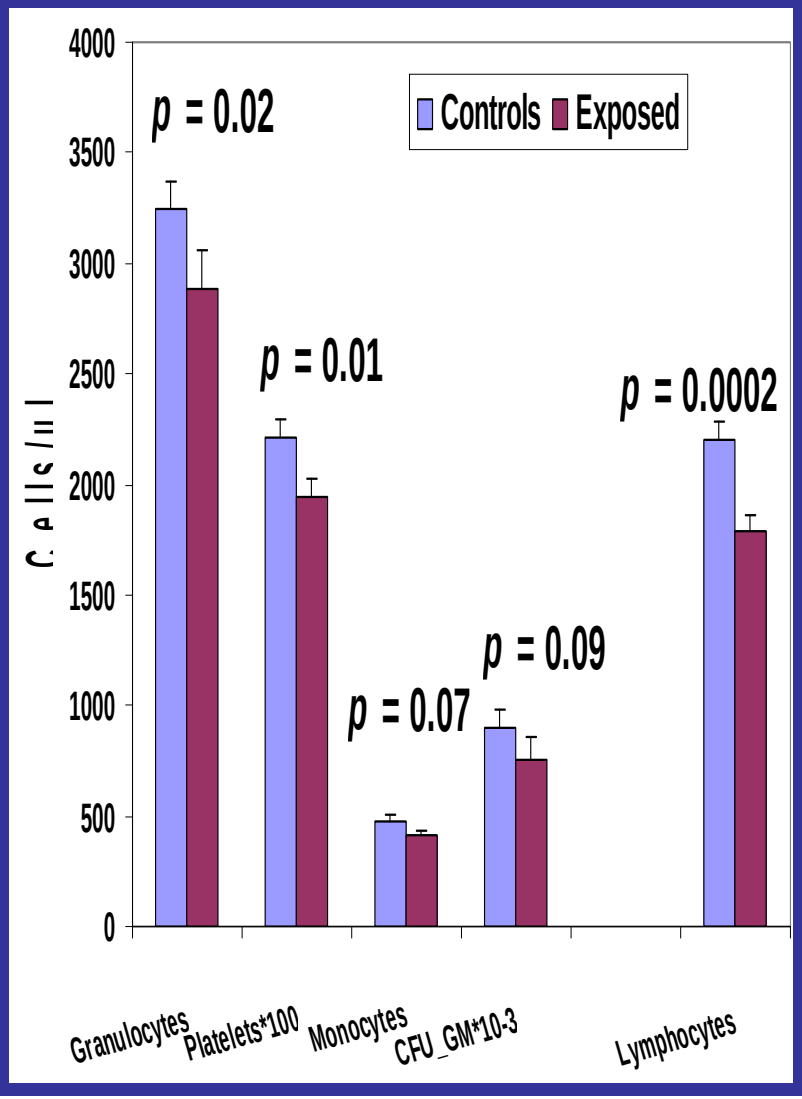
*Study initiated and designed by Drs. Lan and Rothman

Comparison of Benzene and Formaldehyde Exposures and Peripheral Blood Cells

Benzene



Formaldehyde



Hematopoietic progenitor cells from peripheral blood were cultured to measure chromosomal abnormalities relevant for myeloid leukemia

step 1

Prepare Cells

Process human cells by:

- ammonium chloride lysis
- density gradient separation
- progenitor cell enrichment with EasySep®, StemSep®, RosetteSep® or FACSorting (e.g. $CD34^+$)

Wash cells (e.g. in Iscove's MDM plus 2% FBS), then count and adjust cell concentration.

step 2

Add Cells to MethoCult®

Add cells to MethoCult® and vortex.

step 3

Plate and Incubate

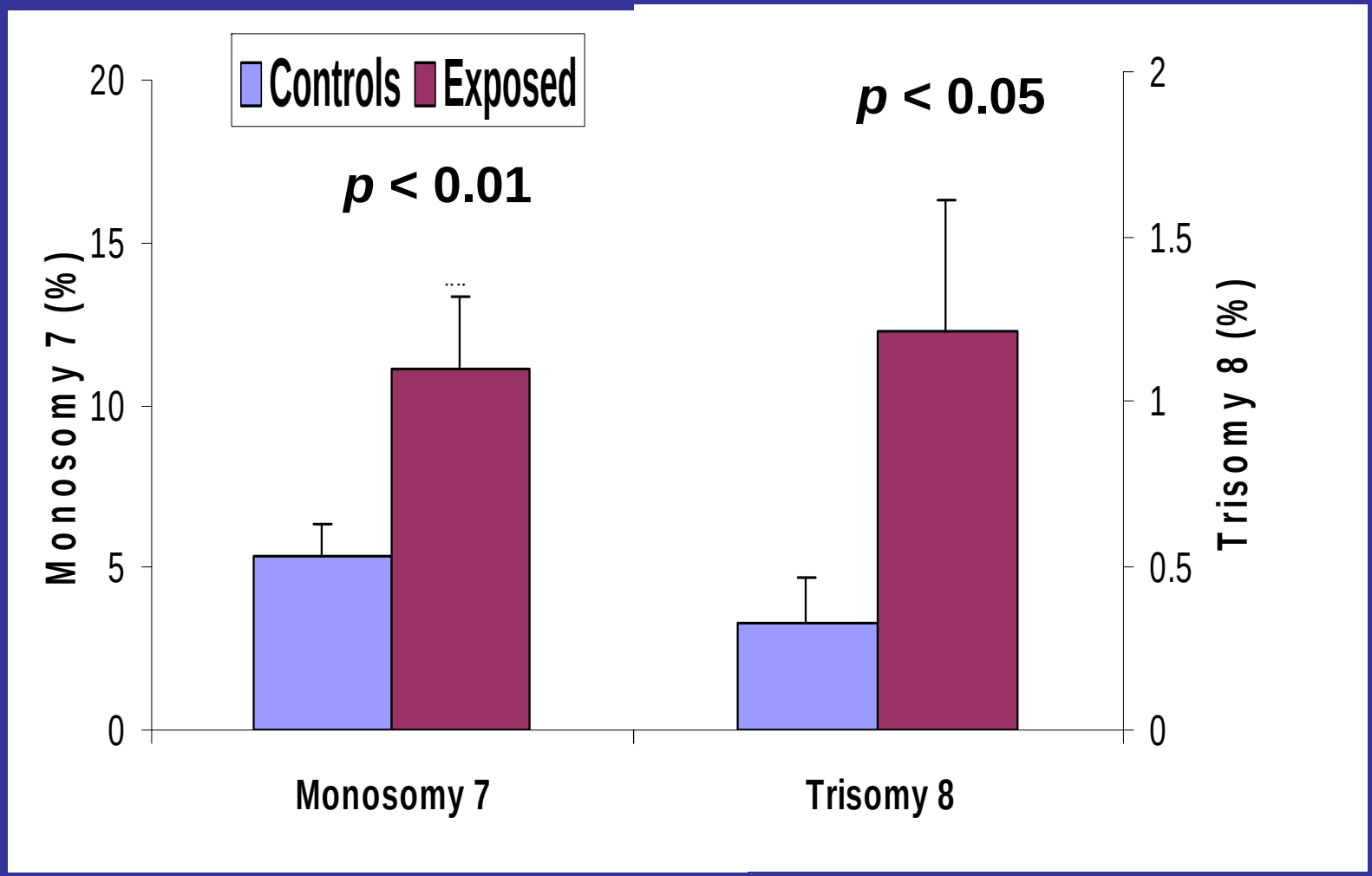
Dispense cells into pre-tested petri dishes using syringe and blunt-end needle. Incubate human cells for 14-16 days in humidified incubator at 37°C and 5% CO_2.

step 4

Count Colonies

Count and evaluate colony types using inverted microscope and gridded scoring dishes. Alternatively, individual colonies may be plucked for routine staining, PCR, or cytogenetic analysis.

Formaldehyde Exposure and Leukemia-specific Chromosome Aberrations in Cultured Myeloid Progenitor Cells (CFU_GM)



Molecular Epidemiology Study: Results

- Among formaldehyde-exposed workers we observed:
  - **Decrease in all cells derived from myeloid lineage progenitor cells**
  - **Elevation of leukemia-specific chromosome changes in myeloid progenitor cells**
- Suggests formaldehyde may cause toxic effects in bone marrow of exposed workers
- Findings support biologic plausibility of leukemia association

Impact of Research Findings

- WHO-IARC review in 2004
  - Sufficient evidence for nasopharyngeal cancer
  - Strong, but not sufficient evidence for leukemia
- WHO-IARC review in 2009
  - Sufficient evidence for leukemia, particularly myeloid
  - Reaffirmed status for nasopharyngeal cancer
- National Toxicology Program Report on Carcinogens 2009
  - Outside Expert Panel
  - Sufficient evidence for nasopharyngeal cancer and myeloid leukemia
- EPA ongoing
  - Updating risk assessment of formaldehyde

Formaldehyde Exposure and Risk of Nasopharyngeal Cancer and Leukemia

- Long-term investment→ recent results with leukemia
- Emerging molecular epidemiologic techniques→ can address important issues (plausibility)
- Combination of strategies useful

Collaborators

Cohort and Case-control Studies

NCI:

Aaron Blair, Joseph F. Fraumeni, Jr., Michael Hauptmann, Richard Hayes, Robert Hoover, Jay Lubin, Trish Stewart

Harvard University:

Robert Herrick

University of Cincinnati:

Richard Hornung

Molecular Epidemiology Study

NCI:

Qing Lan, Nat Rothman, Min Shen, Richard Hayes, Blanche Alter, Aaron Blair, Joseph F. Fraumeni Jr.

Guangdong National Poisoning Control Center (China):

Xiaojian Tang

Utrecht University (Netherlands):

Roel Vermeulen, Boris Reiss

UC Berkeley:

Martyn Smith, Luoping Zhang, Stephen Rappaport