Formaldehyde Exposure and Risk of Nasopharyngeal Cancer and Leukemia

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December 2, 2009
Formaldehyde: An Important Chemical

- Ubiquitous in the atmosphere and life forms
- >5% of yearly U.S. GDP
  - 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)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>&gt;0-&lt;2.0</th>
<th>2.0-&lt;4.0</th>
<th>≥4.0</th>
<th><strong>p-trend</strong>*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphohemato.</strong></td>
<td>1.07</td>
<td>1.0</td>
<td>1.17</td>
<td>1.37*</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td>0.59</td>
<td>1.0</td>
<td>0.98</td>
<td>1.42</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td><strong>Lymphatic leukemia</strong></td>
<td>0.27</td>
<td>1.0</td>
<td>0.81</td>
<td>1.15</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td><strong>Myeloid leukemia</strong></td>
<td>0.82</td>
<td>1.0</td>
<td>1.30</td>
<td>1.78</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Beane Freeman, et al., JNCI. 2009; 101: 751-761.*
RR for Medium and High Peak Formaldehyde Exposure Categories

Myeloid Leukemia

Last known formaldehyde exposure

Relative risk

Calendar year of end of follow-up

RR for Peak

Medium

High
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

- Granulocytes
- Platelets *10
- Monocytes
- Lymphocytes

Formaldehyde

- Granulocytes
- Platelets *10
- Monocytes
- CFU_GM *10^3
- Lymphocytes

Comparisons:
- Benzene:
  - Granulocytes: p < 0.0001
  - Platelets: p = 0.023
  - Monocytes: p = 0.018
  - Lymphocytes: p = 0.018

- Formaldehyde:
  - Granulocytes: p = 0.02
  - Platelets: p = 0.01
  - Monocytes: p = 0.0002
  - CFU_GM: p = 0.07
  - Lymphocytes: p = 0.09
Hematopoietic progenitor cells from peripheral blood were cultured to measure chromosomal abnormalities relevant for myeloid leukemia.
Formaldehyde Exposure and Leukemia-specific Chromosome Aberrations in Cultured Myeloid Progenitor Cells (CFU_GM)

- **Monosomy 7:**
  - Controls (n=12)
  - Exposed (n=10)
  - Significant difference, $p < 0.05$
  - Significance level: $p < 0.01$

- **Trisomy 8:**
  - Significant difference, $p < 0.05$
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