OCCUPATIONAL FORMALDEHYDE EXPOSURE AND CANCER RISK

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April 24, 2012
Formaldehyde: An Important Chemical

- Ubiquitous in 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
Background: Evidence for Carcinogenicity

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

- 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
  - Sufficient evidence for nasopharyngeal cancer and myeloid leukemia

- EPA ongoing
  - Updating risk assessment of formaldehyde
U.S. Occupational Standard

OSHA:

0.75 ppm for 8-h time weighted average

2.0 ppm for short-term exposure limit
Formaldehyde Research:
2 Exposure Scenarios

- Study of Funeral Industry Workers
- NCI Cohort of Industrial Workers
## Leukemia among Professionals

<table>
<thead>
<tr>
<th>Author (year, region)</th>
<th># deaths</th>
<th>Time period</th>
<th>Hematolymphopoietic malignancies</th>
<th>Leukemia</th>
<th>Myeloid leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Funeral Directors and Embalmers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayes (1990, USA)</td>
<td>4,046</td>
<td>1970-85</td>
<td>1.4* (115)</td>
<td>1.5* (51)</td>
<td>1.6* (24)</td>
</tr>
<tr>
<td>Walrath (1983, NY)</td>
<td>1,132</td>
<td>1925-80</td>
<td>1.2 (25)</td>
<td>1.4 (12)</td>
<td>1.5 (6)</td>
</tr>
<tr>
<td>Walrath (1984, CA)</td>
<td>1,007</td>
<td>1925-80</td>
<td>1.2 (19)</td>
<td>1.8* (12)</td>
<td>1.5 (6)</td>
</tr>
<tr>
<td>Milham (1976, WA)</td>
<td>222</td>
<td>1950-71</td>
<td>1.9 (7)</td>
<td>3.0 (5)</td>
<td>NR</td>
</tr>
<tr>
<td>Levine (1984, Ontario)</td>
<td>319</td>
<td>1928-77</td>
<td>1.2 (8)</td>
<td>1.6 (4)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Pathologists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harrington (1975, UK)</td>
<td>156</td>
<td>1955-73</td>
<td>2.0* (8)</td>
<td>0.6 (1)</td>
<td>NR</td>
</tr>
<tr>
<td>Hall (1991, UK)</td>
<td>194</td>
<td>1974-86</td>
<td>1.4 (10)</td>
<td>1.5 (4)</td>
<td>NR</td>
</tr>
<tr>
<td>Matanoski (1989, USA)</td>
<td>3,644</td>
<td>1912-78</td>
<td>1.2 (64)</td>
<td>1.7* (31)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Anatomists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroup (1986, USA)</td>
<td>738</td>
<td>1888-79</td>
<td>1.2 (18)</td>
<td>1.5 (10)</td>
<td>8.8* (3)</td>
</tr>
</tbody>
</table>

* 95% CI does not include 1.0
STUDY OF FUNERAL INDUSTRY WORKERS
Case Control Study of Funeral Industry Workers

- 6,808 deaths among 13,994 inactive/deceased funeral directors/embalmers
- Identified through professional associations and licensing boards (deaths from 1960-86)
- 168 deaths from lymphohematopoietic malignancies
  - 34 from myeloid leukemia
- 265 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
  - Per job: start/end, funeral home, embalming, # embalmings (autopsied/intact), ventilation
  - Per subject: duration of typical embalming, frequency of spills
  - Smoking history
Study of Funeral Industry Workers: Exposure Assessment

- Exposure study
  - 25 embalmings under controlled conditions
    - Ventilation
    - Solution strength
    - Type of case (intact or autopsy)
  - Continuous measurement of formaldehyde concentration in breathing zone
- Exposure levels:
  - Average intensity while embalming: 1.7 ppm
  - 8-hr time weighted average: 0.2 ppm
  - Peak exposure while embalming: 8.6 ppm
Cancer in the Funeral Industry: Results

<table>
<thead>
<tr>
<th>Duration (y)</th>
<th>Non-lymphoid LHPM OR</th>
<th>Myeloid Leukemia OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500 embalmings &lt;20 years</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>20 years</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt;20-34 years</td>
<td>2.0</td>
<td>3.2</td>
</tr>
<tr>
<td>&gt;34 years</td>
<td>2.6</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>p-trend=0.046</td>
<td>p-trend=0.020</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># of embalmings</th>
<th>Non-lymphoid LHPM OR</th>
<th>Myeloid Leukemia OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>&gt;500-1422</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>1423-3068</td>
<td>1.8</td>
<td>2.9</td>
</tr>
<tr>
<td>&gt;3068</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>p-trend=0.247</td>
<td>p-trend=0.314</td>
</tr>
</tbody>
</table>

Hauptmann, et al., JNCI 2009
Cancer in the Funeral Industry: Results

- Similar results for other metrics:
- **Myeloid leukemia:**
  - Cumulative exposure: $p$-trend=0.192
  - Average intensity while embalming: $p$-trend=0.058
  - TWA8 intensity: $p$-trend=0.396
  - Peak exposure: $p$-trend=0.036
- No associations with other LHPM
NCI COHORT OF INDUSTRIAL WORKERS
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: 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>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RR</strong></td>
<td>RR</td>
<td>RR</td>
<td>RR</td>
<td>RR</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphohematopoietic</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

Date of last work history

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

Relative risk vs Calendar year of end of follow-up for Myeloid Leukemia and Lymphatic Leukemia.

RR for Peak
- Medium
- High
RR for Medium and High Peak Formaldehyde Exposure Categories and p-values for Trend Tests Among Exposed Person-years

- All HLP
- NHL
- Multiple Myeloma
- Hodgkin Lymphoma
- Leukemia
- Lymphatic Leukemia
- Myeloid Leukemia

Calendar year of end of follow-up
RR for Medium and High Average Intensity Formaldehyde Exposure Categories and p-values for Trend Tests Among Exposed Person-years

Calendar year of end of follow-up

Relative risk


Leukemia

Myeloid Leukemia

Multi

Hodgkin Lymphoma

Relative risks for average exposure:
Nasopharyngeal Cancer

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

- Consistent with case-control studies of nasopharyngeal cancer and animal studies

Hauptmann, et al., Amer J Epidemiol, 2004
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