Lung Cancer Mortality: Worker Exposed to Styrene, Ethylbenzene, or Naphthalene

James J. Collins, PhD
Styrene – Lung Cancer
Styrene Epidemiology

- Epidemiology studies focus on 3 industries:
  - Styrene-butadiene rubber,
  - Reinforce plastics from styrene, and
  - Styrene monomer /polymer production
- IARC 2002 - “possibly carcinogenetic to humans” – Category 2B
  - Concern - *lymphatic and hematopoietic tissues cancers in epidemiology studies*
  - “The studies of glass fibre-reinforced plastics workers are the most informative ....because these workers had higher styrene exposures and less potential for exposure to other substances than the other cohorts studied.” (519)
Relative Risks for Lung Cancers

- Reinforced Plastics
- Monomer & Polymers
Lung Cancer (Collins et al.)

Exposure/Response

Cumulative TWA

Number of Peak Exposures

Years Since First Exposure

Latency

Cumulative TWA

Number of Peaks

Exposure/Response with Smoking Adjustment
Lung Cancer Etiology – Collins et al.

- Earlier nested c-c study of lung cancer cases indicated smoking cause of lung cancer excess.
- Updated study supported this conclusion:
  - No increased risk with increasing styrene exposure, increasing peak exposures, or latency
  - Increase in cancers (bladder, kidney) & other causes (non-malignant respiratory, heart disease) associated with smoking
  - Adjustment for smoking (bronchitis, emphysema, and asthma) produced flat exposure/response
- Limitation – No formal assessment of smoking in recent update
Lung Cancer (Ruder et al. Study)

Exposure/Response

Duration

Low Exposure  High Exposure

Short Term (1 Year or Less)  Long Term (Over 1 Year)
Lung Cancer Etiology – Ruder et al.

- Workers ever exposed to high levels of styrene had higher lung cancer rates than worker never exposed to high levels.
- Lung cancer excess limited to short term workers.
- Limitations:
  - Relatively small study.
  - Qualitative exposure assessment.
  - Workers classified by longest job held.
Lung Cancer (Kogevinas et al.)

Table 5 (page 258) Poisson regression
Lung Cancer Etiology – Kogevinas et al.

- No excess of lung cancer observed and no relation with exposure to styrene
- Limitations
  - Exposure assessment
    - may not be comparable across all countries in study
    - workers classified by longest held job
Summary of Previous Studies

- No consistent findings across studies for lung cancer
- Little indication of increasing risk with increasing exposure to styrene
- Evidence of confounding by smoking
- In 2002, IARC review of these studies
  - Did not mention lung cancer as an issue
  - “The increased risks for lymphatic and hematopoietic neoplasms observed in some of the studies are generally small, statistically unstable and often based on subgroup analyses.”
Styrene – Immunological Effects
Epidemiology Styrene Immunological Effects

- Several studies examining leukocytes and lymphocyte subpopulations
  - Limitations – control for smoking, small study size, multiple exposures, limited exposure characterization
- IARC 2002 – “Studies of effects on ... immune systems ... in exposed workers did not reveal consistent changes.” (pages 520-521)
Ethylbenzene
Ethylbenzene Studies

- Two studies on ethylbenzene workers cited by IARC in 2000.
  - However, ethylbenzene is used in the production of polystyrene
    - 5 studies of polystyrene workers
Summary Ethylbenzene

- Few studies of workers with exposure to ethylbenzene
- Studies are relatively small with no quantitative estimates of ethylbenzene
  - no evidence of increased lung cancer
Naphthalene
Naphthalene

- EPA: “Adequately scaled epidemiological studies designed to examine a possible association between naphthalene exposure and cancer were not located. Overall, no data are available to evaluate the carcinogenic potential in exposed human populations.
- IARC mentions two case reports
  - Concludes not useful for causal assessment
Additional Slides
Collins et al. Study
## Proportional Hazards Model (Models with Sufficient Fit)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Hazard Ratio (CI)*</th>
<th>p-value cumulative exposure</th>
<th>p-value model**</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Causes</td>
<td>0.999(0.998-1.001)</td>
<td>0.3183</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All Cancer</td>
<td>0.999(0.996-1.001)</td>
<td>0.3737</td>
<td>&lt;0.0001</td>
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<tr>
<td>Respiratory Cancer</td>
<td>0.997(0.993-1.001)</td>
<td>0.1804</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>0.981(0.936-1.027)</td>
<td>0.4017</td>
<td>0.0021</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>0.994(0.972-1.017)</td>
<td>0.6194</td>
<td>0.0110</td>
</tr>
<tr>
<td>Non-malignant respiratory</td>
<td>1.000(0.995-1.004)</td>
<td>0.9063</td>
<td>0.0191</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.001(0.994-1.008)</td>
<td>0.7187</td>
<td>0.0251</td>
</tr>
</tbody>
</table>

*Hazard ratio for 100 part per million-months

** Time variable is age and models include sex, year of hire, year of birth and cumulative styrene exposure
Exposure/Response with Smoking Adjustment
Styrene Average and Range of TWA Exposures

Average & Range of TWA (ppm)

Area

1/3/2014
Ruder at al. Study
Lung Cancer (Ruder et al.)

Exposure/Response

Table III (page 169)
Lung Cancer (Ruder et al.)

Table III (page 169) and Table IV (page 172)
Kogevinas et al. Study
Lung Cancer

Exposure/Response

Table 5 (page 258) Poisson regression
References
References for Cancer

References for Immunological Effects


