Approaches to Determining Carcinogenic Risks in Humans

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Outline

• International Agency for Research on Cancer (IARC) human carcinogenicity criteria

• Epidemiologic study design considerations
  – Population selection impact
  – Exposure assessment strategies
  – Outcome assessment strategies
  – Assessment of potential confounding

• Study design examples
International Agency for Research on Cancer

• Purpose is to identify human cancer causes
• Provides independent scientific opinion
• Expert working group reviews epidemiologic studies, cancer bioassays, exposure, mechanistic data
  – Group 1: Carcinogenic to humans
  – Group 2A: Probably carcinogenic to humans
  – Group 2B: Possibly carcinogenic to humans
  – Group 3: Not classifiable
  – Group 4: Probably not carcinogenic to humans
Evaluation of Carcinogenicity in Humans

- Sufficient: positive relationship between exposure and cancer; chance, bias and confounding is ruled out with reasonable confidence in studies.
- Limited: chance, bias or confounding could not be ruled out with reasonable confidence
- Inadequate: insufficient quality, consistency or statistical power to permit a conclusion
- Lack of risk: several adequate studies; bias and confounding be ruled out with reasonable confidence
IARC Overall Evaluation

• Group 1: sufficient evidence in humans OR sufficient evidence in animals and strong human evidence of a relevant mechanism (i.e. ethylene oxide, genotoxic)
• Group 2A: limited evidence in humans and sufficient evidence in animals OR sufficient evidence in animals and strong mechanistic considerations
• Group 2B: limited evidence in humans and less than sufficient evidence in animals OR inadequate evidence in humans but sufficient evidence in animals OR strong mechanistic and other data
## IARC Assessment of Workshop Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Year</th>
<th>Human</th>
<th>Animal</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>styrene</td>
<td>2002</td>
<td>Limited lymphatic, hematopoietic</td>
<td>limited</td>
<td>2B</td>
</tr>
<tr>
<td>naphthalene</td>
<td>2002</td>
<td>inadequate</td>
<td>sufficient</td>
<td>2B</td>
</tr>
<tr>
<td>ethylbenzene</td>
<td>2000</td>
<td>inadequate</td>
<td>sufficient</td>
<td>2B</td>
</tr>
<tr>
<td>cumene</td>
<td>2013</td>
<td>no data</td>
<td>sufficient</td>
<td>2B</td>
</tr>
<tr>
<td>coumarin</td>
<td>2000</td>
<td>no data</td>
<td>limited</td>
<td>3</td>
</tr>
</tbody>
</table>

Group 2B = possibly carcinogenic in humans
Group 3 = not classifiable
US National Toxicology Program
Workshop Agent Assessment

Reasonably anticipated to be human carcinogens

- styrene (2011): limited human evidence, sufficient animal evidence, supporting mechanistic data
- naphthalene (2004): sufficient animal evidence
- cumene (2013): draft document under review, proposed based on sufficient animal evidence
Challenge to Epidemiologists

• Human lung cancer takes >20 years or more to develop – prospective studies have not been feasible
• Reliance on occupational registries/work records not designed for health studies
• Ensuring quality linkage between job title or work records with quantitative or semiquantitive (categorical) exposure estimates
• Assessment of historical exposures
• Assessment of factors other than the agent of interest (smoking)
Impact of Population Selection

• General population based cancer/hospital registry
  – Large number of lung cancer cases, but potentially few with exposure of interest
  – Self reported exposure, or based on job title

• Industry specific cohort
  – Potential for small number of lung cancer cases unless industry is large
  – Opportunity to identify specific, long term exposures
  – Healthy worker effect - exposure effect underestimated or not detected if compared to general population (SMR)
  – Prevalent hires, healthier workers survive longer, may distort/invert relationship with exposure duration
Exposure Assessment

• Employment in a industry does not mean a worker has significant exposure to the agent under study
• Must determine linkage between job title and duties with current and historical exposures
• Approaches:
  – Industrial hygiene assessment to measure exposure in representative jobs, review historical exposure measures
  – Link exposure model to employment record
  – Alternative: job - exposure matrix to assign exposures based on job and expert review of industry
Outcome Assessment

• Mortality records detect majority of cases
• Death certificate detects ~95% compared to registry
• Approaches:
  – Retrospective industry-based occupational cohort study: job records linked to death certificate data (i.e., National Death Index), histology unavailable
  – Cancer/hospital based registry: histology available
• Tissue for molecular studies, biomarkers have not available as intermediate outcome
• Rarely, tissue retrieved from paraffin-embedded blocks for immunohistochemistry
Confounding

- Factor independently associated with lung cancer risk and agent of interest
- Often raised: cigarette smoking
- Not likely differentially related to exposure within an occupational cohort
- Others: family history, COPD history, other exposures

Approaches:
- Nested case-control study in an occupational cohort, obtain history from worker or next-of-kin
- Survey of current workers
- Interview of cancer/hospital registry cases/controls
Example: Diesel Exhaust Case-Control Study
Olsson et al. 2011

• 11 pooled lung cancer case-control studies
  Europe/Canada

• 13,304 cases/16,282 controls ~1990-2005

• Lifetime smoking history and occupational
  histories by interview (85% with person)

• Expert review (job exposure matrix)
  – intensity score (none=0, low=1, high=4)
  – $\sum$ Cumulative exposure (intensity x duration)
Pooled Diesel Exhaust Case-Control Data
Results and Effects of Smoking Adjustment

<table>
<thead>
<tr>
<th>Cumulative Exposure/cases</th>
<th>Odds Ratio, Smoking Unadjusted*</th>
<th>95% CI</th>
<th>Odds Ratio, Smoking Adjusted**</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (6954)</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Quartile 1 (1034)</td>
<td>1.05</td>
<td>0.96-1.15</td>
<td>0.98 (↓7%)</td>
<td>0.89-1.09</td>
</tr>
<tr>
<td>Quartile 2 (1091)</td>
<td>1.15</td>
<td>1.06-1.26</td>
<td>1.07 (↓13%)</td>
<td>0.97-1.18</td>
</tr>
<tr>
<td>Quartile 3 (1223)</td>
<td>1.28</td>
<td>1.17-1.39</td>
<td>1.10 (↓14%)</td>
<td>1.00-1.21</td>
</tr>
<tr>
<td>Quartile 4 (1412)</td>
<td>1.49</td>
<td>1.37-1.62</td>
<td>1.35 (↓9%)</td>
<td>1.23-1.49</td>
</tr>
<tr>
<td>Trend, P</td>
<td>&lt;0.01</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, study,
**Additionally adjusted for pack-years, time since quitting smoking
N=11,714; excludes 1,590 persons in occupations known be associated with lung cancer.
Example: Retrospective Cohort Study and Exposure Assessment

- Retrospective cohort study to assess lung cancer mortality from diesel exhaust
  - 31,135 men with 1+ yrs of work employed in 1985 in 4 US trucking companies
  - Personnel files: all jobs, dates, terminal locations

- Mortality assessed through 2000

- Personnel files linked to US National Death Index to identify 779 lung cancer cases

Garshick et al. 2008, 2012
Exposure Assessment

- Elemental carbon (EC) is a marker of vehicle exhaust exposure, mainly from traditional diesel engines
- > 4000 shift/area samples of EC in PM$_{1.0}$ in 36 trucking terminals
- Terminal based worker exposure model:
  - Personal EC (dock worker, mechanic) : $f$ (Work area EC)
  - Area EC: $f$ (terminal characteristics, ventilation, terminal yard)
  - Terminal yard (background) EC : $f$ (local temperature/wind, proximity to major road, %-industrial land, US region)
- Truck driver model: $f$ (terminal background EC and temperature)
- Background linked to historical air pollution levels

Lung Cancer Mortality and Cumulative Exposure

<table>
<thead>
<tr>
<th>Cumulative EC, 5-yr lag</th>
<th>Employment duration adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg/m³-months</td>
<td>Lung cancer deaths</td>
</tr>
<tr>
<td>&lt;371</td>
<td>122</td>
</tr>
<tr>
<td>371 to &lt; 860</td>
<td>191</td>
</tr>
<tr>
<td>860 to &lt;1803</td>
<td>202</td>
</tr>
<tr>
<td>≥1803</td>
<td>226</td>
</tr>
<tr>
<td>Trend</td>
<td></td>
</tr>
</tbody>
</table>

*Healthy worker survivor effect: lung cancer risk decreased with total employment duration

Garshick et al. 2012
Summary

• Epidemiologic study consideration
  – What is the nature of the exposure assessment?
  – How is job or cohort membership related to exposure intensity and duration?
  – Are workers followed for >20 to 30 years?
  – Appropriate comparison group?
  – Evidence of a healthy worker survivor effect?
  – Is confounding a concern?

• Mechanistic information may contribute to the assessment of human carcinogenicity potential