Challenges in Data Pooling
Exposure Assessment in a Pooled Nested Case-Control Study

Deborah Glass, Monash University; Lesley Rushton, Imperial College; Gong Tang, University of Pittsburgh; Rob Schnatter, EpiSolutions LLC.
I declare the following conflicts of interest

<table>
<thead>
<tr>
<th>Type</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>This research funded by</td>
<td>CONCAWE, Canadian Petroleum Products Institute, Aromatic Producers Association, Energy Institute Australia, Australian Institute of Petroleum, American Petroleum Institute</td>
</tr>
<tr>
<td>Other research support</td>
<td>Australian Institute of Petroleum</td>
</tr>
<tr>
<td>Consultant</td>
<td>Exxon-Mobil, Australia</td>
</tr>
</tbody>
</table>
Overview of the Pooled Study

Assess effect of low level benzene exposure on specific lymphohaematopoietic diseases in petroleum workers.

3 case-control studies nested in petroleum industry cohorts.

Similar design, case identification, control matching, exposure assessment, exposure metrics and analytical methods.

Opportunity to update studies and pool data to improve power to examine dose response and specific leukaemia subtypes.
## Original Studies

<table>
<thead>
<tr>
<th>Sector</th>
<th>Period of study</th>
<th>Cohort size</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Canada</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminals, &amp; Marine Distribution</td>
<td>Employees &amp; annuitants 1964 - 1983</td>
<td>6,672 men</td>
<td>Leukaemia 1,154 deaths</td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribution Terminals</td>
<td>1950 - 1997</td>
<td>23,306 men</td>
<td>Leukaemia 8,743 deaths/incident cancers</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extraction, Refineries, Terminals</td>
<td>1980 - 1999</td>
<td>16,252 men, 1,273 women</td>
<td>Leukaemia, MM and NHL 883 deaths 520 incident cancers</td>
</tr>
</tbody>
</table>
Original Exposure Assessments Similar Methodology

- Job history for each case/control included:
  - Job title, dates of starting and leaving, location

- Each job/task, estimated exposure intensity
  - Base Estimate (BE), benzene ppm based on local measured data

- Each line of work history
  - Adjusting BEs for site- and era-specific variables e.g. loading technology, % Bz in product
  - To calculate Workplace exposure estimates (WE) in ppm

- Exposure metrics for each person:
  - Career average intensity (ppm), Maximum intensity (ppm)
  - Duration of employment (years)
  - Cumulative exposure (ppm-years)

- Peak and skin metrics different in each study.
Canada:

UK:

Australia:
Comparing Exposure Estimates between Studies

Appointed external experienced researcher as arbitrator

Step 1: Reviewed original methodology
Step 2: Agreed which jobs were in each job category
Step 3: Comparison of Workplace Estimates (WEs) for the category
Step 4: Debated face to face & agreed changes to exposure estimates
Step 5: Developed & allocated of common definitions of peak & skin exposure
Step 6: Allocated job certainty score
Allocation of Certainty Score

Low = 1
  – job title or site not fully identified, BE or modifying factor allocation uncertain e.g. pre 1945;

Medium = 2
  – reasonable confidence but some uncertainty regarding BEs or whether modifiers should apply;

High = 3
  – confident of the estimate.
Exposure Estimates Comparable?

- WEs allocated to generic Job Categories, e.g. Tanker Driver (by technology e.g. bottom loading), Motor Mechanic
- AM calculated for each WE by study/era/Job Category
- AMs regarded as substantially similar if: within 20% in all three studies in one era or two studies in two eras
- If AM differed by >20%, data examined to see if: difference was justified by local exposure conditions, e.g. enclosed/open work area
- Estimates were adjusted if no justification for difference
Distribution of Cumulative Benzene Exposure (ppm-years)

Revised some background exposures
  site if benzene present, population background if not

Revised some BE values
  AU mechanics 0.33 to 0.22 ppm
  background 0.14 to 0.016 ppm

for all subjects before and after the exposure revisions
Results

- Initially 45 Job Categories identified
- Created 4 new Job Categories:
  - tankage inventory, separated road & rail loaders,
  - management & supervision hands on/off
- 27 Job Categories had insufficient overlap between studies.
  - Defined *a priori* as <5 five jobs in more than 1 study at least 1 era
    - e.g. lorry boy or driver’s mate UK-only
    - Canadian study 3 marine distribution Job Categories
    - Australian 6 refinery & 5 upstream Job Categories
- 22 Job Categories able to be compared between studies
  - 12 Job Categories similar
  - 10 were judged to be justifiably different
Compared Exposure Outcomes Between Studies

Pooling data problematic if:
- Differences in exposure outcome because the exposure assessments differed by study,
- Or unexplained interactions between study & other factors.

Modelled interactions between job, study and era. Needed to identify jobs with sufficient overlap between studies. Possible for workers at terminals not other sectors,
- 4 terminal worker job groups,
- Present in all 3 studies,
- Jobs held over most decades of study.
Modelling suggested:

- Study was not significant as a main effect variable ie it did not explain the exposure outcome differences.
- Job and decade were significant predictors of exposure, Actual work done e.g. drum filling should predict exposure, Decade likely to predict extent and efficacy of control measures.
- Interaction terms (study × Job) and (study × decade) significant predictors, Not surprising, each study had different mix of jobs & different eras.
Pooled Study References

Exposure assessment
Glass et al (2010) Ensuring comparability of benzene exposure estimates across three nested case-control studies in the petroleum industry in support of a pooled epidemiological analysis Chemico-Biological Interactions, 184(1-2) 101-111

Health outcomes
Schnatter et al (2012). Myelodysplastic Syndrome and Benzene Exposure Among Petroleum Workers: An International Pooled Analysis. JNCI 104(22) 1724
Rushton et al (2014) Acute myeloid and chronic lymphoid leukaemias and exposure to low level benzene among petroleum workers Brit J Cancer 110(3), 783
Conclusion

Important quality control check on exposure estimates.

Identified similarly exposed Job Categories to group.

Showed where adjustment between studies needed.

Much better carried out by original investigators who understood both the precision and the variability of their exposure assessments.

Needed trust and openness.

Good opportunity to allocate exposure quality scores used in sensitivity analyses.
Acknowledgements

- Exposure assessment team included:
  - Tom Armstrong TWA 8hr
  - Eileen Pearlman ExxonMobil Biomedical Sciences
  - Dave Verma McMaster University

- Disease classification team included:
  - John Ryder and Richard Irons University of Colorado
  - Malcolm Sim Monash University