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

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I declare the following conflicts of interest

Type	Company
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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

	Sector	Period of study	Cohort size	Number of cases
Canada	Terminals, & Marine Distribution	Employees & annuitants 1964 - 1983	6,672 men	Leukaemia 1,154 deaths
UK	Distribution Terminals	1950 - 1997	23,306 men	Leukaemia 8,743 deaths/incident cancers
Australia	Extraction, Refineries, Terminals	1980 - 1999	16,252 men, 1,273 women	Leukaemia, MM and NHL 883 deaths 520 incident cancers

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.

Original Outcome & Exposure Assessm't Papers

Canada:

[Schnatter et al. \(1996\)](#) Lymphohaemotopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. *Occup Environ Med.*; **53**:773-81

[Armstrong et al \(1996\)](#) Retrospective benzene and total hydrocarbon exposure assessment for a petroleum marketing and distribution worker epidemiology study. *Am Ind Hyg Assoc J.* **57**:333-43.

UK:

[Rushton & Romaniuk \(1997\)](#) A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med.* **54**:152-66.

[Lewis et al \(1997\)](#) Retrospective estimation of exposure to benzene in a leukaemia case-control study of petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med.* **54**:167-75

Australia:

[Glass et al. \(2003\)](#) Leukemia risk associated with low level benzene exposure. *Epidemiology.* **15**(5):569-77

[Glass et al. \(2000\)](#) Retrospective exposure assessment for benzene in the Australian Petroleum Industry. *Ann Occup Hyg.* **44**(4):301-20.

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;

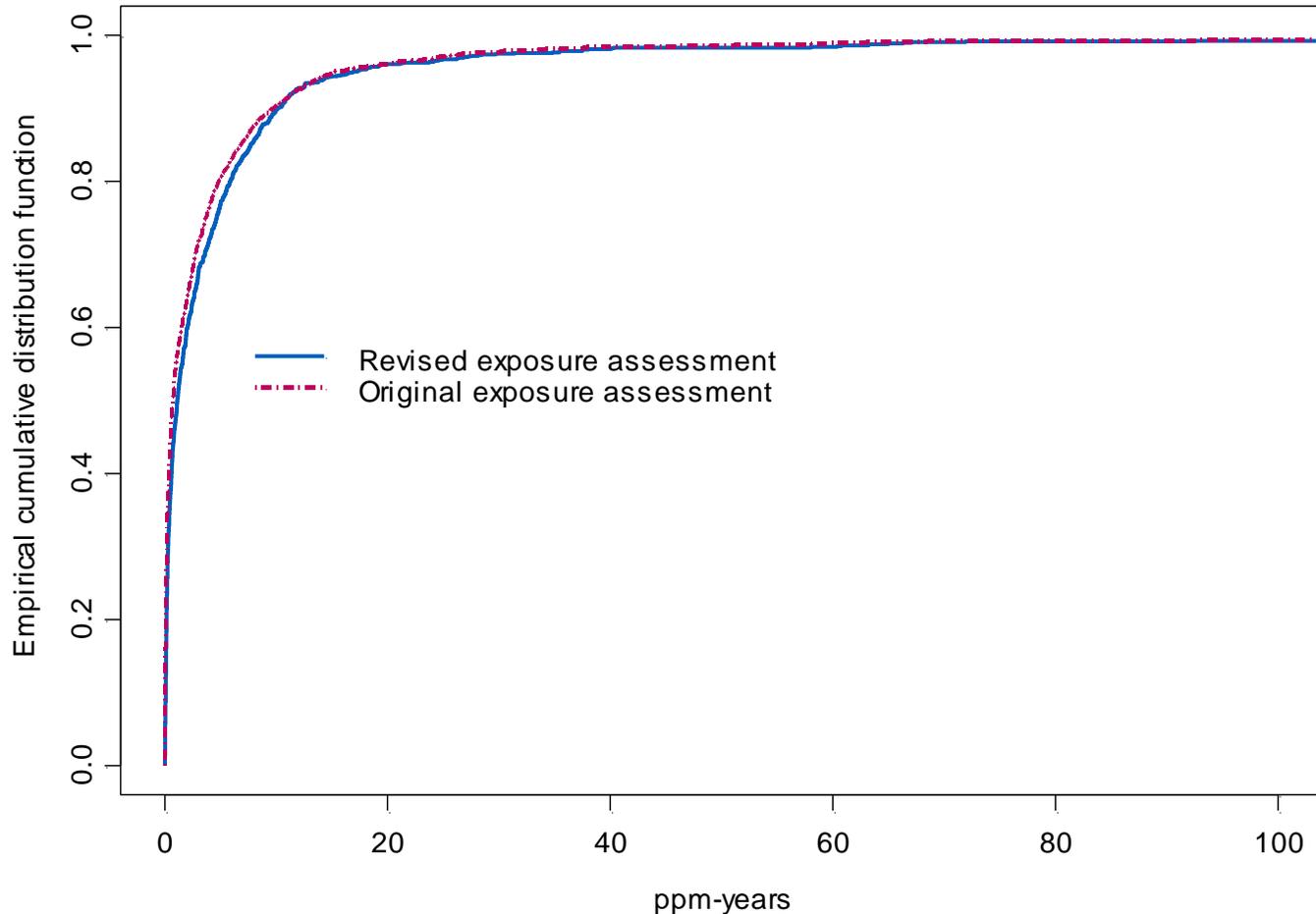
High = 3

- 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
- WEs stratified into eras (pre 1945, 1945–1959, 1960–1979 & 1980 onwards)
- 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)



for all subjects before and after the exposure revisions

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

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 Results

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 \times Job) and (study \times 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

[Glass et al \(2017\)](#) Exposure to Benzene in a Pooled Analysis of Petroleum Industry Case-Control Studies *J Occup Environ Hyg*;14 (11):863-872.

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

[Glass et al \(2014\)](#) Risk of myeloproliferative disease and chronic myeloid leukaemia following exposure to low level benzene in a nested case-control study of petroleum workers *Occup Environ Med.* 71 (4):266

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.

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