National Cancer Institute

Use of Exposure and Outcome Assessment in Epidemiologic Studies of TCE

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Outline

1) The importance of exposure specificity
2) Exposure metrics used in statistical analyses
3) Assessing the quality of exposure & outcome assessment in TCE studies

1)The importance of exposure specificity

Exposure Sensitivity and Specificity

Assessed as Exposed	Truly Exposed: Yes	Truly Exposed: No
Yes	N_{11}	N_{01}
No	N_{10}	N_{00}
	$N_{1\bullet}$	$N_{\bullet 1}$

Sensitivity = $N_{11} / N_{1\bullet}$

1- Sens = False Negative Rate

Specificity = $N_{00} / N_{\bullet 1}$

1- Spec = False Positive Rate

Exposure Sensitivity and Specificity

- Imperfect sensitivity and specificity introduce exposure misclassification
- If independent of outcome status, likely effect (with some caveats) is to **bias associations towards the null**
- For exposures with low prevalence, the bias from low specificity is particularly strong

Example: Cohort Study

1) Prevalence = 10%; Sensitivity = 100%; Specificity = 100%

Assessed as Exposed	N_{Total}	N_{Cases}
Yes	1,000	60
No	9,000	180
	10,000	

Relative Risk = 3.0

Example: Cohort Study

1) Prevalence = 10%; Sensitivity = 99%; Specificity = 99%

Assessed as Exposed	N_{Total}	N_{Cases}
Yes	1,080	61
No	8,920	179

10,000

Relative Risk = 2.8

Example: Cohort Study

1) Prevalence = 10%; Sensitivity = 80%; Specificity = 99%

Assessed as Exposed	N_{Total}	N_{Cases}
Yes	890	50
No	9110	190

10,000

Relative Risk = 2.7

Example: Cohort Study

1) Prevalence = 10%; Sensitivity = 99%; Specificity = 80%

Assessed as Exposed	N_{Total}	N_{Cases}
Yes	2,853	96
No	7,147	144

10,000

Relative Risk = 1.7

Example: Cohort Study

1) Prevalence = 5%; Sensitivity = 99%; Specificity = 80%

Assessed as Exposed	N_{Total}	N_{Cases}
Yes	2,466	69
No	7,534	151

10,000

Relative Risk = 1.4

Example: Cohort Study

1) Prevalence = 1%; Sensitivity = 99%; Specificity = 80%

Assessed as Exposed	N_{Total}	N_{Cases}
Yes	2,156	47
No	7,844	157

10,000

Relative Risk = 1.1

Summary

- Assessing exposure with high specificity important for minimizing bias due to measurement error
- Especially so for rare exposures (like TCE)

Specificity and Exposure Assessment Approach

1) Cohorts

High Specificity

Low Specificity

- Biomonitoring
- Onsite exposure measurement (e.g., air monitoring)
- Site-specific processes, tasks
- Other sources

Specificity and Exposure Assessment Approach

1) Case-control studies

Expert review (using subject-specific data re. exposures, tasks)

Job task - exposure matrix (JEM)

Self-reported exposure | Job-exposure matrix (JEM)

Job-Exposure Matrix

Exposure probability, intensity assigned on the basis of:

- Occupation (and, in some studies, industry)
- Calendar period of employment

Limitation: assumes that exposure is uniform within categories of occupation & calendar period

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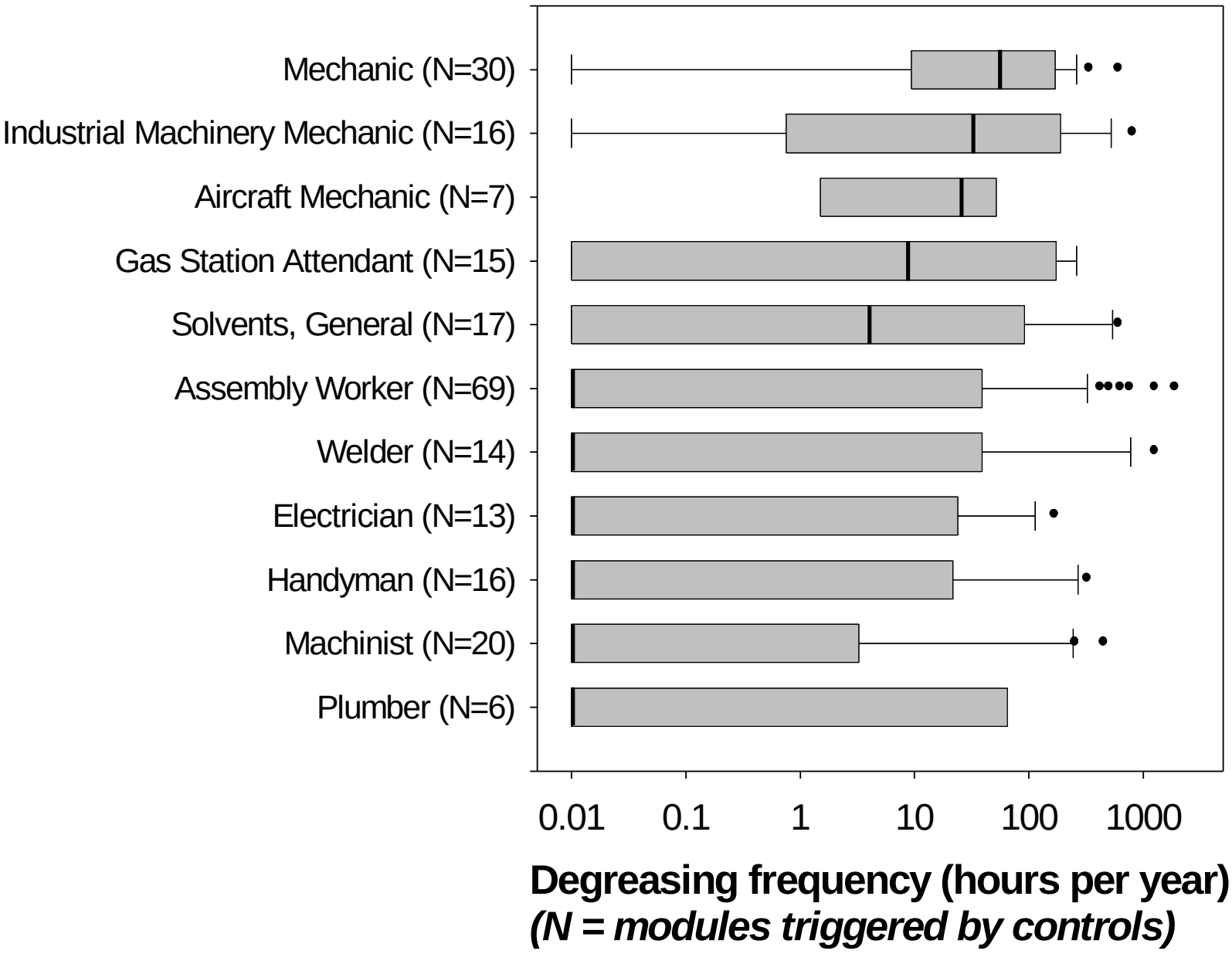
TCE Exposure Probability

Mechanic		High
Industrial Machinery Mechanic		High
Aircraft Mechanic		High
Gas Station Attendant	Medium	
Solvents, General	Medium	
Assembly Worker	Medium	
Welder	Low	
Electrician	Low	
Handyman	Low	
Machinist	Low	
Plumber	Low	

Self-Reported Degreasing Among Controls (Purdue 2010)



Job / Task - Exposure Matrix

More detailed matrix for assigning exposure that incorporates information on selected job tasks performed within a given occupation

Assumption of uniformity in exposure within JTEM task / occupation / period categories more robust than for JEM

2) Exposure metrics used in statistical analyses

Qualitative Exposure Metrics

- Ever vs. never exposed
- Highest exposure probability across jobs

Crude; do not take into account variation in duration or intensity

(Semi-) Quantitative Metrics: Overview

Three most common metrics:

- Exposure duration
- Average intensity
- Cumulative exposure (e.g., ppm*years, lifetime hours, lifetime ppm*hours)

(Semi-) Quantitative Metrics: Pros and Cons

Exposure duration:

Good when high % of subjects have uniform, high exposure intensity

Problematic when average intensity varies widely.

(Semi-) Quantitative Metrics: Pros and Cons

Average intensity:

Good when duration irrelevant to risk or subjects had similar duration

Problematic when duration relevant & varies considerably between subjects, and effects from peaks

(Semi-) Quantitative Metrics: Pros and Cons

Cumulative exposure

Good when risk increases linearly with total exposure accumulation

Problematic with nonlinear effects, effects from peaks

Exposure Metrics: Summary

- No single exposure metric has been identified as best (dependent on underlying toxicology)
- Exposure metrics restricted to high-probability / -confidence jobs recommended (i.e., maximize specificity)
- Result for highest-exposed category can be important for detecting potential association (i.e., maximize contrast)

Outcomes

- Incidence vs. Mortality
  - Mortality a weaker surrogate for incidence for cancers with high survival

Cancer	SEER 5-Year Relative Survival, 1988-2001
Liver	8%
Myeloma	32%
NHL	60% (non-HIV/AIDS)
Kidney	66%

- Specificity (e.g., NHL vs. “lymphosarcoma”)
- NHL subtype – important to the extent that there are differences in association by subtype (unclear)

3) Assessing the quality of exposure & outcome assessment in TCE studies

Cohort Studies

Group 1: Exposure assessment using urinary TCA measurements (TCE metabolite); cancer incidence endpoints

Anttila

Axelson

Hansen 2001

Hansen 2013 (pooled analysis with updated F/U)

Limitations:

- U-TCA a biomarker of recent exposure
- Limited number of measurements per person
- Concentrations suggest generally low exposure levels
- U-TCA also metabolite of other chlorinated solvents (Perc, 1,1,1-TCA

Cohort Studies

Group 2: Assessment using company records, walkthroughs, interviews; 1+ exposure metrics used

Boice*

Lipworth

Morgan*

Radican*†

Zhao* ‡

* Conducted analyses by level of intensity or cumulative exposure
† air-sampling measurements were available
‡ Cancer incidence

Cohort Studies

Group 3: Ever/never exposed only, use of generic JEM, or other issues

Bahr	Poorly described design; used prevalent cases
Greenland	Incomplete access to worker records; ever/never exposed
Henschler†	Ever vs. never exposed; based on reported cluster
Raaschou-Nielsen*	Exposure not based on subject-level tasks or exposures
Wilcosky	Individual-level exposure uncertain; ever/never exposed; broad lymphoma disease category
Vlaanderen * ‡	Generic JEM involving job categories, calendar period

* Cancer incidence
† Highly exposed study population
‡ Population-based cohort

Case-Control Studies

Group 1: Exposure assessment by expert review

Charbotel* †
Christensen *
Cocco 2010 *
Cocco 2013 * ‡
Costantini
Gold *
Miligi * ‡
Moore *
Pesch
Purdue * ‡
Seidler ‡
Vamvakas*†

* Analyses (some or all) restricted to high-prob or high-conf exposure
† High-prevalence study population
‡ Analyses by NHL subtype
Cocco 2013: pooled analysis, includes multiple studies listed here

Case-Control Studies

Group 2: Exposure assessment by generic JEM or self-report

Bruning *

Deng

Dosemeci

Hardell

Nordstrom

Persson

Wang †,‡

* Highly exposed study population

‡ Some analyses restricted to high-prob or high-conf exposure

† Analyses by NHL subtype

Case-Control Studies

Investigations of gene*environment interaction (Deng et al. -- NHL; Moore et al. -- Kidney)

- Observed TCE associations found to vary across genotypes of selected polymorphisms
- However, these findings have not been replicated in other studies
- Without replication, interpret reported evidence of such interaction with caution

Studies in Arnsberg, Germany

- Area with long history, high prevalence, of industrial TCE use
- Very high exposure levels described in studies
- But, study design limitations:

  1)Henschler (cohort): based on a reported RCC cluster

  2)Vamvakas, Bruning (case-control): choice of control groups; potential recall bias from self-reported exposures

In reviewing TCE literature, assess how influential these studies are on overall conclusions (i.e., review with & without)

Heterogeneity Between Studies

Factors to consider in evaluating differences in findings between studies

- Cohort vs. case-control
- Cohorts: incidence vs. mortality; internal vs. external reference group
- Case-control: source of control group
- Quality of exposure assessment
- Specificity in outcome ascertainment
- Populations with high exposure intensity/prevalence
- Individual potentially influential studies

Conclusion

When evaluating evidence from cohort and case-control studies, essential to consider

- Quality of exposure assessment (specificity)
- Results across levels of exposure metrics
- How endpoints defined