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College of Pharmacy and Pharmaceutical Sciences

Can misclassification of disease change the conclusion of significant dose-response associations

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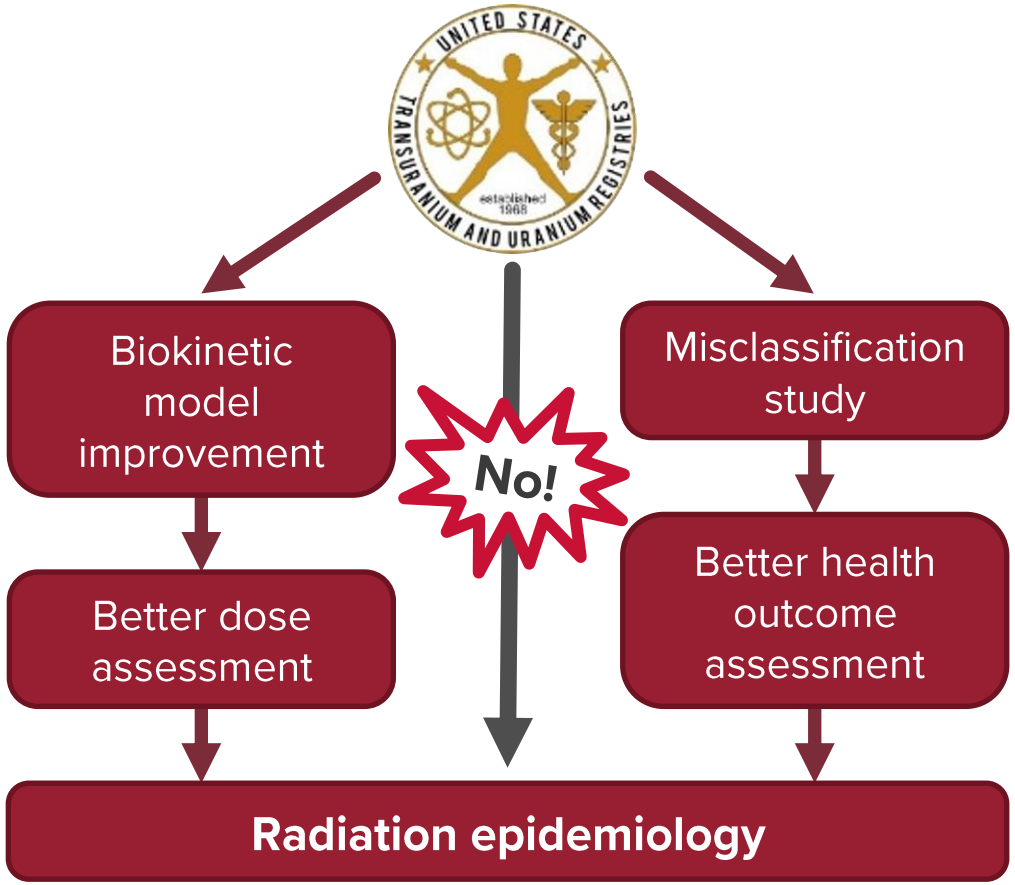
US Transuranium and Uranium Registries

1968: established as a research program

Since 1992: US Department of Energy grant to Washington State University

Focus on: studying the biokinetics and tissue dosimetry of actinides - **in support of radiation epidemiology studies**

Registrants: workers with documented history of occupationally exposure to the actinides (mainly plutonium)



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Misclassification Study

PLOS ONE

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RESEARCH ARTICLE

Misclassification of causes of death among a small all-autopsied group of former nuclear workers: Death certificates vs. autopsy reports

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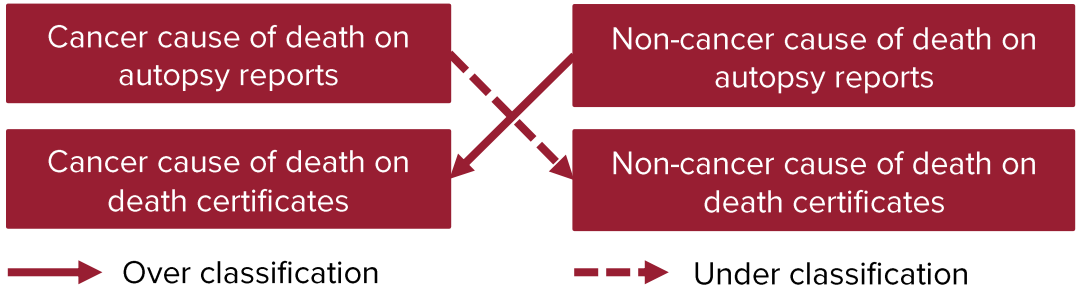
$$\text{Over-classification rate} = \frac{\text{Number of false positives}}{\text{Total number of non disease on ARs}}$$

$$\text{Under-classification rate} = \frac{\text{Number of false negatives}}{\text{Total number of disease on ARs}}$$



Death certificates vs. autopsy reports: misclassification of causes of death among USTUR Registrants

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Abstract

The U.S. Transuranium and Uranium Registries performs autopsies on each of its Registrants as a part of its mission to follow up occupationally-exposed individuals. This provides a unique opportunity to explore death certificate misclassification errors, and the factors that influence them, among this small population of former nuclear workers. Underlying causes of death (UCOD) from death certificates and autopsy reports were coded using the 10th revision of the International Classification of Diseases (ICD-10). These codes were then used to quantify misclassification rates among 275 individuals for whom both death certificates and autopsy reports were available. The ICD-10 categorizes diseases using 22 chapters. Death certificates incorrectly identified the UCOD ICD-10 disease chapter in 25.5% of cases. The misclassification rates for the most common disease chapters were: 9.9% neoplasms, 16.4% circulatory, 37.5% nervous system, 59.3% respiratory, and 18.7% external causes. A logistic regression revealed that both clinical history and the use of autopsy findings have a statistically significant influence on the match rate. Calculating the odds ratio for clinical history indicates that the odds of a match were 2.7 times higher when clinical history was mentioned on the autopsy report than when it was not. Similarly, when cases in the unknown autopsy influence group were excluded, the odds of a match were 4.0 times higher when death certificates were completed using autopsy findings than when autopsy findings were not used.

U.S. Transuranium and Uranium Registries

- Research program that studies biokinetics of actinides in the human body.
- Former nuclear workers (Registrants) donate organs and tissues, or entire bodies, for postmortem radiochemical analysis.
- Autopsy is performed on each Registrant.

Background

- Effort is often invested into improving the reliability of epidemiological findings by improving dose estimates. However, the quality of mortality data is also important.
- Gold and Kathren (1998) studied causes of death among the first 260 autopsied Registrants.

Questions

- What is the level of agreement between death certificates and autopsy reports?
- How does the use of autopsy findings to complete death certificates influence

Misclassification Metrics

If the underlying cause of death on the death certificate belonged to the same International Classification of Diseases Revision 10 (ICD-10) disease chapter as the underlying cause on the autopsy report, the case was coded as a match.

$$\text{Mismatch Rate} = 1 - \frac{\text{Number of Matches}}{\text{Total Number of DCs}}$$

$$\text{Over classification} = \text{False Positive Rate} = \frac{\text{Number of False Positives}}{\text{Total Number of Non Disease on ARs}}$$

$$\text{Under classification} = \text{False Negetive Rate} = \frac{\text{Number of False Negatives}}{\text{Total Number of Disease on ARs}}$$

Results – Mismatch Rates and Logistic Regression

Significance codes were calculated using a logistic regression where Mismatch was the dependent variable and the independent variables were AR Used, Clinical History, Circulatory, Respiratory, External Nervous, and Other Diseases. AR Use Unknown cases were excluded from the regression.

* $p \le 0.05$; ** $p \le 0.01$; *** $p \le 0.001$

Top 5 disease categories

- n = 110 Circulatory, 16.4%*
- n = 82 Neoplasms, 9.9% (reference category)
- n = 27 Respiratory, 59.3%***
- n = 16 Nervous system, 37.5%**
- n = 16 External causes, 18.7%
- n = 25 Other, 76.0%***

25.5% Mismatch rate All cases

Autopsy Report Use Categories

- n = 49 Used, 12.5%*
- n = 116 Not used, 36.2% (ref. category)
- n = 103 Unknown, 20.4% (excluded)

Odds ratio = 4.0 (AR used vs. AR not used)

Conclusions

- This all-autopsied population of former nuclear workers provides insight into the rates of misclassification in a major target population for epidemiological studies.
- There was significant misclassification of underlying causes of death, when death certificates were compared to autopsy reports.
- Use of autopsy findings to complete death certificates and availability of clinical history to pathologists resulted in higher match rates, emphasizing the vital role of good communication between physicians and pathologists.

Reference

Gold B, Kathren RL. Causes of death in a cohort of 260 plutonium workers. Health Phys. 1998;75(3):236-40. doi: 10.1097/00004032-199809000-00001

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Objectives

From previous study

? What would be the impact of misclassification

General belief

- Misclassification impact tends to weaken the significance of conclusion
- Incorporating outcome misclassification would make significant dose-response associations more significant

Our research objectives

- Verify if the general belief of misclassification is correct
- Quantify the impact of disease misclassification on dose-response associations

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Methods: Overview

1. Generation

1(a) Extract dose data

1(b) Generate pure outcome data

1(c) Integrate into initial dataset

2. Simulation

2(a) Start with initial dataset

2(b) Apply misclassification

2(b) Calculate summary statistics

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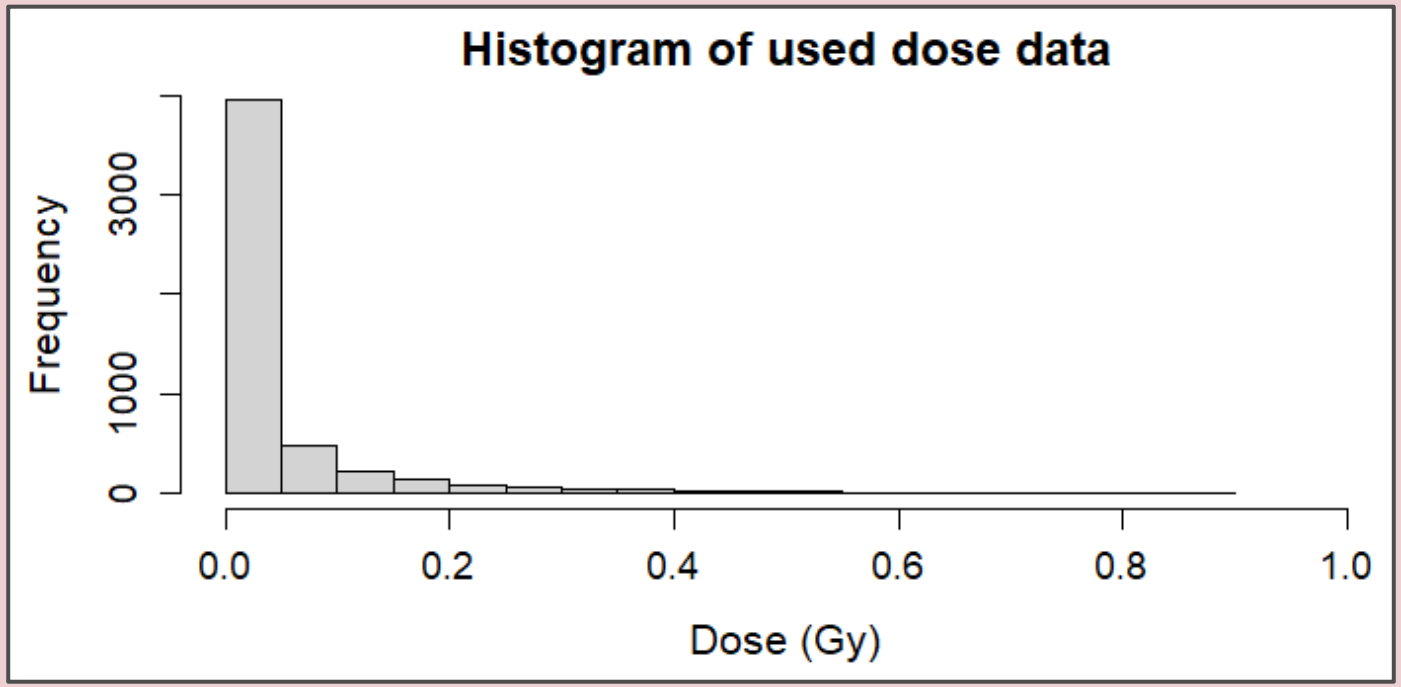
Methods: Initial Dataset Generation (a)

1(a) Extract dose data

- Use total cumulative colon doses from **Rocky Flats cohort**



Methods: Initial Dataset Generation (b)

1(b) Generate pure outcome data

- Calculate **outcome probabilities** using logistic function

$$p(x) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x)}}$$

x: The **dose** value

β_0: The constant derived from a **baseline** disease incidence of 30% when $x = 0$

β_1: The logarithm of the **odds ratio**

- Randomly generate **pure outcome** - unknowable true causes of death without misclassification - by probabilities

Repeat 1(b) × 1,000 times

Methods: Initial Dataset Generation (c)

1(c) Integrate into initial dataset

- Combine outcome data with dose data into initial dataset (× 1,000 times)
- Use logistic regression to calculate odds ratio and p-value between doses and outcomes (× 1,000 times)
- Select a borderline non-significant initial dataset with p-value just above the significance threshold

	Significance level	0.05
Initial dataset	odds ratio	1.81
	p-value	0.05003

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Methods: Misclassification Simulation

2(a) Start with initial dataset

- Use the selected borderline non-significant initial dataset

2(b) Apply misclassification

- Preset over-classification and under-classification rate
- Recalculate odds ratio and *p*-value of misclassified dataset

2(c) Calculate summary statistics

- Calculate **percentage of significant *p*-values** after 20,000 times misclassification for each combination of over- and under-classification

Results: Misclassification Rate of 30%

	Significance level	0.05
Initial dataset	odds ratio	1.81
	p-value	0.05003
Misclassified datasets	percentage of significant *p*-values (change to statistically significant association)	9.4%

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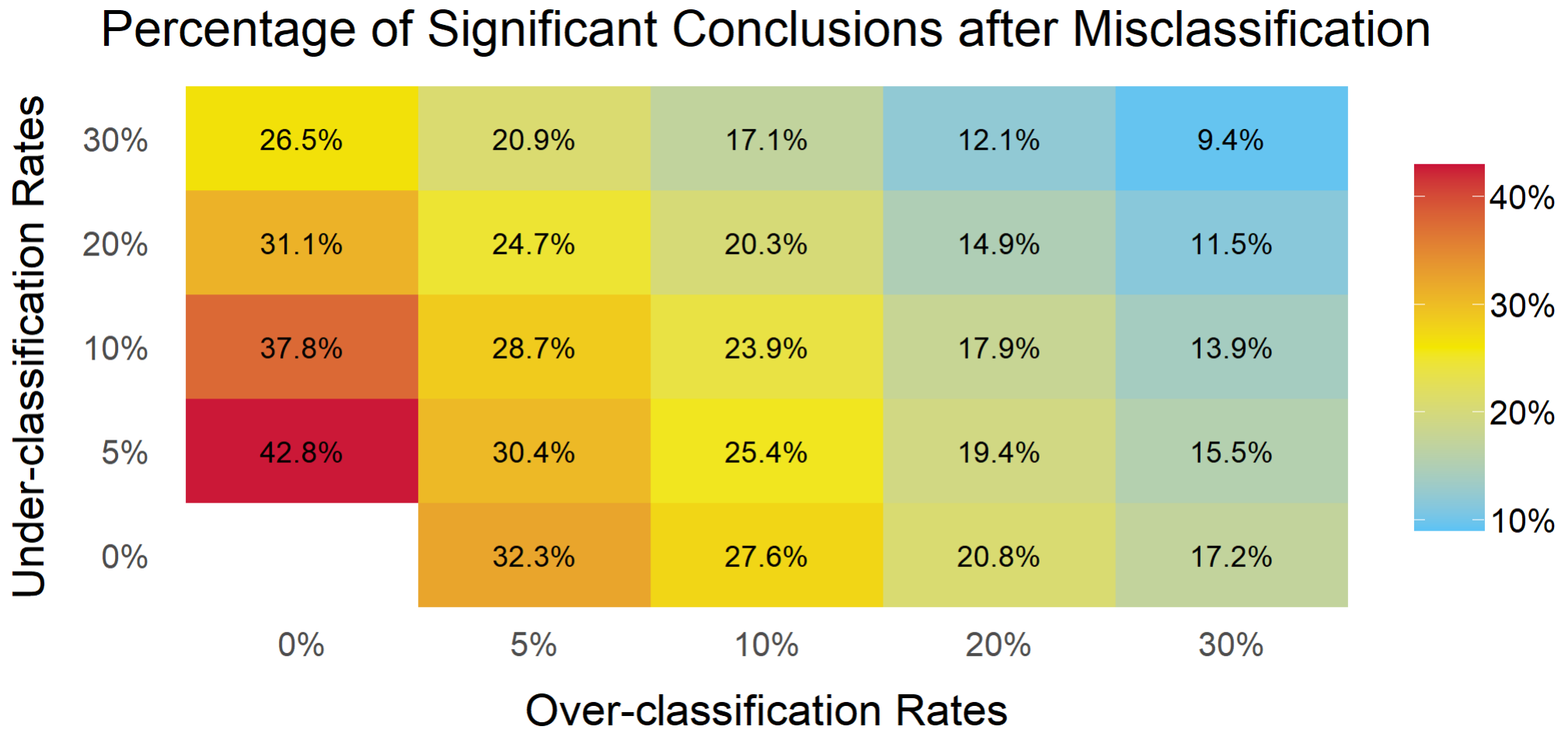
Results: Varied Misclassification Rates



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Summary

General belief

- Misclassification impact tends to weaken the significance of conclusion
- Incorporating outcome misclassification would make significant dose-response associations more significant

Our research objectives

- Verify if the general belief is correct
- Quantify the impact of disease misclassification on dose-response associations

Our research findings

- ✓ General belief is not always correct
- ✓ The disease misclassification could change the conclusion of dose-response associations from 9.4% to 42.8% of the time

Future Work

1) Investigate cancelling out effect between over- and under-classification
2) Analyze impact of various factors:
   - Radiation dose distributions
   - Outcome baselines
   - Risk levels
   - Significance levels
   - Sample sizes
   - Confounding variables
3) Test different models (e.g., Poisson model with person-year tables)
4) Simulate with misclassified initial dataset to better reflect real-world situations

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Thank you!