

# Issues in exposure response analysis

Leslie Stayner

### Searching for the Right Model

Or How to Recognize Whether You are Chasing a Windmill or a Giant?



And Others  
Randy Smith  
John Bailer  
Robert Park  
Faye Rice  
Eileen Kuempel  
Steve Gilbert  
Jim Bena  
Eileen Kuempel  
David Dankovic

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### What is the “Right” Exposure-Response Model for QRA?

“All models are wrong  
some are useful” – Box  
1972

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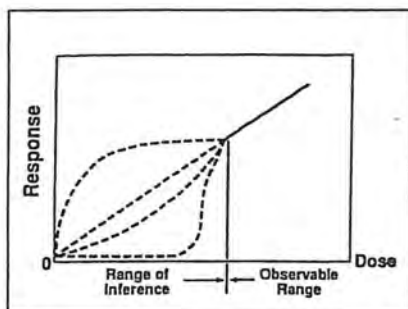
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### Hypothetical Dose-Response Relationships



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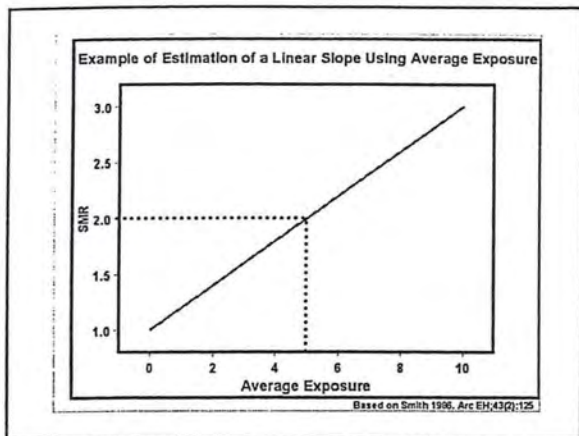
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### ADDITIVE AND MULTIPLICATIVE MODELS USED FOR MODELING HAZARD RATES IN OCCUPATIONAL STUDIES

1) Additive;  $\lambda(t) = \lambda_0(t) + x(t)\beta$

2) Multiplicative;  $\lambda(t) = \lambda_0(t) r\{x(t)\beta\}$

Exponential;  $r\{x(t)\beta\} = \exp(x(t)\beta)$

Additive Relative Risk;  $r\{x(t)\beta\} = (1 + x(t)\beta)$

Power;  $r\{x(t)\beta\} = (x(t) + 1)^\beta$

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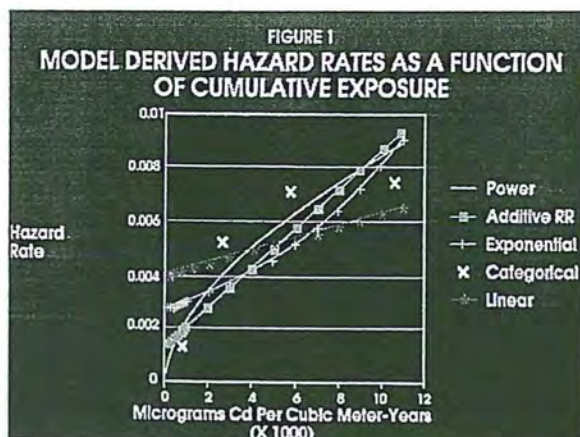
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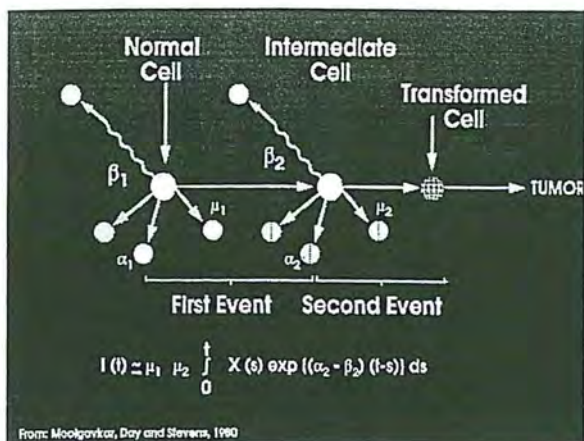
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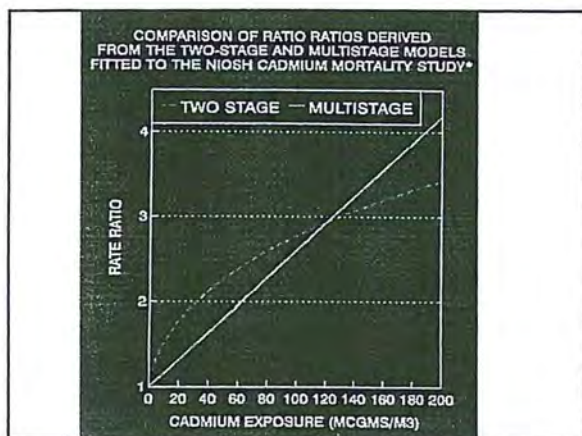
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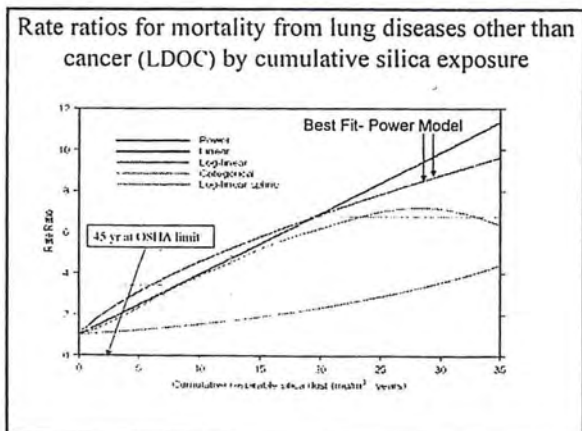
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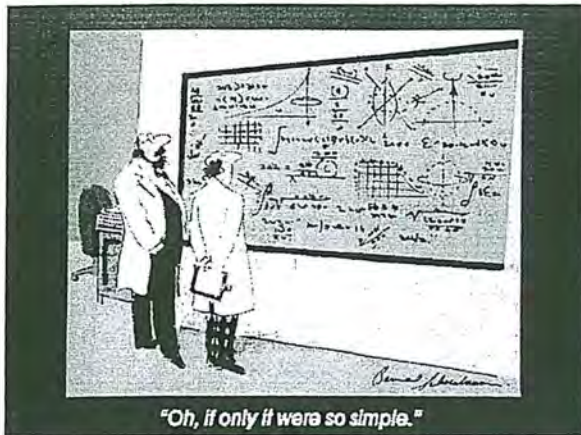
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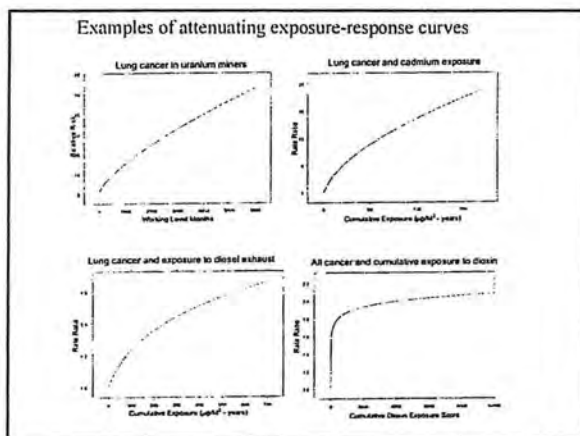
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Por que?

- Natural Limit on the Relative Risk
- Depletion on the Number of Susceptible
- Unrecognized Effect Modification
- Saturation of Key Metabolic Pathways
- Exposure Misclassification
- HWSE

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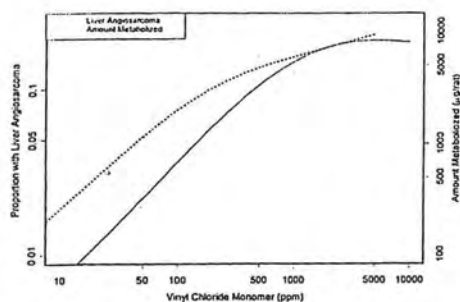
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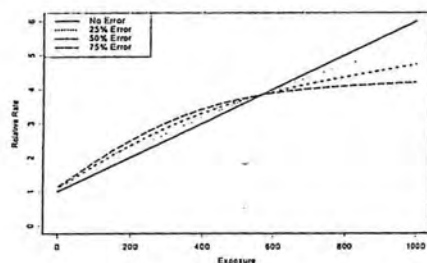


Example of saturation of metabolic systems: Metabolism of liver cancer in rats exposed to vinyl chloride exposure in rats\*

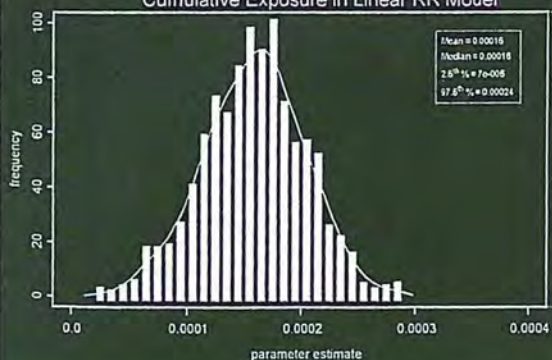


\*Adapted from studies by Watanabe et al. (1976) and Maltoni and Lefiminc (1975)

Hypothetical e.g. of Effect of Exposure Misclassification on Exp-Resp



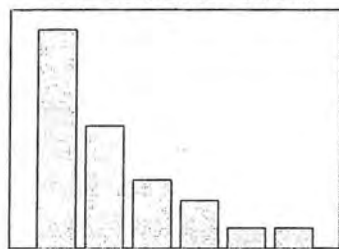
Frequency of Parameter Estimates for Cumulative Exposure in Linear RR Model



## Healthy Worker Effect Bias on Exposure-Response

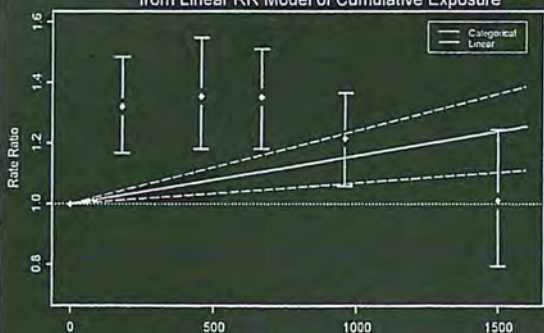
- Effect Related to Initial Selection – Solution avoid using SMRs, use internal regression methods or model adjustments.
- Effect Related to Continued Employment (HWSE) – Solution?

All Cause SMR Results by Duration of Exposure, Combined Results from 10 NIOSH Cohort Studies



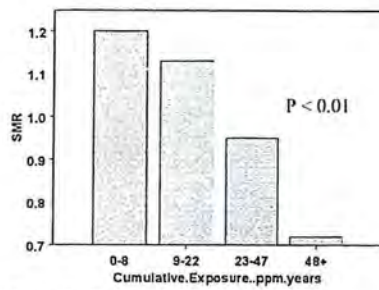
Adapted from Steenland and Stayner 1991

Median and 95% Bounds of the Predicted Rate Ratios from Linear RR Model of Cumulative Exposure



\* Excludes shipworkers and heaters. Computations for exposure are (30-50) (50-100) (100-150) (150-200) (200-250) and (250-300).

Mortality from Bronchitis, emphysema & asthma  
By cumulative exposure to pulp or paper dust



From: Boffetta et al, 2001

### Conclusion

“Nothings for certain and that’s  
for sure”- John McCutcheon

- Great New Statistical Methods,  
–GLM, GAM, Biologic Models
- But it’s the Data Stupid!
- Methods Needed For  
–Describing Uncertainty  
–Correcting for HWSE

Fin



2002

16th

**EPICOH**

**Congress on Epidemiology in  
Occupational Health**

**and**

**Jack Peboys Symposium on Prevention  
of Occupational Asthma**

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3rd

**International Congress on Women's Health  
Occupation, Cancer and Reproduction**

**Course on New methods  
in Epidemiology**

**Saturday, 14 September 2002  
Barcelona, Spain**



IMAS

