Criteria for Causal Inference

Chance

Bias

Consistency

Strength

Dose-Response

Temporality

Plausibility

Meta-Analysis of Diesel Exhaust Exposure and Lung Cancer

Twenty-nine published cohort and case-control studies. Twenty-three studies met inclusion criteria (Bhatia *et al*.)

Exposure was defined as work in an occupation or industry in which diesel engines and diesel equipment were in use

Studies which were excluded:

- **Coal and metal miners because of potential role of multiple occupational carcinogens**
- **Studies with inadequate latency (less than 10 years) from first exposure**
- **Studies in which work with diesel equipment or engines could not be confirmed or reliably inferred**

TABLE 3. Summary of Pooled Relative Risks

Group	Number	RR	95%CI
All studies	**29**	**1.33**	**1.27-1.40**
Case-control studies	**14**	**1.33**	**1.21-1.47**
Cohort studies	**15**	**1.33**	**1.26-1.42**
Internal comparison group	**8**	**1.43**	**1.32-1.55**
External comparison group	**7**	**1.22**	**1.12-1.34**
Smoking adjusted	**16**	**1.35**	**1.22-1.49**
Smoking not adjusted	**13**	**1.33**	**1.25-1.41**
Subanalysis by occupation	**24**	**1.37**	**1.30-1.46**
Railroad workers	**6**	**1.44**	**1.30-1.59**
Equipment operators	**3**	**1.11**	**0.95-1.29**
Truck drivers	**10**	**1.49**	**1.36-1.64**
Bus workers	**5**	**1.24**	**1.07-1.43**

Criteria for Causal Inference
Probability That Findings are Due to Chance

- Pooled Relative Risk Estimate =
  1.33 (95% C.I. =1.27-1.40)

- 21 of 23 Studies had risk estimates > 1.0

Criteria for Causal Inference
Selection Bias

- **Studies with internal comparisons had higher risk estimates**

- **Health Worker Effect leads to an underestimation of an effect**

- **Pooled analysis was heavily weighted by Wong *et al*, 1985. All Cause SMR of 0.81 indicated presence of Healthy Worker Effect**

Criteria for Causal Inference
Information Bias

- **Mainly concerns exposure misclassification**
- **In most studies would be nondifferential therefore reducing the relative risk estimates**

Criteria for Causal Inference
Confounding Bias

- **Most important potential confounder is smoking**

- **Pooled relative risk estimates for smoking-adjusted and unadjusted studies similar**

- **In those studies giving both smoking-adjusted and unadjusted risk estimates, there was only a small reduction in the pooled RR**

- **Pooled RR estimate was 1.43 (95% C.I. = 1.32-1.55) in studies with internal comparison populations**

TABLE 6. Treatment of Smoking Data for Studies Included in Pooled Analysis and Smoking-Adjusted and -Unadjusted RR Where Available

Study	Treatment of Smoking Data in Main Analysis	Crude RR (95% CI)	Adjusted RR (95% CI)
Boffetta *et al*, 1988	Categorical Never-smoker Current 1-20 cigarettes/day Current ≥21 cigarettes/day Ex-smoker Pipe or cigar smoker	1.41 (1.19-1.66)	1.31 (1.10-1.54)
Boffetta *et al*, 1990	Continuous: cigarettes/day	1.31 (1.09-1.57)	0.95 (0.78-1.16)
Damber &Larsson, 1987	Dichotomous: smoker vs. nonsmoker	1.5 (0.9-2.6)	1.2 (0.6-2.2)
Garshick *et al*, 1987	Continuous: pack-years	1.39 (1.05-1.83)	1.41 (1.06-1.88)
Lerchen *et al*, 1987	Categorical Never-smoker Ex-smoker Current smoker	1.0 (0.34-2.90)*	0.6 (0.2-2.0)

* Confidence intervals are calculated from the published data as described in Methods

Criteria for Causal Inference
Consistency

- **Twenty-one of twenty-three studies in the meta-analysis had risk estimates > 1.0**

- **Both of the two studies with risk estimates < 1.0 had less than ten lung cancer cases**

Criteria for Causal Inference
Evidence of an
Exposure-Response Relationship

- **Majority of the studies relied on job descriptions as a surrogate for exposure status**

- **Garshick *et al*, 1987, 1988 and Steenland *et al*, 1990 examined quantified exposure measures. None had access to historical exposure measures**

- **Although measures of exposure in the studies are limited, bias from exposure misclassification is unlikely to create an artificially observed effect**

TABLE 5. Observed Risks by Employment Duration in Studies Using Internal Comparisons

Reference	Type	Smoking Adjusted	Occupation	Subgroup (Years)	RR	95% CI
Boffetta *et al*, 1990	CC	Yes	Diesel-exposed	1-15	0.52	0.15-1.86
				16-29	0.7	0.34-1.44
				≥30	1.49	0.72-3.11
Damber & Larsson, 1987	CC	Yes	Driver	1-19	1	0.7-1.5
				≥20	1.2	0.6-2.2
Garshick *et al*, 1987	CC	Yes	Railroad worker	5-19	1.02	0.72-1.4
				≥20	1.64	1.18-2.2
Garshick *et al*, 1988	RC	No	Railroad worker	1-4	1.2	1.01-1.44
				5-9	1.24	1.06-1.44
				10-14	1.32	1.13-1.56
				≥15	1.72	1.27-2.33
Hayes *et al*, 1989	CC	Yes	Equipment operator	<10	1.5	0.4-4.3
				≥10	1.3	0.6-3.1
			Truck driver	<10	1	0.8-1.3
				≥10	1.5	1.1-1.9
			Bus driver	<10	1.1	0.6-2.1
				≥10	1.6	0.9-2.8

TABLE 5. Observed Risks by Employment Duration in Studies Using Internal Comparisons (page 2)

Reference	Type	Smoking Adjusted	Occupation	Subgroup (Years)	RR	95% CI
Steenland *et al*, 1990	CC	Yes	Diesel truck driver	1-24	1.27	0.7-2.27
				25-34	1.26	0.74-2.16
				≥35	1.89	1.04-3.42
Swanson *et al*, 1993	CC	Yes	Railroad worker	1-9	1.57	0.8-3.11
				≥10	2.46	1.24-4.87
			Heavy truck driver	1-9	1.56	0.95-2.58
				10-19	1.67	0.87-3.18
				≥20	2.44	1.43-4.16

Criteria for Causal Inference
Biological Plausibility

- **Diesel exhaust has been shown to induce lung and other cancers in laboratory animals**

- **Diesel exhaust has been shown to contain highly mutagenic substances including PAHs and nitro-aromatic compounds**

- **Diesel exhaust contains many substances which occur in recognized complex mixtures of human respiratory carcinogens, including cigarette smoke and coke oven emissions**

Diesel Exhaust Exposure and Lung Cancer in California

Estimated lifetime risk of dying from lung cancer for general U.S. population is about 1 in 20 and is primarily due to smoking

Average relative risk of lung cancer for workers exposed to diesel exhaust is on the order of 1.5, or an excess relative risk of 0.5

Therefore, the incremental risk for a diesel exposed worker is approximately 0.5 in 20 or 25 in 1000

Study with the best quantitative exposure estimates showed that RR = 1.5 is associated with average worker exposure of 50 *u*g/m^3 diesel exhaust

Statewide average estimate (heavily weighted toward urban areas) is about 4.0 *u*g/m^3

Assuming a roughly linear relationship between exposure and excess risk, this air level could be responsible for an additional 2 lung cancer deaths per 1000 persons exposed

Diesel Exhaust Exposure and Lung Cancer Risk

Lifetime risk of lung cancer due to diesel exhaust exposure is comparable to cancer risks of other pollutants of concern

Diesel Exhaust in California Air	**2 per 1000**
Environmental Tobacco Smoke	
Not married to a smoker	**4 per 1000**
Married to a smoker	**10 per 1000**
Radon in Homes	
High exposure; 1-3% of US homes	**20 per 1000**
Arsenic in Drinking Water	
50 *u*g/liter-US water standard	**21 per 1000**