Childhood leukemia and EMF

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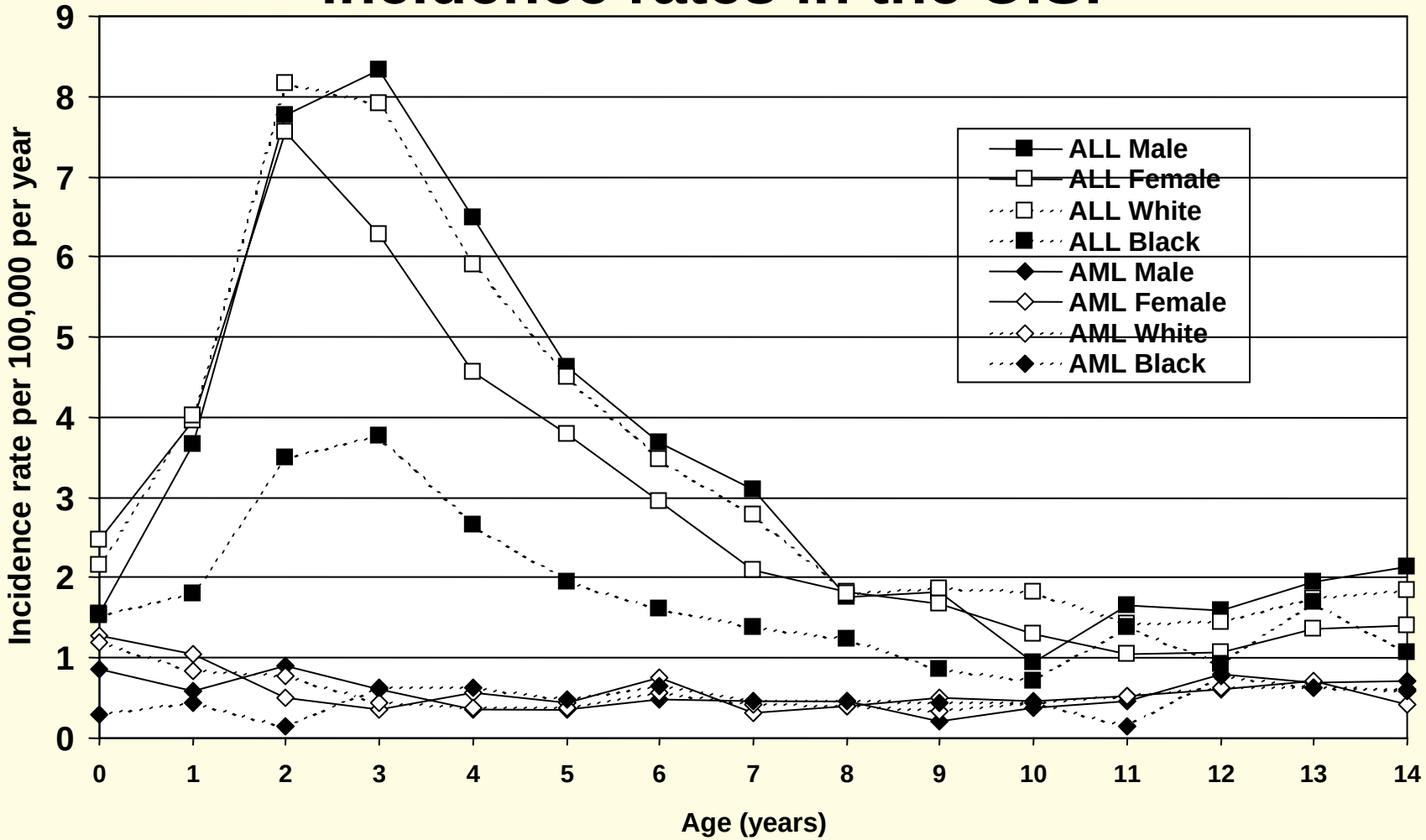
Age-specific childhood leukemia incidence rates in the U.S.



Putative Causes of Childhood Leukemia

- Leukemia results from chromosomal alterations and mutations that disrupt the normal process by which lymphoid or myeloid progenitor cells differentiate
- Underlying triggers for molecular damage may be inherited at conception, may occur during fetal development or during infancy
- Most likely, a series of detrimental genetic changes accumulate over time
- Confirmed associations explain only 10% of childhood leukemia incidence

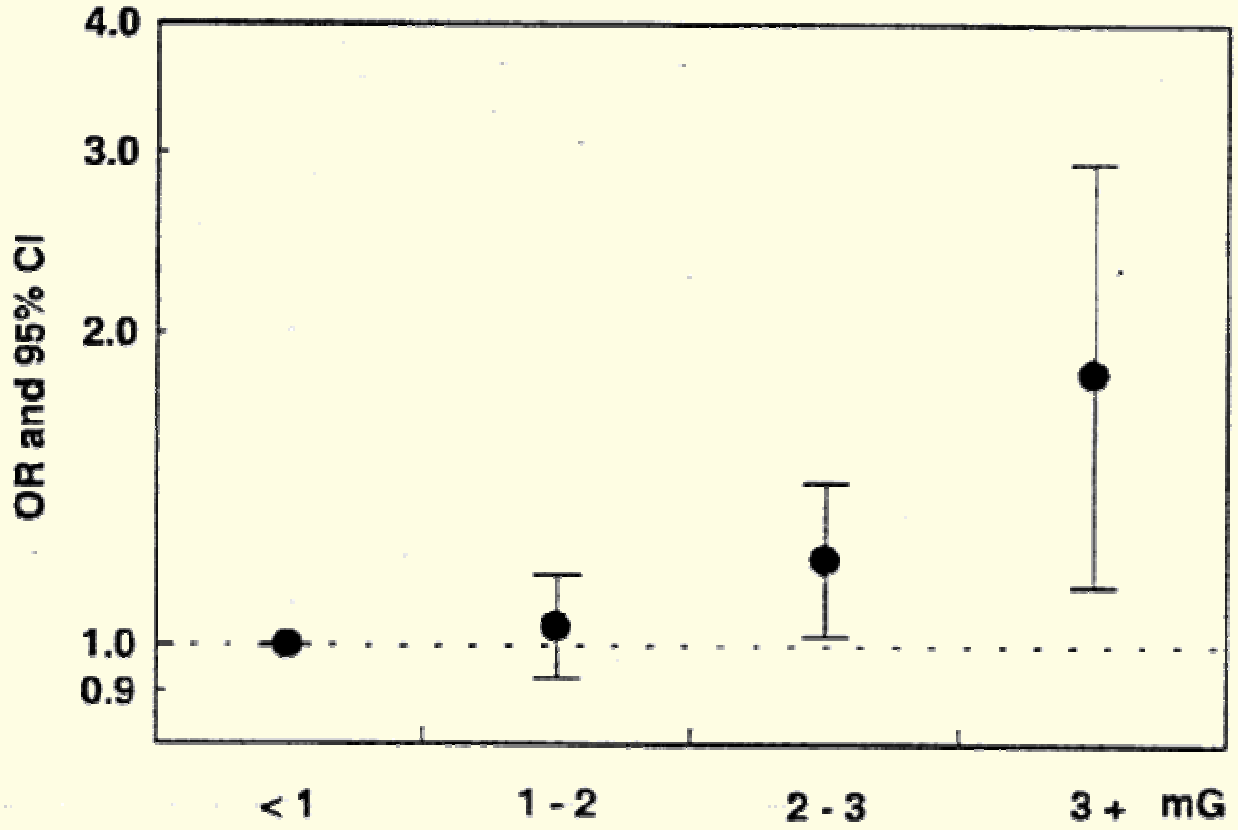
EMF and childhood leukemia

Study	>.3μT		>.4μT	
	RR	95% CI	RR	95% CI
Wertheimer & Leeper*	3.1	1.1-8.5		
Fulton	0.5	0.2-1.4		
Tomenius	1.5	0.4-5.7		
Coghill		1/0		
Savitz	3.5	0.8-15.4		
Coleman	1.5	0.7-3.5		
Myers*	0.8	0.1-9.6		
London	1.6	0.7-3.5		
Feychting	4.5	1.7-12.0	3.7	1.2-11.4
Olsen	2.0	0.4-10.0		2/0
Verkasalo	2.0	0.2-18.0	6.2	0.7-56.9
Tynes		0/0		0/0
Michaelis	2.4	0.8-7.6	2.0	0.3-15.2
Linet	1.5	0.9-2.4	3.4	1.2-9.6
Dockerty		3/0		0/0
McBride	1.4	0.6-3.2	1.6	0.7-3.7
Green*	4.5	1.3-15.9		
UKCCS	1.7	0.4-7.0	1.0	0.3-3.4
Kabuto*	1.7	0.7-3.8		

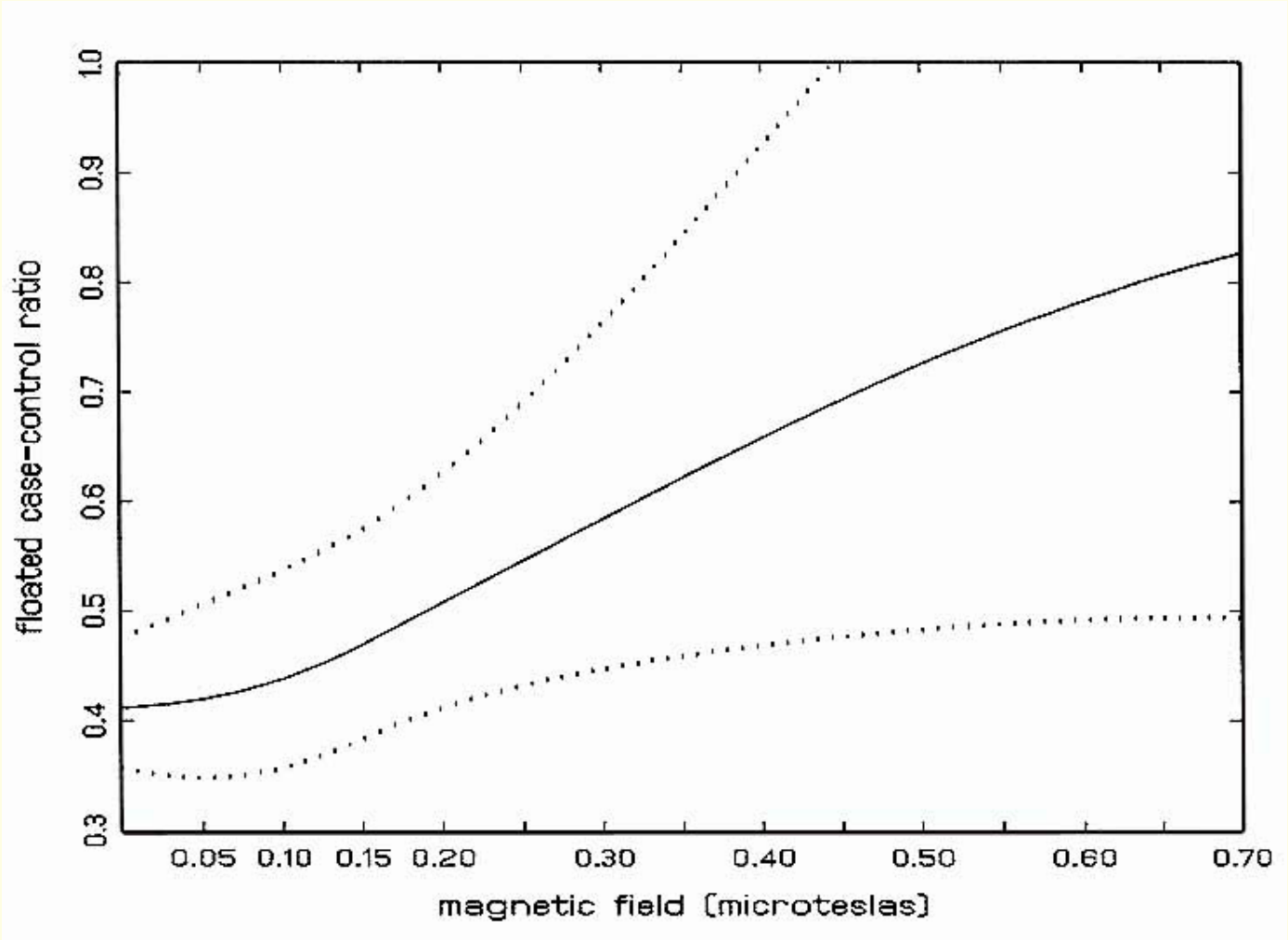
Pooled Analyses of Childhood Leukemia

- **Greenland et al., *Epidemiology*, 2000**
  - 12 studies with fields; 8 with wire codes
  - 2,656 cases; 7,084 controls
  - Metric of choice: time-weighted average
- **Ahlbom et al., *British J. Cancer*, 2000**
  - 9 studies with fields; 2 with wire codes
  - 3,247 cases; 10,400 controls
  - Metric of choice: geometric mean

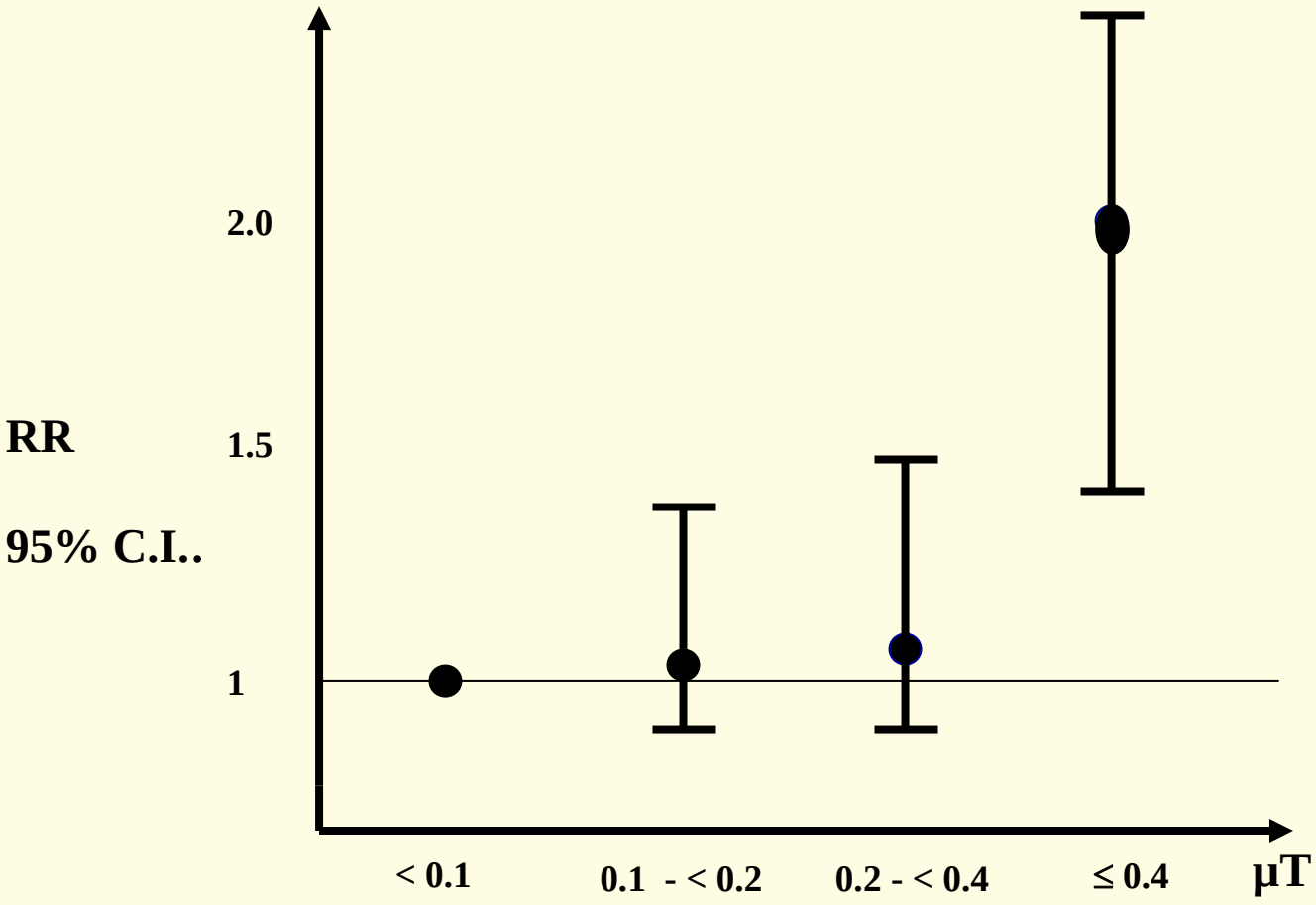
Pooled analysis. Greenland, 2000



Greenland et al., 2000



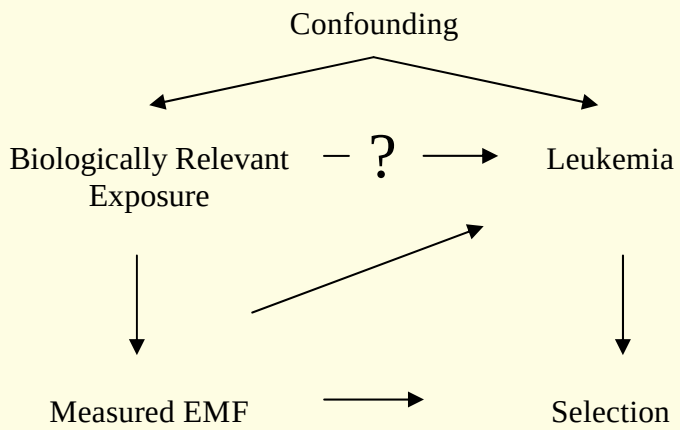
Ahlbom et al., 2000



Consistent association between childhood leukemia and exposure > 0.3-0.4 μT

Possible explanations:

- Chance????
- Misclassification???
- Confounding??
- Selection bias?
- Other?
- Causal relationship?

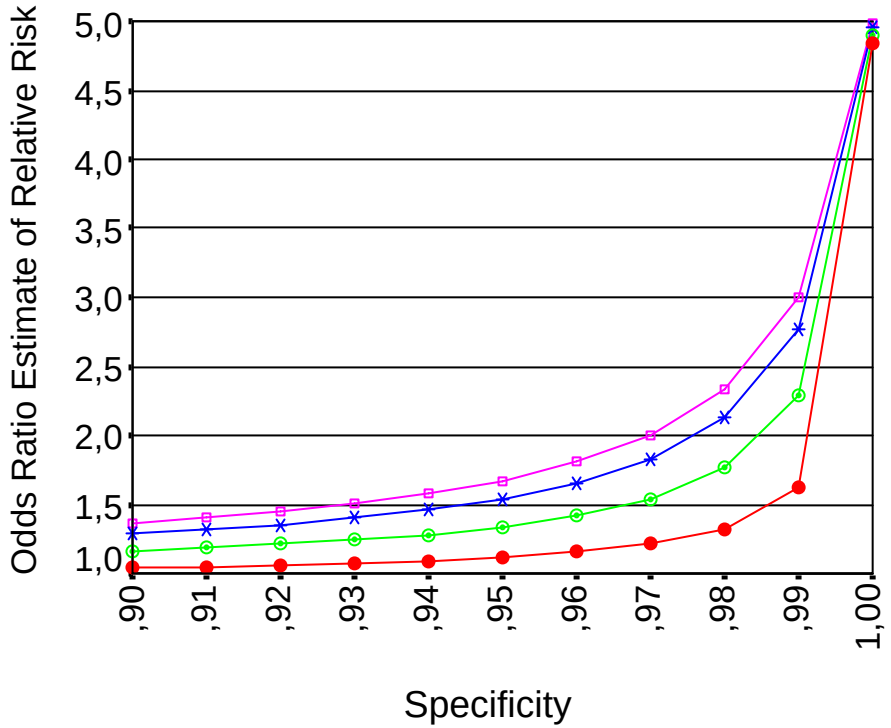


Chance????

Not a chance…

p-value of 0.0001

Misclassification???



- Probably non-differential
  - Usually dilutes the effect
  - Misclassification in mid categories can lead to the distortion of dose-response

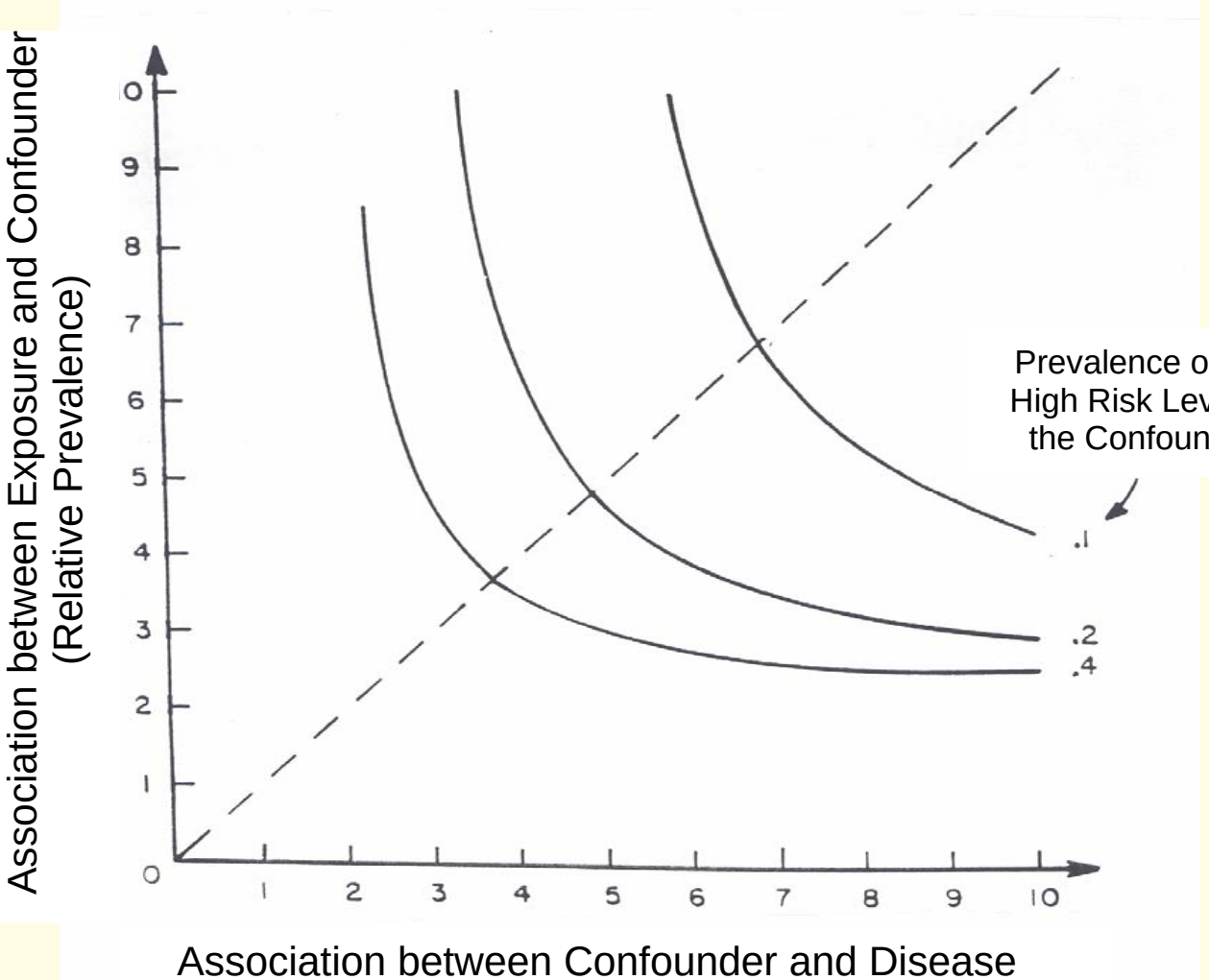
- Small reduction in specificity ⇨ dilutes the effect
  - Classification of unexposed as unexposed
  - Big problem, for rare exposure

Confounding??

- **Numerous factors examined:**
  - –SES
  - –Traffic Density
  - –Chemical exposures
  - –Environmental tobacco smoke
  - –Dietary agents
  - –Viral or other infectious agents
- **Not one confounds the association**

Simultaneous effect?

Combination of Selected Values Sufficient for a Confounder to Account for an Observed Relative Risk of 2



Selection bias?

- Participation:
  - 94-100% in registry based studies
  - 37-68% among eligible participants interviewed
  - 9-31% with measurements in matched analysis
- Much worse for controls in most studies
- Rarely the complete selection/participation picture is presented
- Reporting minimizes the problem

Selection bias?

- Selection might occur through SES or mobility
- Previous efforts to quantify the magnitude of selection bias mostly ecological or based on wire codes
- Evidence for :
  - Inclusion of partial participants lowered risk in one study

  Evidence against :
  - Similar risk in studies with and w/out the high potential for selection bias
  - Lack of association w/childhood brain tumors?

Selection bias?

	≥0.4 μT
All studies	2.0 (1.3-3.1)
Nordic countries	2.1 (0.9-4.9)
Rest of the world	1.9 (1.1-3.2)

Ahlbom et al., 2000

Other?

- Contact Current?
- Melatonin???

- Susceptible subpopulation

(e.g. children with fusion genes generated by chromosome translocation TEL-AML1)

Causal relationship?

- Con
  - Lack of supportive laboratory evidence
  - No known biophysical mechanism for carcinogenesis
- Pro
  - Consistent Epidemiology
  - Specificity

Multiple-Bias Modeling

- Selection bias likely present, but unlikely to fully explain the association
- Confounding is probably less important
- Misclassification greatly increases uncertainty, making both no association and a strong association more plausible
- Probability that the combination of misclassification, selection bias, confounding and random error explain the association 2-4%

Greenland, 2005

Some Observations….

- Role of pooled and meta-analysis
- Study is only as large as its smallest cell
- Childhood Leukemia and SES
- Selection bias – implications for case-control studies

IARC Criteria

International Agency for Research on Cancer (IARC)

Centre International de Recherche sur le Cancer (CIRC)

- For each type of cancer, classify human and animal data separately as:
  - Sufficient
  - Limited
  - Inadequate
  - Lack of effect

Group 1: Is carcinogenic to humans
Group 2A: Probably is carcinogenic
Group 2B: Possibly is carcinogenic
Group 3: Not classifiable
Group 4: Is probably not carcinogenic

N.B. Greatest weight given to epidemiology

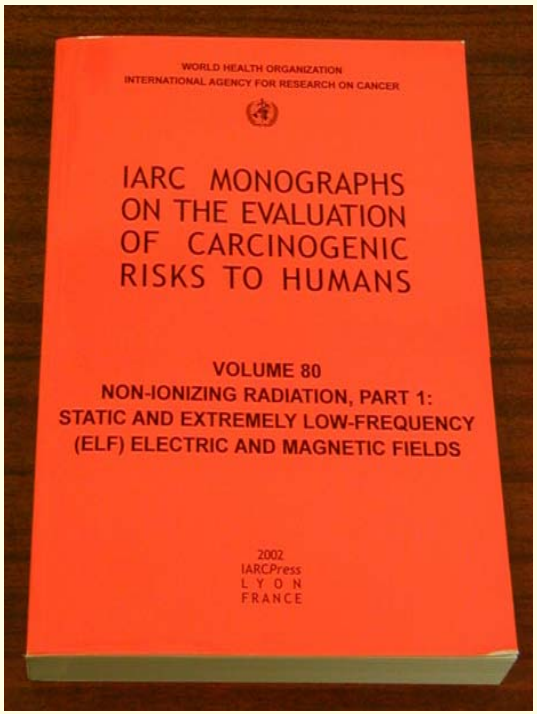
Limited evidence of carcinogenicity

….usually based on evidence in humans which is considered credible,

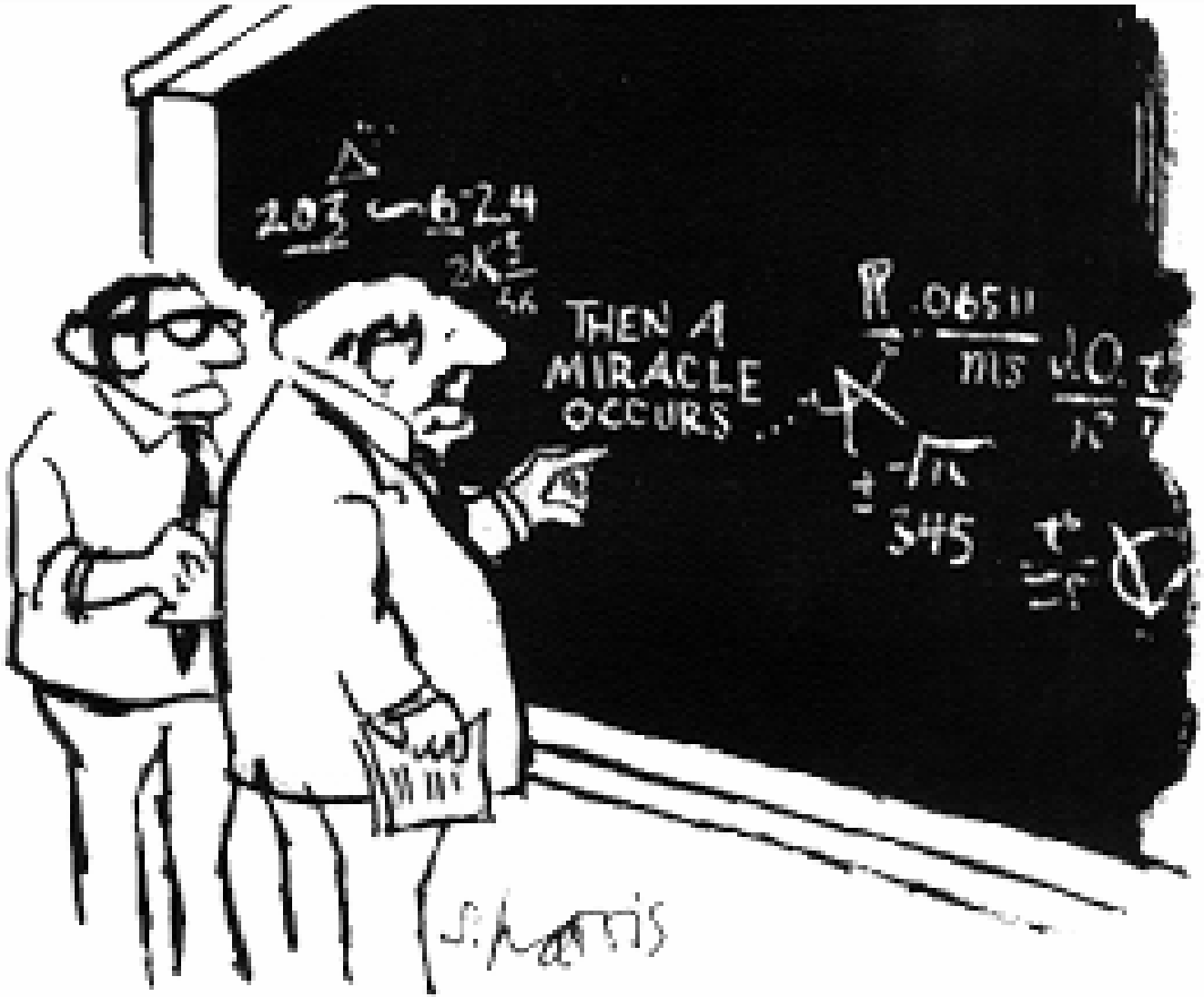
but chance, bias or confounding could not be ruled out with reasonable confidence

IARC Evaluation

Extremely Low Frequencies (ELF) 2002

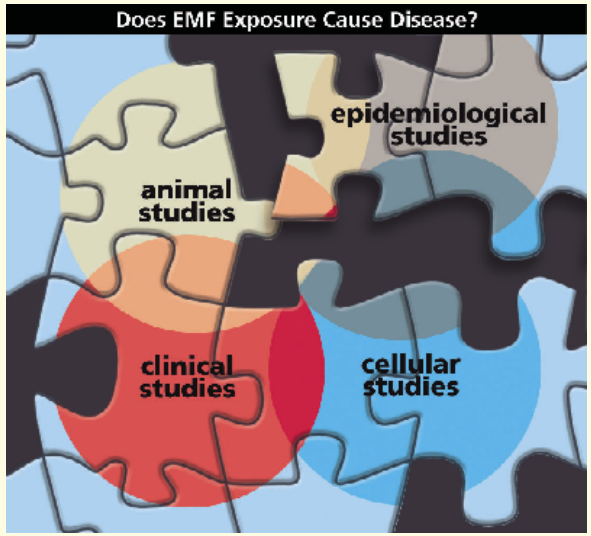


- ELF **magnetic fields** classified as **Group 2B "Possibly Carcinogenic"** based on
  - **limited** human data based on childhood leukemia studies
  - **inadequate** animal data
- Other exposures and outcomes considered "inadequate to classify"



"I think you should be more explicit here in step two."

Animal studies



- Good animal model for childhood leukemia?
- Relevant exposure?
- Intensity within 1 order of magnitude of human exposure?
- Power to detect small risk?

Scientific Issues in ELF Risk Assessment

- Relevance and weight of biophysical arguments
- Reconciling epidemiologic and toxicological data

		Animal +	Animal −
Human	+	✓	??
	−	?	✓

- Uncertainty and misclassification in epidemiologic studies
- Exposure distribution, risk function and how to combine them
- Refutation of alternative hypotheses

RF Towers and Childhood Leukemia

Study	N	RR	95%CI
Selvin	52	0.7	NS
Maskarinec	12	2.0	0.1-8.3
Hocking		1.6	1.1-2.3
Dolk	79	1.1	0.6-2.0
McKenzie		0.9	0.6-1.4
Cooper	1	1.1	0.0-6.3
Michelozzi	8	2.2	1.0-41

RF and Childhood Leukemia

- Small numbers
- Previously identified clusters
- Exposure assessment based on distance

N.B. Studies completely uninformative

What can new epidemiologic studies of ELF childhood leukemia contribute?

- Unlikely to substantially change the observed association

- Need to be designed to test specific hypotheses:
  - other aspects of exposure
  - selection bias
  - susceptible subgroups

Childhood Leukemia and RF

- No evidence to date
  - numerous case reports
- ELF exposure from mobile phones
  - need data
- Low environmental exposures
  - virtually no relevant information
- Feasibility of well designed studies unknown
  - can do a lot to improve existing attempts