National Cancer Institute

Occupational Cancer Epidemiology: Contributions and Future Needs

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Overview of Presentation

- What do we know about occupational cancer and when did we know it?
- What are we doing now and what should we do in the future?
- Is there a need for occupational studies in the genomic era?
- Methodologic issues in epidemiology

What Do We Know About Occupation and Cancer?

- A number of established occupational carcinogens
- Many possible carcinogens with some human data, e.g., 2A and 2B IARC categories
- Occupations with elevated rates for some cancers
- Many chemicals cause cancer in animals but lack human data
- Growing understanding of mechanisms of action

Some Established Occupational Causes of Cancer

Cancer Site	Exposure
Bladder	Benzidine
	Coal tars
	2-Naphthylamine
	4-Aminobiphenyl
Lung	Arsenic
	Asbestos
	Beryllium
	Chloromethyl ether
	Chromium
	Coal tar pitch volatiles
	Radon
	Silica
	Mustard gas
Mesothelioma	Asbestos
Bone	Radium
Larynx	Sulfuric acid mist
Liver	Arsenic, Vinyl chloride
Nasal Cavity/ Sinuses	Nickel, radium, chromium
Skin	Arsenic, coal tars
Leukemia	Benzene
Nasopharynx	Formaldehyde

What Do Established Carcinogens Teach Us?

- **Affect many different cancer sites (respiratory predominates, but also blood, digestive, bone)**
- **Carcinogens include no clear grouping**
- **Inhalation predominant route of exposure, but other routes not well investigated**
- **Not sure this chart tells us where to look next**

Partial List of Chemicals Causing Cancer in Animals, but With No Adequate Epidemiologic Data (From IARC, Supplement 7)

Chlordecone
Chloro-ortho-toluidine
Dichloroethane
Ethylhexyl phthalate
Diethylhydrazine
Ethyl acrylate
Methylene dianiline
Mirex
Nitropropane
Potassium bromate
Safrole
Styrene oxide
Sulfallate
Thioacetamide
Toluene diisocyanate
Vinyl bromide

Conclusion: These suggest not particular pattern by chemical type.

Percentage of Chemicals by IARC Category That Are Largely Occupational Exposures

1 - Sufficient evidence	-	31%
2A - Probably carcinogenic	-	42%
2B - Possibly carcinogenic	-	43%

From: Siemiatycki J et al. Environ Health Perspect 112:1147-1459, 2004.

Contribution of Occupational Studies to Cancer Etiology

- **Major contributor to understanding of carcinogenicity in the past**
- **Diminished effort over past two decades as indicated by:**
  - **Reduction in research groups focused on occupational research**
  - **Reduction in funding**
  - **Fewer sessions on occupational cancer at most scientific meetings**

Why the Reduction in Research on Occupational Cancer?

Many believe:

- **Occupation not an important contributor to the cancer burden**
- **No new leads**
- **Most occupational exposures well controlled**
- **Cannot contribute much in the “omic” era**

Proportion of Cancer Due to Various Factors (from Doll and Peto, 1981)

Factor	%
Diet	35
Tobacco	30
Infections	10
Reproductive/sexual behavior	7
Occupation	4
Geophysical factors	3
Alcohol	3
Pollution	2
Medicines	1

Occupational Exposures and Cancer Burden

- **Two categories of causal factors**
  - **Major - diet and tobacco**
  - **Minor - occupation, infections, alcohol, pollution, reproductive/sexual behavior, medicines**
- **Occupational contribution larger (25%) among blue-collar workers**
- **Role of occupational exposures varies by cancer site**
- **Occupational exposures not voluntary**

What Don't We Know About Occupational Carcinogens

- **Women and minorities seldom studied**
  - **Survey of 1233 occupational cancer reports (Zahm, 1994)**
    - **Only 14% with any analyses of women**
    - **Only 7% with more than 5 risk estimates**
- **Workers in small businesses rarely studied in detail**
- **Most studies in developed countries. (This is changing somewhat)**

Epidemiologic Leads: Suggested Associations Requiring Further Evaluation (adapted from Monson, 1996)

Substance	*Cancer*
Asbestos	Gastrointestinal
	Kidney
	Larynx, Lung
Cadmium	Prostate
Cutting oils	Lung
	Skin
Formaldehyde	Leukemia,
	Nasal sinuses
Silica	Stomach
Talc	Lung
	Ovary
Vinyl chloride	Brain
	Ovary
Shift work	Breast, prostate

Substance	*Cancer*
Butadiene	Leukemia
	Lymphoma
Herbicides	Non-Hodgkin's lymphoma
Diesel fumes	Lung
	Bladder
Dust	Stomach
Mineral fibers	Lung
Pesticides	Lymphoma, lung, leukemia, prostate, brain
Solvents	Lymphatic and hematopoietic, kidney, lung

Epidemiologic Leads: Occupations Associated with Cancer Where Agent Has Not Been Clearly Identified (adapted from Monson, 1996)

Occup Group	*Cancer Site*
Farmers	Leukemia
	NHL
	Lung
	Prostate
	Lip
	Stomach
	Brain
	Myeloma
Chemists	Various Sites
Pattern makers	Colon
Welders	Lung

Occup Group	*Cancer Site*
Dry cleaners	Bladder
	Esophagus
	Kidney
	Liver
	Cervix
Embalmers	Leukemia
Petrochemical workers	Leukemia
	Brain
	Kidney
	NHL
Rubber workers	Leukemia
	Lung

Epidemiologic Leads: Occupations Associated with Cancer Where Agent Has Not Been Clearly Identified (adapted from Monson, 1996)

Occup Group	*Cancer Site*
Veterinarians	Leukemia
Waiters	Lung
Artists	Bladder
Bakers	Lung
Cement workers	Lung
	Stomach
Coal miners	Stomach
	Leukemia
Coke plant worker	Pancreas
	Colon
Beauticians	Leukemia

Occup Group	*Cancer Site*
Lead workers	Lung
	Brain
Meat workers	Lung
	Leukemia
Painters and paint manufacturers	Lung
	Bladder
	Myeloma
Plumbers	Lung
	Leukemia
Truck drivers	Bladder
	Lung

Methodologic Needs for Future Studies

- Improve exposure assessment
- Collect of information on non-occupational risk factors to evaluate effect modification and interaction
- Evaluate gene-exposure and exposure-exposure interactions
- Assess mechanisms of action
- Probably requires more use of cross-sectional, case-control, and prospective designs than in the past

Type of Exposure Assessment in Occupational Studies of Cancer

Type of Exposure Assessment	Number of Studies	%
Occupation or Industry only	23	32
Occupation/Industry and duration	19	26
Ever/never for specific exposures	7	10
Qualitative estimates	15	21
Quantitative estimates	8	11
Total	72	100

From articles on occupational cancer published in the Scand. J. Work Environ. Health and the Amer. J. Industr. Med. over a two year period.

Uses of Molecular Epidemiology

- **Biologic markers of exposure**
  - **Closer approximation of dose**
  - **Includes all routes of exposure**
- **Biomarkers as measures of early outcomes**
  - **Enzymatic effects**
  - **Changes in cell populations**
  - **DNA effects**
  - **Epigenetic changes**
- **Gene-exposure interactions**

Sources of Information on the Contribution of Genes and the Environment on Cancer Development

Genes

- Family history increases risk
- Concordance among twins
- Role of specific genes

Environment

- Estimates of environmental contribution
- Changes in rates over time
- Immigrants assume risk of new location
- Risk factor studies

Heritable Portion of Selected Cancers

Cancer	Heritable Proportion	Environmental Proportion
Stomach	0.28	0.62
Colorectum	0.35	0.60
Pancreas	0.36	0.64
Lung	0.26	0.64
Breast	0.27	0.67
Cervix	0.0	0.80
Ovary	0.22	0.78
Prostate	0.42	0.58
Bladder	0.31	0.69
Leukemia	0.21	0.66

From: Lichtenstein P. et al. Environmental and heritable factors in the causation of cancer. New England J Med 343:78-85, 2000.

Cancer – Nature, Nurture, or Both
Conclusions by Robert Hoover, M.D.

- Cancer is largely environmental (65 to 80%), but –
- Heritable component is not inconsequential (20 to 40%)
- Recent successes in molecular genetics have over shadowed studies of environmental factors
- Increase in knowledge in one area will benefit the other
  - Information on exposures should help identify genes
  - Study of genes related to cancer may help identify previously unrecognized environmental factors
- Risks from gene – exposure interactions can be reduced by removal of either

Summary Regarding Genes and Environmental Exposures

- **Cancer is largely of environmental origin**
- **BUT genetic contributions are important**
- **Many, many, many environmental and occupational leads**
- **Incorporate genetic components into traditional epidemiologic to strengthen studies and enhance understanding of causes and mechanisms**

Role of Occupational Epidemiology in Cancer Etiology

- Has uncovered many of the established human carcinogens
- Many leads currently exist
- Both genes and exposures important
- Studies integrating epidemiology, toxicology, and genetics offer special opportunities
- High-quality exposure assessment essential

What Might Future Occupational Studies Look Like

Use non-Hodgkin's lymphoma as an example

Characteristics of Non-Hodgkin's Lymphoma Pertinent to Study Design

- **Complicated pathology, i.e. not a homogeneous disease**
- **Clear relationship with immune system alterations**
- **Involvement of chromosomal translocations (e.g., t8;14 and t14;18)**
- **Known or suggested role for several environmental factors including solvents, pesticides, hair dyes, PCBs, PAHs, and viruses**
- **Role for genetic polymorphisms, particularly those related to immune system, i.e., Th1, Th2 (cytokine genes) and TNF (tumor necrosis factor)**

Genes and Pathways Relevant to Non-Hodgkin's Lymphoma

Immune Pathways:

- **Pro-inflammatory cytokines (TNF, IL-1a, IL-1b)**
- **Anti-inflammatory cytokines (IL-1RN, Il-6, LTA)**
- **Th1/Th2 cytokines (IL-10)**

Metabolic Pathways:

- **Organophosphate metabolism (PON1)**
- **Organochlorine metabolism (Ahr, P4501A1)**
- **Solvent metabolism (CYP2E1, MPO, GSTT1, NQ01)**
- **Aromatic amine metabolism (NAT1, NAT2, GSTM1, CYP1A1)**

From: Wang S et al. Protocol for the study of genetic susceptibility to non-Hodgkin's lymphoma. National Cancer Institute, 2001.

Occupation and NHL: Study Elements

- **Collect biologic tissues to:**
  - **Characterize NHL subtypes by traditional and gene/protein methods**
  - **Evaluate immune genes and occupational exposures**
  - **Evaluate metabolic genes and occupational exposures**
- **Develop quantitative estimates of occupational exposures**
- **Obtain information on lifestyle factors**
- **Evaluate lifestyle factors and occupational exposures**
- **Assess risk by NHL subtypes**

Limitations Often Raised About Occupation Cancer Findings
(actually all epidemiologic findings)

- Confounding
- Exposure Misclassification
- Mainly raised about positive findings

Control for Smoking Confounding in a Case-Control Study of Lung Cancer and Occupation

Occupational Category	Unadjusted OR	Smoking/Age Adjusted OR
Professionals/technicians	0.9	1.1
Office/related personnel	1.0	1.1
Agric/forestry/fishery workers	1.4	1.5
Metal smelting and treatment	1.2	1.1
Chemical workers	1.6	1.4
Textile workers	0.7	0.7
Food/beverage workers	0.9	1.0
Printers	1.2	1.5
Pipe fitters/welders	0.9	0.9
Painters	1.6	1.4
Transportation equipment	1.1	1.1
Construction workers	1.6	1.4

From: Levin et al. Br J Ind Med 1988;450-458.

Control for Confounding by Tobacco and Asbestos in a Case-Control Study of Lung Cancer and Occupation

Industry	Age Adj OR	Age/Smk Adj OR	Age/Smk/ Asbestos Adj OR
Agric/forestry/fishing	1.3	1.3	1.3
Energy/mining	1.7	1.5	1.4
Chemical/oil	1.2	1.2	1.2
Stone/glass/pottery	1.8	1.6	1.5
Metal production	1.4	1.4	1.3
Electrical/sheet metal	0.9	0.9	0.9
Leather/textile	1.0	1.0	1.0
Construction	1.6	1.4	1.3
Financing/insurance	0.8	0.8	0.8
Restaurants/hotels	1.4	1.0	1.1

From: Bruske-Hohlfeld et al. Am J Epid 2000;151:384-395.

Relative Risks (# Exposed Deaths) for Lung Cancer by Cumulative Exposure to Acrylonitrile

	Quintile of Estimated Exposure				
Analysis Group	**Lowest**	**2nd**	**3rd**	**4th**	**Highest**
% Ever Smoked Cigarettes	62%	64%	68%	72%	75%
RR for Entire Cohort	1.1 (27)	1.3 (26)	1.2 (28)	1.0 (27)	1.5 (26)
RR for Smoking Subcohort (Not Adj. for Smoking)	0.8 (27)	1.1 (26)	1.0 (28)	0.9 (27)	1.5 (26)
RR for Smoking Subcohort with Smoking Data (Not Adj.)	0.3 (5)	0.9 (6)	1.0 (7)	1.0 (13)	1.7 (9)
RR for Smoking Subcohort Adj. for Ever Used Cigarettes	0.3 (5)	0.8 (6)	1.0 (7	0.9 (13)	1.6 (9)

From: Blair et al. Scand J Work Environ Health 1998;24:suppl 2:25-41.

Summary of Comparisons of Unadjusted and Adjusted RRs from Six Recent AJE Articles

- **Four of 92 comparisons differed by >0.3**
- **Four of 92 might result in a different conclusion using adjusted RR**
  - **Two with a change in magnitude**
  - **Two with a change to no effect**

Conclusions About Confounding

- **My Conclusion:**
  - **Confounding is rare – only 5% occurrence in this sample**
  - **If rare, we should not assume confounding occurs without some evidence that it exists in the study under review**
- **What if you cannot adjust for confounding directly?**
  - **Are requirements for confounding evident?**
  - **Are other effects of confounding apparent?**
  - **Has this confounding occurred in other studies?**
  - **Estimate possible effect (Axelson method for smoking)**
- **These usually provide an clear indication of the level of concern**

Misclassification of Exposure

Could be an important limitation in epidemiology because:

- **Biologic measures to characterize dose extremely rare**
- **The few measurements available usually clustered in recent years**
- **Quantitative estimates are possible (even desirable) desirable), but fraught with error**

Exposure Misclassification: Bias towards the Null

True Exposure Classification

	Yes	No	
Case	150	350	500
Control	50	450	500
	200	800	

With 20% Non-differential Misclassification of Exposure

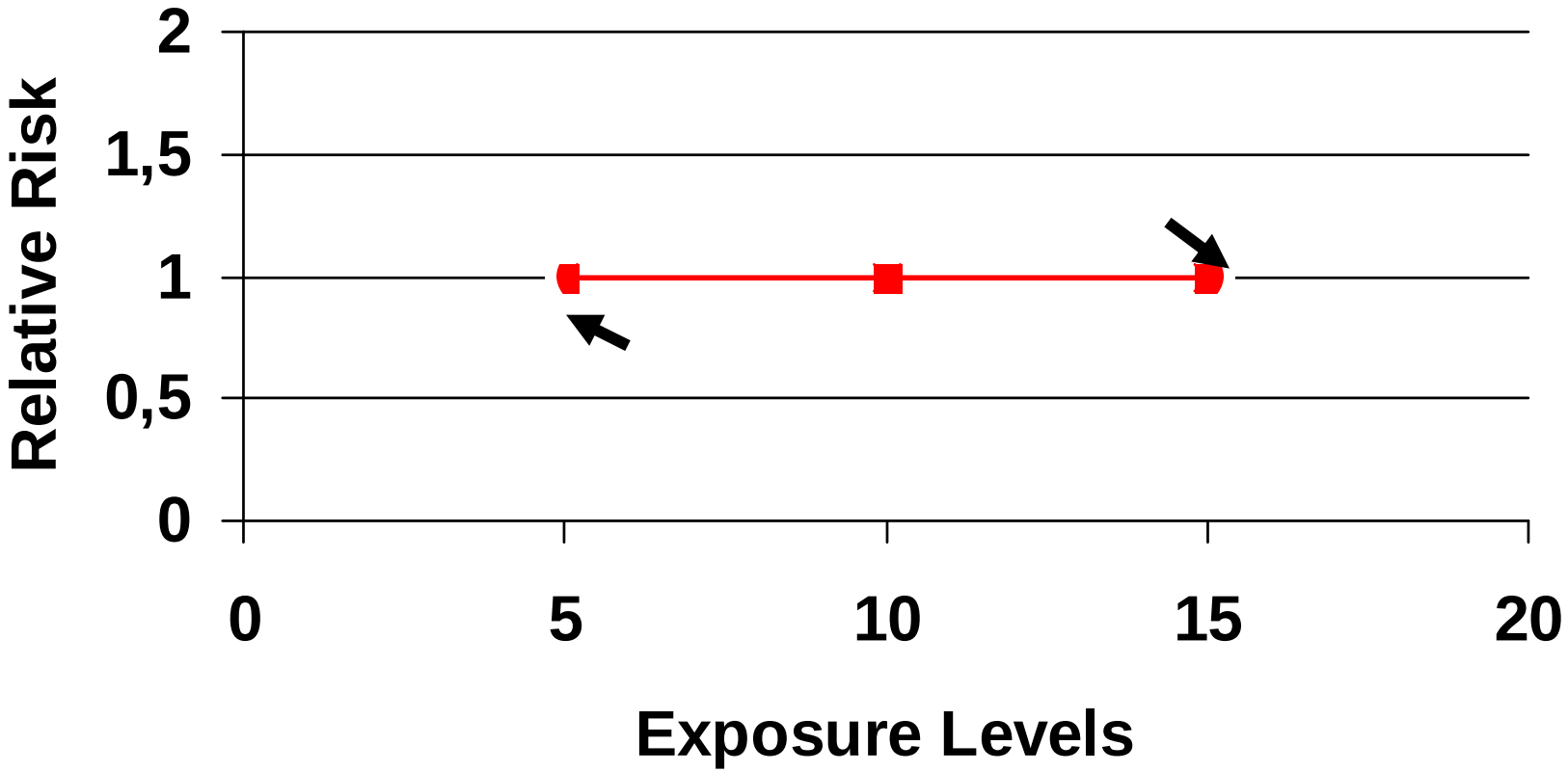
	Yes	No	
Case	190	310	500
Control	130	370	500
	320	680	

OR = 3.9 ▬ ▬ ▬ ► OR=1.7

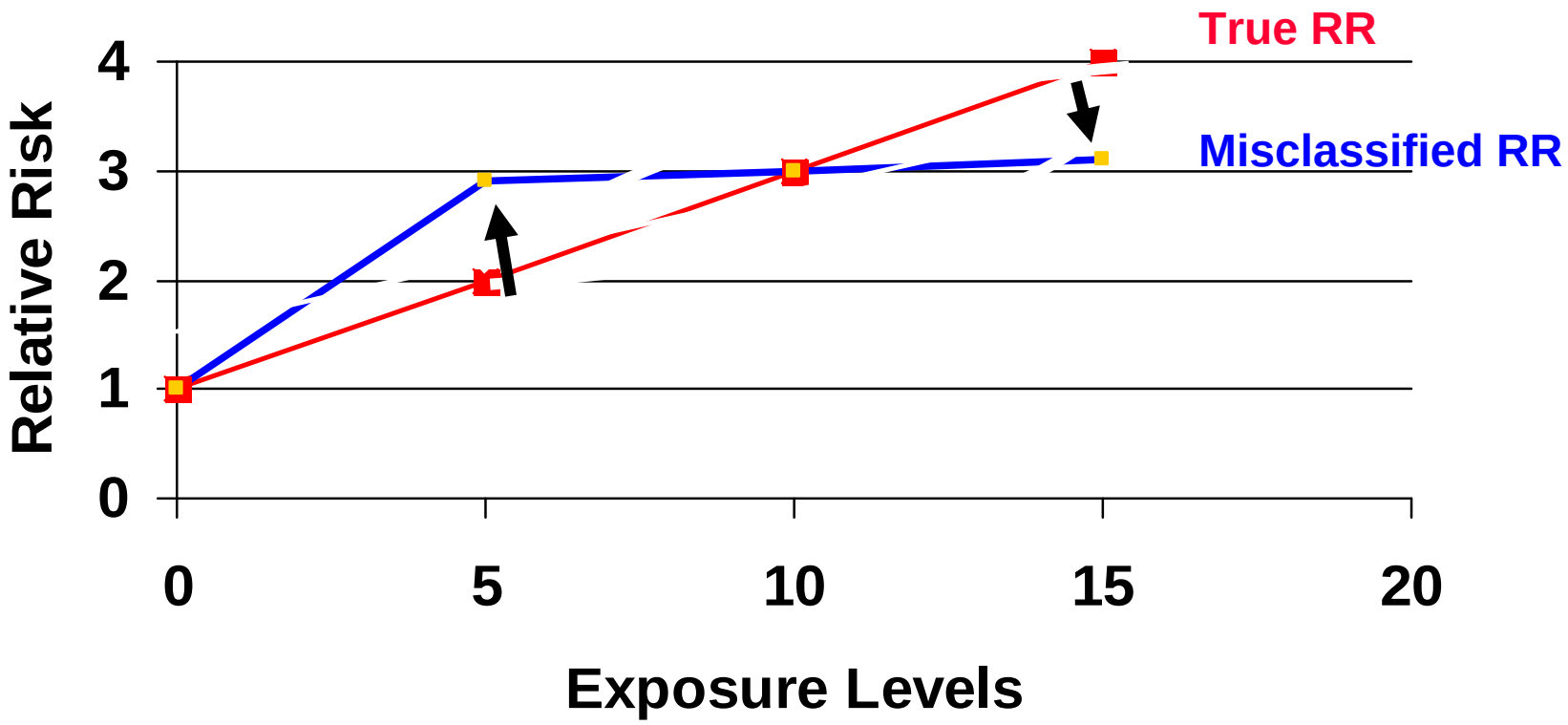
In this example, the observed OR is attenuated by 56% when 20% of exposed cases (n=30) and controls (n=10) are misclassified as non-exposed, and 20% of non-exposed cases (n=70) and controls (n=90) are misclassified as exposed.

Misclassification of Exposure: True Association

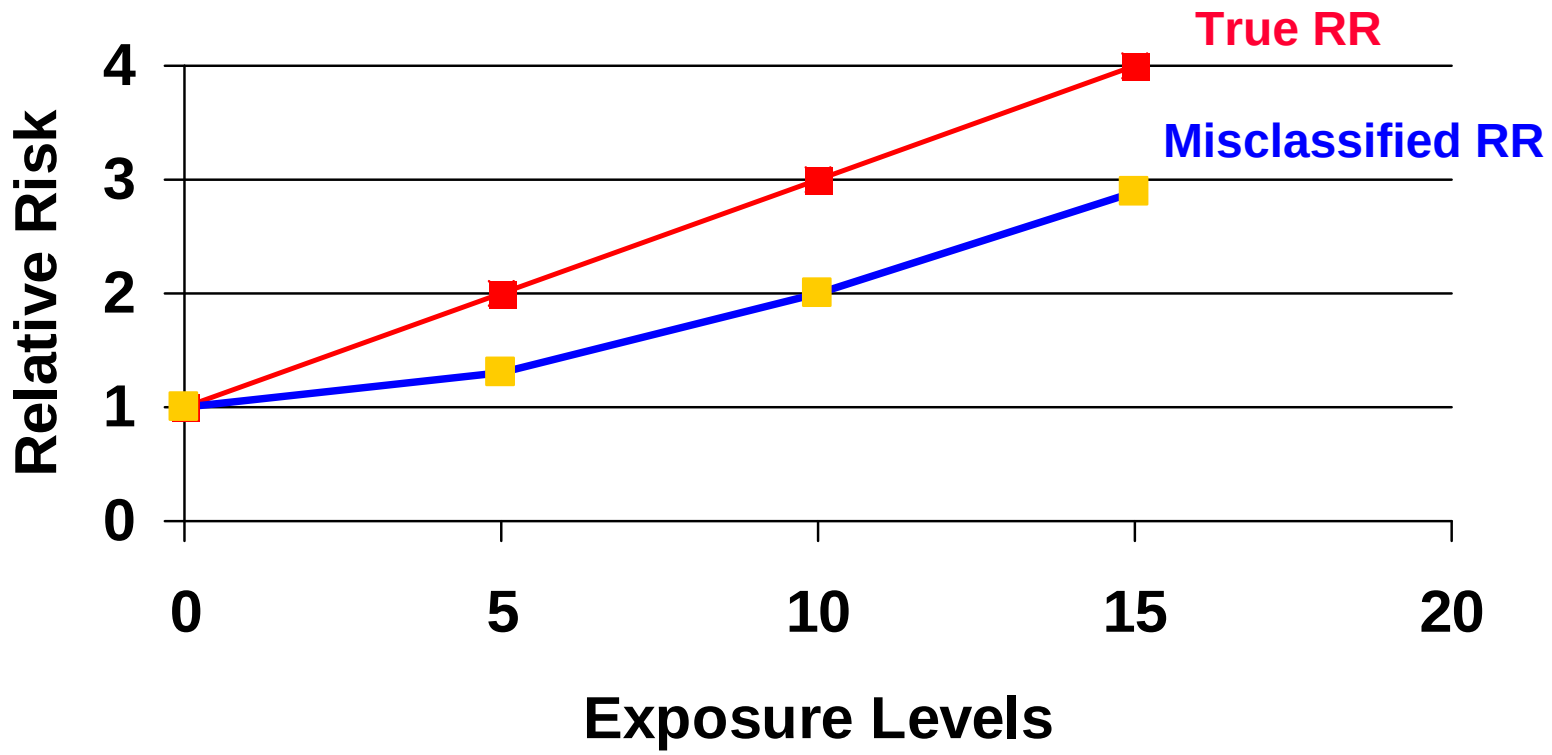
with nondifferential misclassification



Misclassification of Exposure: True Association



Misclassification of Exposure: True Association



Levels of Misclassification in Occupational Studies as Indicated by Different Exposure Assessment Approaches

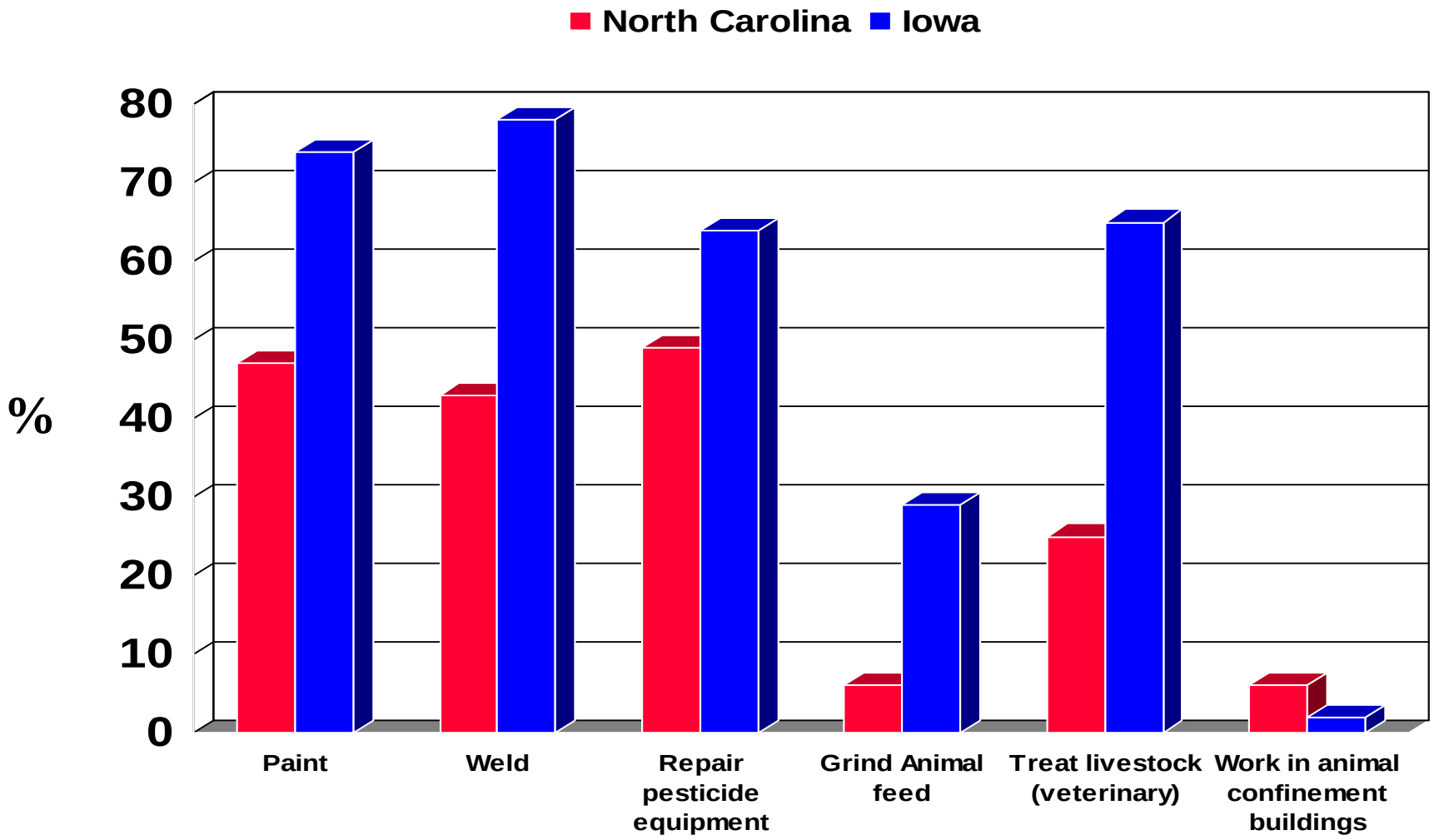
- Acrylonitrile – Measurements/estimates, r = 0.6
- Dioxin – Serum levels/estimates, r = 0.70
- Coal tar volatiles – Measurements/estimates, r = 0.42
- Formaldehyde – Different estimates, r = -0.1 to 0.7
- Jobs – Reported/recorded jobs, 83% agreement
- Welding fumes- Measurements/experts, r = 0.42
- Asbestos – Supplementary Qx/JEM, Kappa = 0.39
- 2,4-D – PK Model/urinary measurements, r = 0.65

Exposure Among Farmers as an Example of Assessment Limitations

- **Multiple exposures**
- **Variations over time**
- **Some exposure patterns contrary to expectations**

Agricultural Health Study

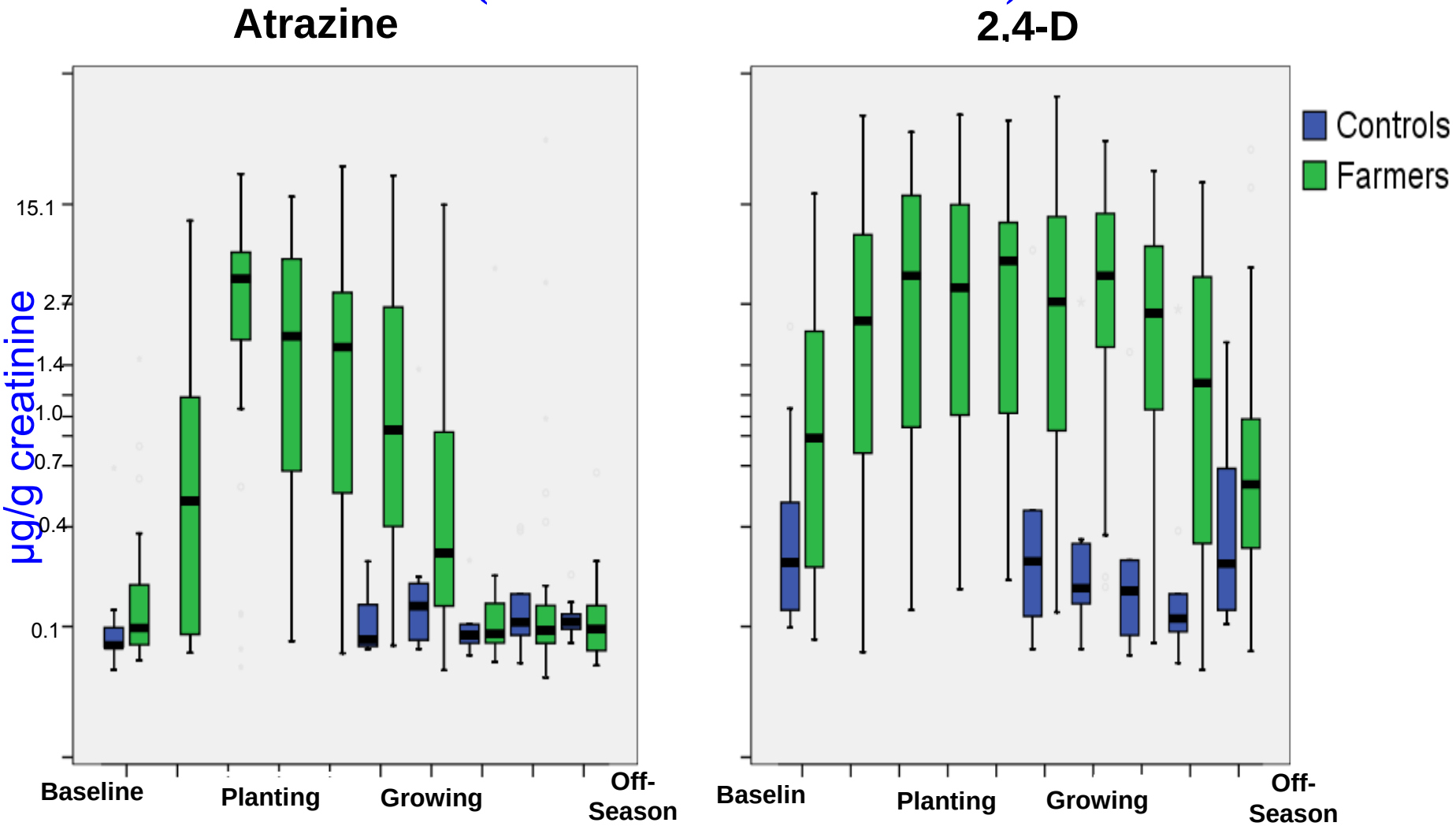
Activities Performed at Least Once a Year by Farmers



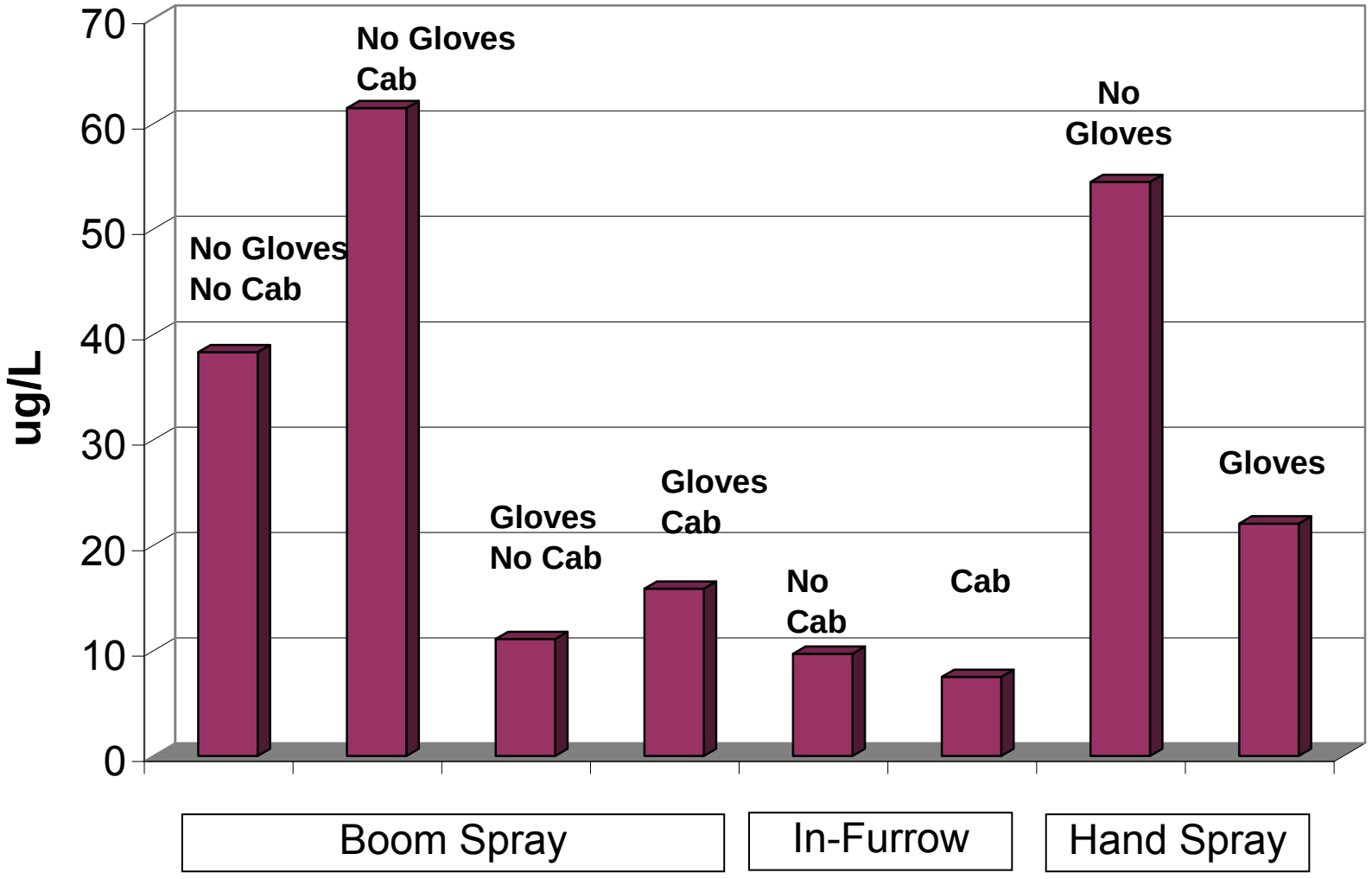
From: Coble J et al. J Exposure Anal Environ Epid 12:418-426, 2002

Urinary concentrations of atrazine and 2,4-D by study time points

(From Bakke. 2005. EPICOH)



CONCENTRATIONS IN POST-APPLICATION URINE - GEOMETRIC MEAN (ug/L)



Observed Relative Risks Based on Sensitivity, Specificity, Exposure Prevalence and True Risks

True RR and Exposure Prev.	Specificity=1.0	Specific=0.7
True RR = 2.0		
Exposure prev.=10%	1.94 (0.81)	1.15 (0.19)
=30%	1.80 (0.76)	1.30 (0.36)
=50%	1.63 (0.70)	1.31 (0.40)
True RR = 3.0		
Exposure prev.=10%	2.82 (0.81)	1.29 (0.19)
=30%	2.44 (0.76)	1.53 (0.36)
=50%	2.05 (0.70)	1.50 (0.40)

( ) = Kappas for corresponding sensitivity, specificity and exposure prevalence.

Misclassification of Exposure in Epidemiology

- **My Conclusion:**
  - **Misclassification is the major weakness**
  - **Not well considered in data interpretation**
  - **Ignoring it leads to false negative conclusions**
- **What Should We Do?**
  - **Evaluate degree of misclassification in each study**
  - **Scour literature for relevant data and examples**
  - **Perform sensitivity analyses to estimate effects**
  - **Assess magnitude of misclassification in relation to other study biases and problems**

Studies of Occupational Cancer: Past and Future

- Major contributor to understanding of carcinogenicity in the past
- Probably as important as other risk factor areas, expect smoking and diet
- Currently many new leads
- Can still make significant contributes to understanding the biology of cancer
- Accurate exposure assessment the major limitation

Conclusions

- With many new leads, we need more occupational studies of cancer
- Need studies that include women and minorities
- Global level of occupational exposure may be increasing with movement of industry to developing countries
- Occupational exposures never stay in the workplace, thus are relevant to the general population