Evaluations of Epidemiology and Human Studies for Risk Assessment

Presented by
Rebecca Nachman and Rachel Shaffer

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Moderator

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Ronald Hines, MS, PhD, ATS
Yale University School of Public Health
(Past President of SOT 2019 – 2021)

- Ph.D. in biochemistry; University of Texas Southwestern Medical School, 1980
- Postdoctoral fellowship, University of Vermont College of Medicine (1980-1983)
- Assistant Professor (1983-1988) and Associate Professor (1988-1989), Eppley Institute for Research in Cancer and Allied Diseases and Department of Biochemistry, University of Nebraska Medical Center.
- Associate Professor of Pharmacology (1989-1995), Wayne State University School of Medicine
- Professor of Pharmacology)1995-1999), Wayne State University School of Medicine
- Professor of Pediatrics and Pharmacology and Toxicology (1999-2012), Medical College of Wisconsin
- Co-Section Chief, Clinical Pharmacology, Pharmacogenetics, and Teratology (1999-2012), Medical College of Wisconsin
- Associate Director, Children's Research Institute, Children's Hospital and Health Systems, Milwaukee (2005-2012)
- Associate Director for Health, National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency (2013-2020)
- Adjunct Professor, Department of Environmental Health Sciences, Yale School of Public Health (2021-present)

Instructor

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Rebecca Nachman, PhD, MPH
US Environmental Protection Agency

- Epidemiologist at US EPA, ORD, Center for Public Health and Environmental Assessment (CPHEA) in Washington, DC since 2017
- Selected activities since joining IRIS
  - Senior Epidemiologist, methylmercury assessment (in development)
  - Contributor, hexavalent chromium and ethylbenzene assessments (in development)
  - Co-chair, Epidemiology Working Group (2017-2021)
  - Co-chair, EPA Summit on Systematic Review and Exposure Science (2019)
  - Planning committee, NASEM Workshop on Triangulation of Evidence in Environmental Epidemiology
- Public Health Education and Training
  - PhD, Environmental Health Sciences, Johns Hopkins University
  - MPH, Johns Hopkins Bloomberg School of Public Health
  - Postdoctoral Fellow, Johns Hopkins Bloomberg School of Public Health
  - Certificate in Risk Sciences and Public Policy, Johns Hopkins University

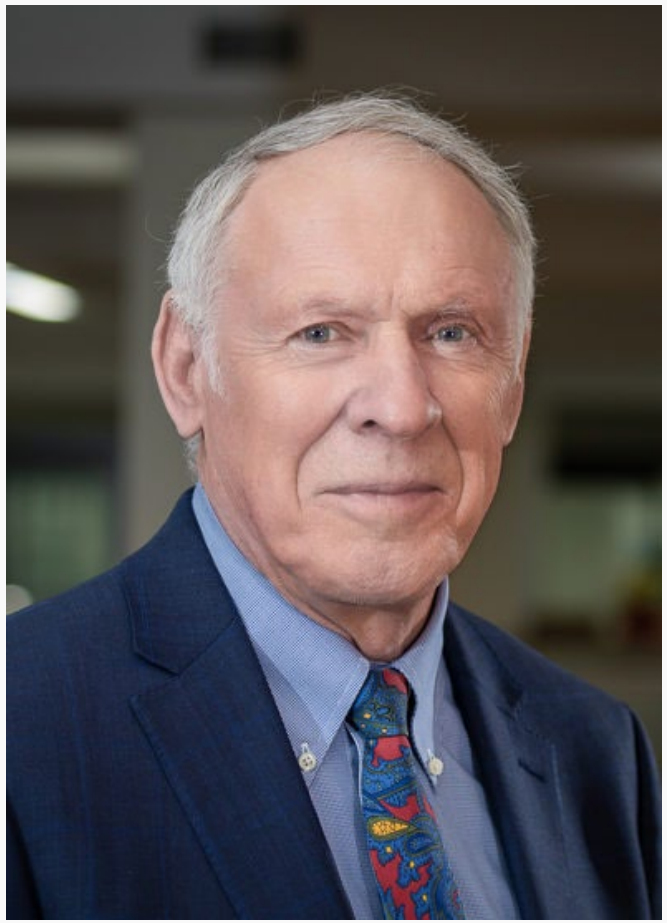
Instructor

Shaffer.Rachel@epa.gov

Rachel M. Shaffer, PhD, MPH
US Environmental Protection Agency

- Epidemiologist at US EPA, ORD, Center for Public Health and Environmental Assessment (CPHEA), Chemical Pollutant Assessment Division (CPAD) in Washington, DC since Sept 2020
- Selected activities since joining CPAD:
  - IRIS assessment contributions: arsenic, PCBs, chromium, naphthalene, ethyl benzene
  - Assessment-adjacent research on manganese and lead
  - Co-chair of Epidemiology Working Group
- Graduate training at University of Washington-Seattle School of Public Health
  - PhD: $PM_{2.5}$ & dementia (Dr. Lianne Sheppard)
  - MPH: Phthalates & gestational diabetes (Dr. Sheela Sathyanarayana)

Panelist



Daniel Krewski, PhD, MHA
University of Ottawa

- Dr. Daniel Krewski is a Fellow of the Society of Risk Analysis and the American Statistical Association, and a lifetime National Affiliate of the US National Academy of Sciences.
- In 2013, he received the Distinguished Achievement Award from the Society for Risk Analysis, for excellent performance in the practice of risk analysis.
- He has contributed to over 900 scientific and technical publications in the field of risk science during the course of his career to date.
- Dr. Krewski's first major research project upon joining the University of Ottawa in 1998 was a major re-analysis of data from the Harvard Six Cities Study

Panelist

Raghavendhran (Raga) Avanasi, PhD

Syngenta Crop Protection

- PhD in Environmental Toxicology – Exposure and Risk Assessment, UC Irvine;
  Masters in Environmental Toxicology, Texas Tech University;
  Bachelor Technology in Biotechnology, Vellore Institute of Technology
- Areas of interest: Exposure modeling, Risk assessment, Environmental Epidemiology, Uncertainty and Variability Analysis
- Roles:
  - Technical Expert- Human Safety, Risk Assessment
  - Member of HESI Environmental Epidemiology for Risk Assessment committee
  - Chair of the Crop Life America Epidemiology Working Group (2019-2021)

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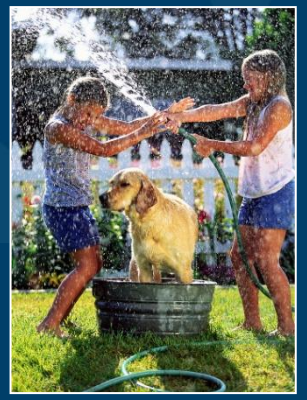
HSR 302: Introduction to Epidemiology





RATE Risk Assessment Training & Experience

Rachel M. Shaffer, PhD, MPH.
Rebecca M. Nachman, PhD, MPH.

Office of Research and Development
National Center for Environmental Assessment

Disclaimer

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency

What You Can Expect to Learn From This Course

Course Goals

- Understand principles of epidemiology
- Understand how epidemiology research is used in risk assessment

Course Outline

- Definitions and principles
- Study designs
- Evaluation of chance, bias and confounding
- Interpreting individual and collections of studies

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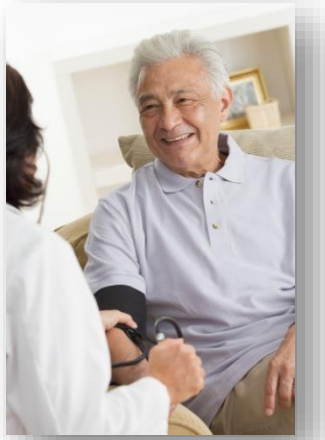
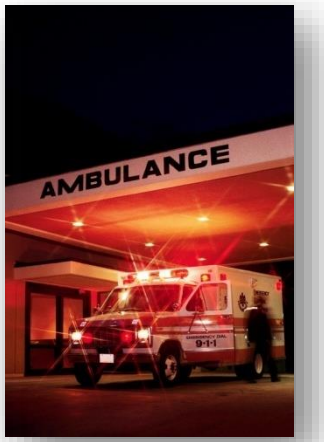
INTRODUCTION TO EPIDEMIOLOGY

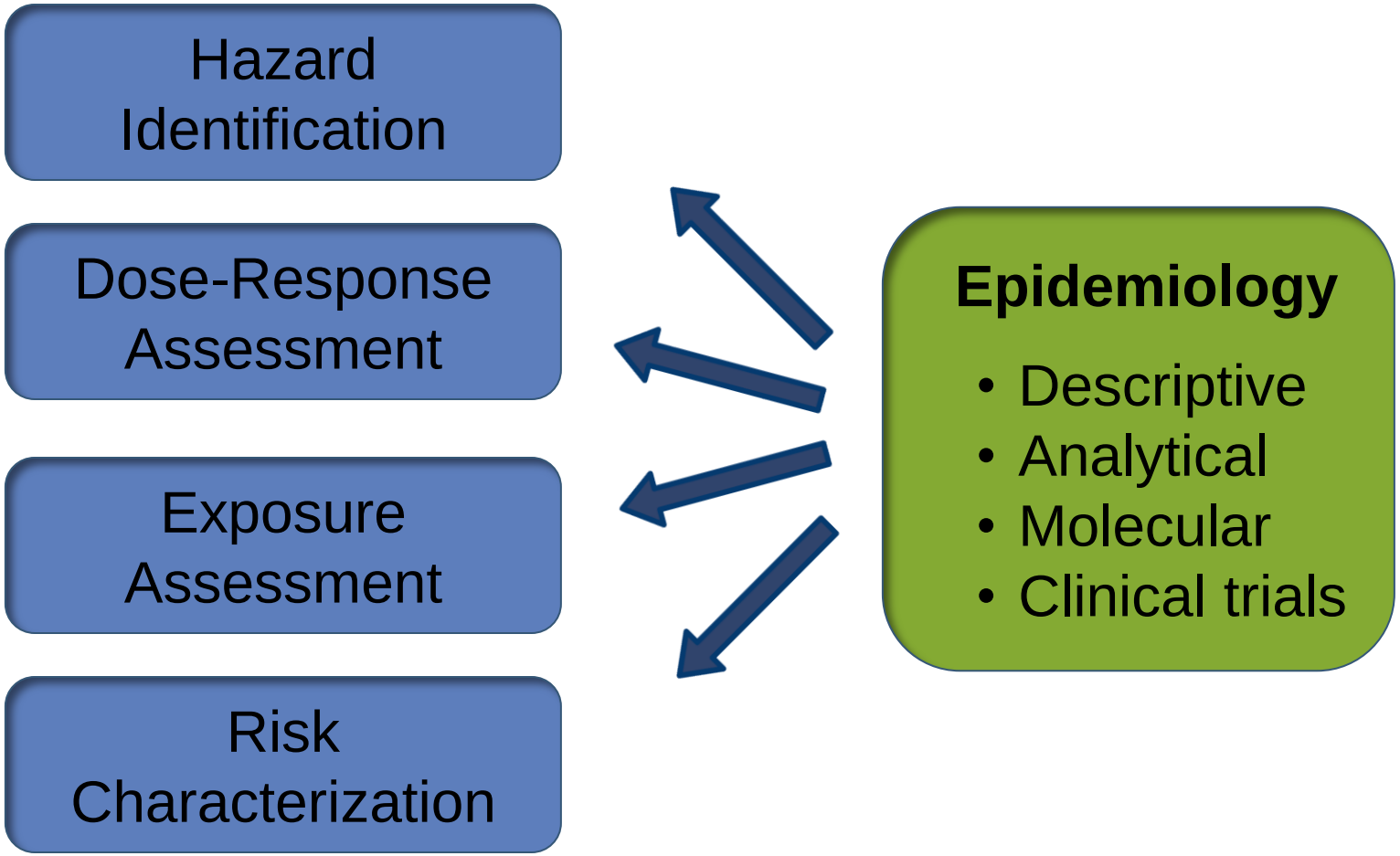
What is Epidemiology?

The study of the distribution and determinants of health, disease, or injury in human populations





Epidemiology in Risk Assessment



Adapted from Nurminen et al. 1999, p. 586

Basics of Epidemiologic Research

- General principles of good epidemiologic research
  - Comparability between study groups
    - »*Exposed and unexposed; cases and controls*
  - Ethical conduct
- Ability of a study to find an association if one exists
  - Frequency of exposure and outcomes
  - Magnitude of associations
  - Study design
  - Sample size

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MEASURES OF ASSOCIATION & STUDY DESIGNS IN EPIDEMIOLOGICAL RESEARCH

Common Measures of Association

- Ratio measures ("relative risk")
  - 1.0 = "no association"
  - Used for etiologic inference
  - Examples: Rate ratio, odds ratio, risk ratio, hazard ratio, and standardized mortality ratio
- Difference measures
  - 0.0 = "no association"
  - Used to evaluate public health impact or intervention
  - Examples: Rate difference, risk difference

Measures of Association in Observational Studies

Relative Risk Measures	Type of Study
Rate Ratio	Cohort Time-Series
Standardized Mortality Ratio Standardized Incidence Ratio	Cohort
Odds Ratio	Cohort Case-Control Case-Crossover
Prevalence Ratio	Cross-Sectional

Measures of Disease Occurrence

Measure	Expresses	Features
Incidence $\frac{\text{\# Affected}}{\text{Population} \times \text{Time}}$	• Number of **new** cases in a population during a time period; rate of occurrence	• Denominator = person-time (i.e., per 100,000 person-years)
Prevalence $\frac{\text{\# Affected}}{\text{Population}}$	• Number of cases in a population at a given time	• Denominator = persons (i.e., per 100,000) • Reflects incidence and duration (survival)
Mortality Rate $\frac{\text{\# Deaths}}{\text{Population} \times \text{Time}}$	• Number of deaths in a population in a time period	• Denominator = person-time (i.e., per 100,000 person-years)

Risk: Likelihood of future events

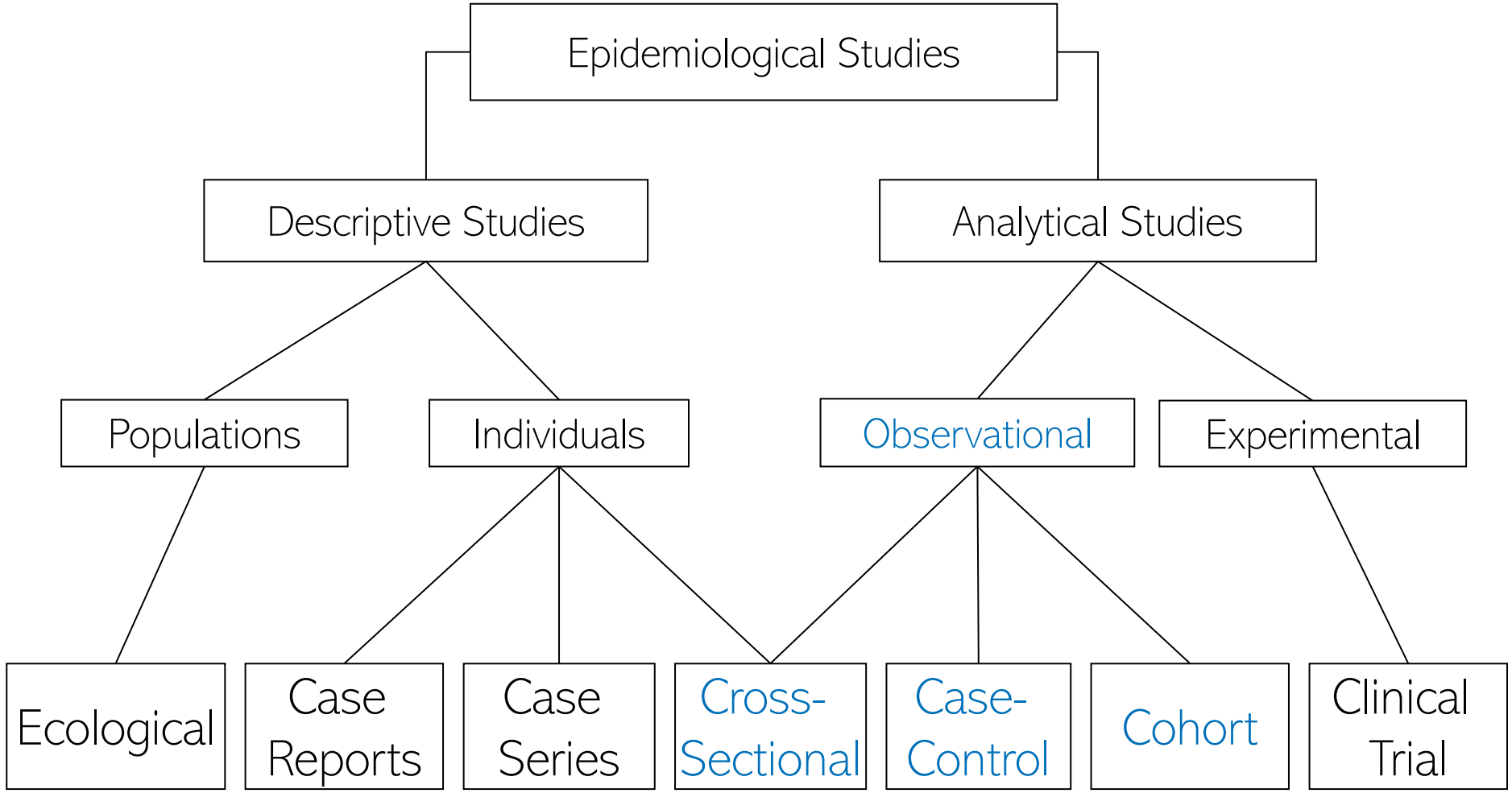
Some Measures of Excess Risk

Measure of Excess Risk	Formula	Question that this measure addresses
Attributable Risk % (AR%)	(RR-1)/RR x 100%	What % of the disease in the **exposed population** was due to the exposure?
Attributable Risk to the Population % (PAR%)	$(I_t - I_o)/I_t$ x 100%	What % of disease in the **entire population** was due to the exposure?

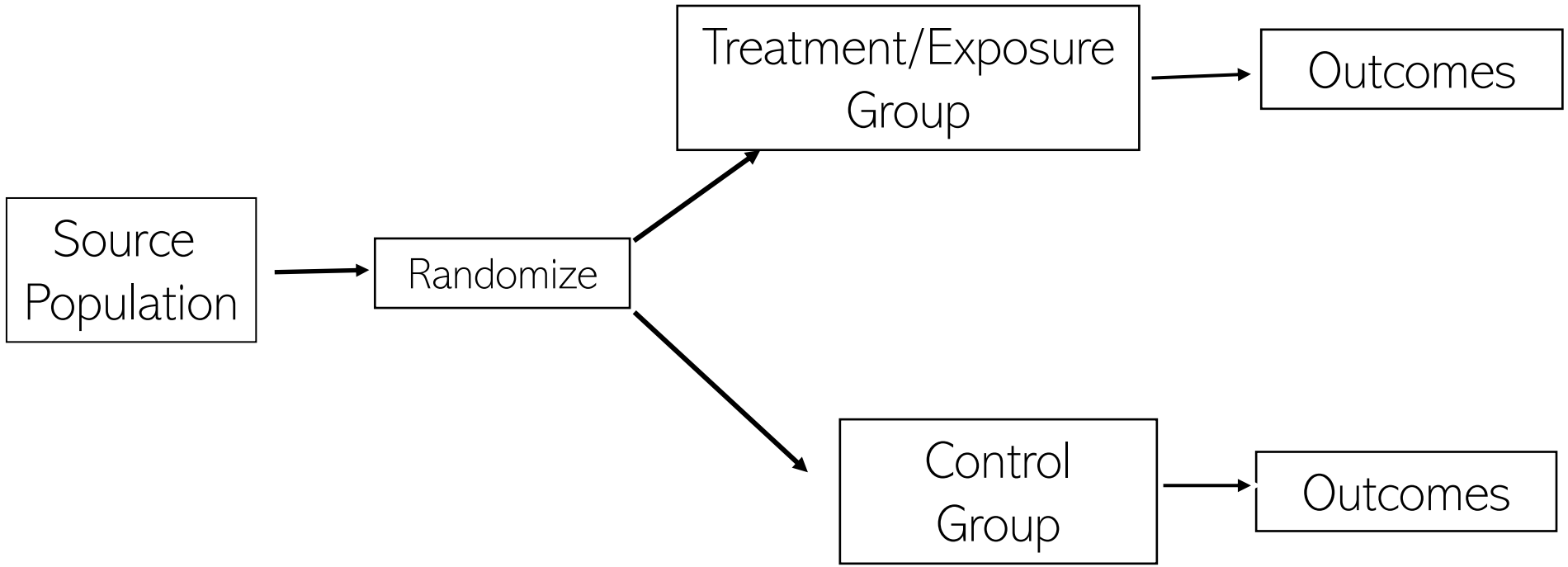
For risk management purposes, these measures assume that causality is established based on WOE before examining

RR = relative risk
I_t = incidence in the whole population
I_o = incidence in non-exposed

Epidemiologic Study Designs



Experimental Study Design



Experimental Studies

- **Exposure is assigned by the investigators**
- **Types of experimental studies:**
  - Clinical studies
    - Randomized clinical trials
  - Controlled exposure studies

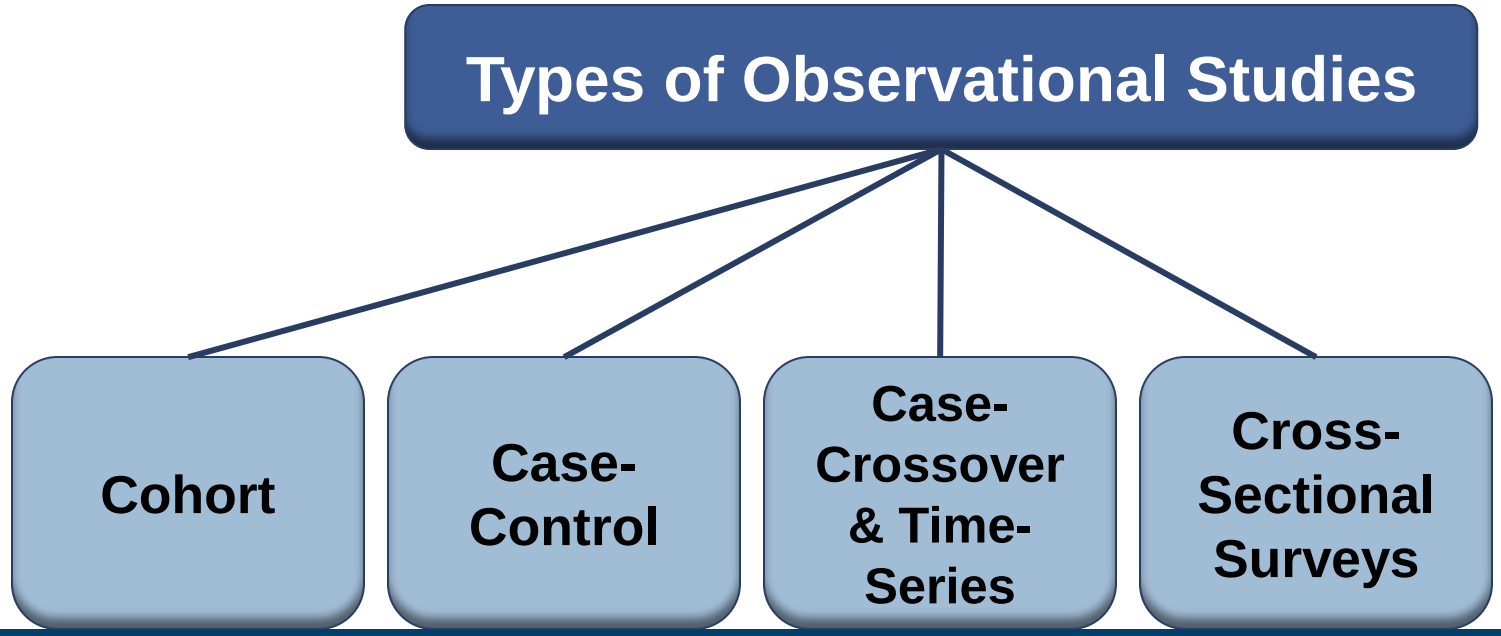
Images of EPA's Human Study Facilities Chamber

Considerations for Controlled Exposure Studies

- Selection of subjects
  - Follow guidance from EPA on human subject research
- Assignment of exposure – 2 approaches
  - Individuals serve as own control
    - Randomize order of exposure
  - Control groups
    - Randomize exposure
    - Matching by known potential confounders
- Data collection: Masking (or blinding)
    - Subjects do not know exposure received
    - Data collectors or analysts do not know which exposure received

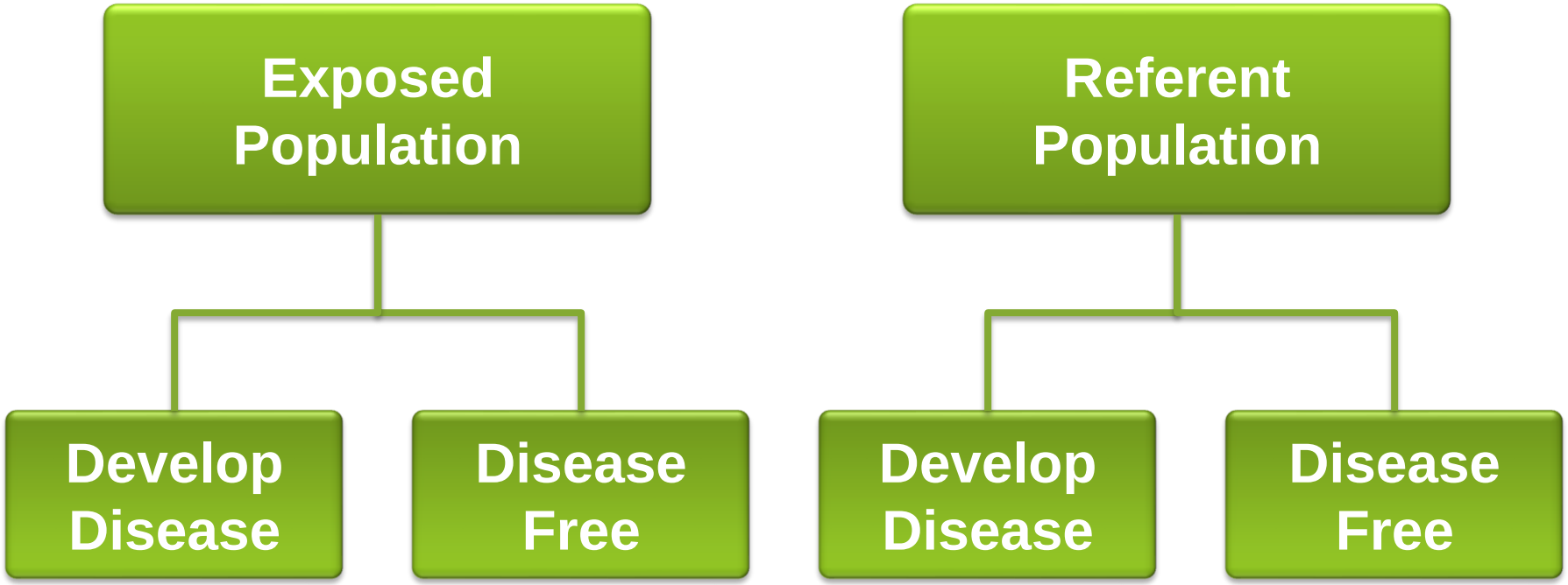
Observational (Non-Experimental) Studies

Exposure is not assigned or controlled; instead, reflects experiences at work, in homes, and in communities



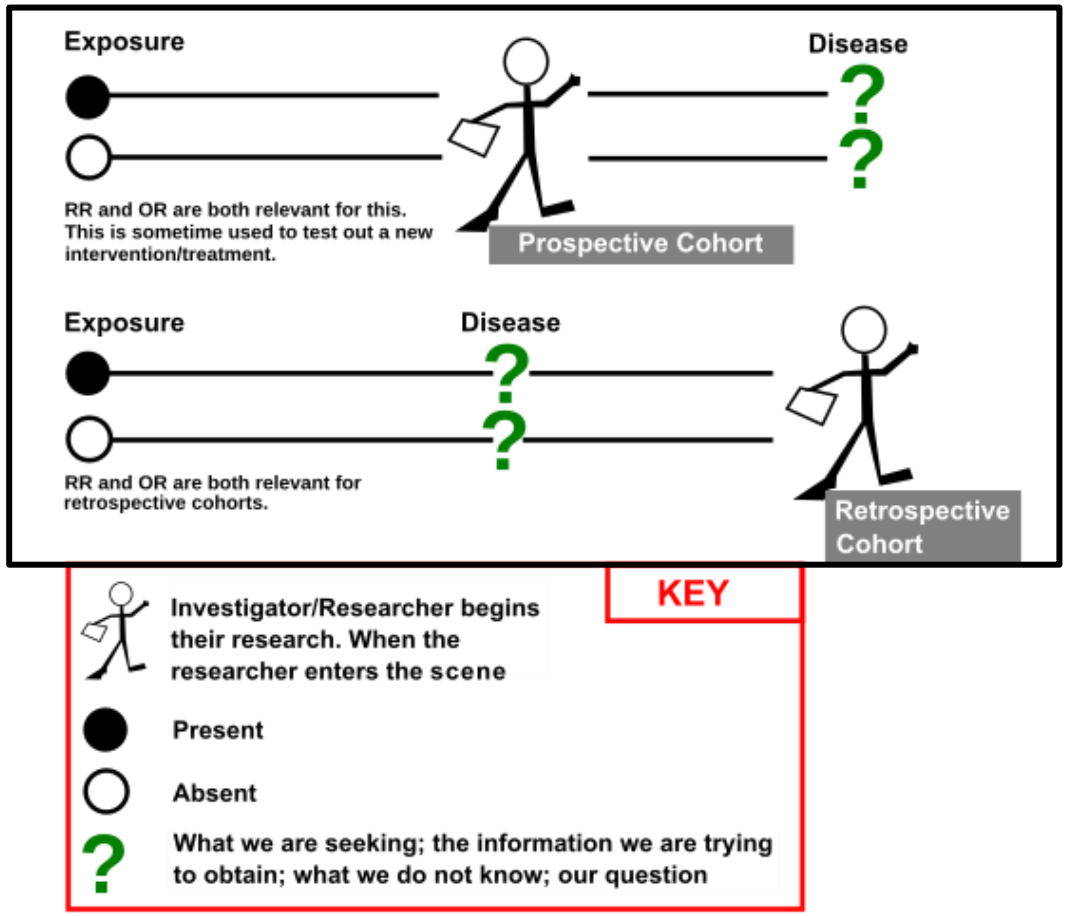
Cohort Studies

Cohort studies are defined by **exposure status**



Adapted from Leon Gordis, 2nd edition

Types of Cohort Studies:
Prospective vs. Retrospective



Considerations for Cohort Studies

- Comparability of exposed and referent groups
  - Internal or external referent groups
    - "Healthy worker effect" – bias towards the null
  - Consideration of important demographic factors (e.g., age, sex)
- Ascertainment of outcome
  - Loss to follow-up
  - Disease incidence or mortality
  - Blinded to exposure status
- Frequency of outcome
  - Rare "events" (e.g., rare cancers) difficult to study

Common Measures of Association in Cohort Studies

	Develop Disease	Disease Free	Total
Exposed	a	b	a + b
Referent	c	d	c + d

Risk (Probability)

Probability of Disease

= Pr (D)

Disease Incidence (Risk)

Pr (D) in Exposed: $\frac{a}{a+b}$

Pr (D) in Referent: $\frac{c}{c+d}$

Risk Ratio (Risk in Exposed ÷ Risk in Referent)

$$\frac{\text{Pr (D) in Exposed}}{\text{Pr (D) in Referent}}$$

$$\frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

Another Measure: Standardized Mortality Ratio

- Standardized mortality ratio (SMR) = ratio of observed to expected
  - SMR of 1.0 indicates “no association”

- Compares the mortality **observed** in cohort to “expected” mortality in referent population
  - What is the **expected** number of deaths in the study cohort if their mortality experience was the same as that of the referent population?

→ Apply age- and gender-specific mortality rates of the referent population to the cohort, taking into account the age and gender structure of the cohort.

Example of an Occupational Cohort Study

- Lung cancer among workers in a chromium chemical production facility
- Design
  - Chromate production plant, Baltimore; n = 2,357 men
  - Worked at the plant between August 1, 1950 and December 31, 1974; workers were followed until Dec 31, 1992
- Endpoint
  - Lung cancer
- Exposure
  - Air and personal monitors and work records used to develop Job Exposure Matrix
    - Monitoring data (mean of values):
    - 74 $\mu g/m^3$ Cr^{+6} in old plant
      - 31 $\mu g/m^3$ Cr^{+6} in new plant

Chromium and Lung Cancer Cohort Study: Design

- Outcome measure:
  - Lung cancer, based on underlying cause of death (National Death Index)
- Analysis
  - **External referents**: Standardized mortality ratios, based on Maryland rates, adjusted for age, race, and calendar year
  - **Internal referents**: Proportional hazards model, including adjustment for smoking history, using age as the time variable and cumulative exposure as a time-varying covariate

Chromium and Lung Cancer Cohort Study: Results

Cumulative Cr^{+6} Exposure (mg CrO_3/m^3-years)	Lung Cancer (Observed-to-Expected Ratio, 95% Confidence Interval, Observed and Expected Deaths, Person-Years of Observation)
0–0.00149 Mean = 0.00045	O/E = 0.96 (95% CI = 0.63, 1.38) O = 26, E = 27.1 PY = 28,512
0.0015–0.0089 Mean = 0.0042	O/E = 1.42 (95% CI = 0.95, 2.01) O = 28, E = 19.80 PY = 14,879
0.009–0.0769 Mean = 0.030	O/E = 1.57 (95% CI = 1.07, 2.20) O = 30, E = 19.1 PY = 15,194
0.077–5.25 Mean = 0.449	O/E = 2.24 (95% CI = 1.60, 3.03) O = 38, E = 17.0 PY = 13,409

Cumulative Hexavalent Chromium Exposure (mg CrO_3/m^3-years)	Coefficient	Relative Risk	*p*-Value
Log_{10} cumulative hexavalent chromium exposure	0.509	1.66	0.045
Log_{10} cumulative trivalent chromium exposure	-0.177	0.17	0.449
Cigarette smoking	1.8	6.05	0.004

Relative risk is for each 10-fold increase in cumulative exposure

Am J Ind Med. 2000 Aug;38(2):115-26.
Lung cancer among workers in chromium chemical production.
Gibb HJ, Lees PS, Pinsky PF, Rooney BC.

Example of Environmental Cohort Study: Arsenic and Diabetes

- Endpoint
  - Long-term arsenic (As) exposure and incidence of non–insulin-dependent diabetes mellitus
- Design
  - 3 villages in southwest Taiwan
    - Drinking water As concentrations ranged from 0.70-0.93 mg/L
      - EPA standard for arsenic in drinking water is 0.05 mg/L
  - Population survey and health exam, 1988-1989, ages > 30
    - 891 out of 1,081 (82%) agreed to full participation
      - Survey plus test for diabetes
    - Of these 891, 632 subjects were eligible for the study (nondiabetics)

Arsenic and Diabetes: Additional Aspects of Study Design (Environmental Cohort Study)

- Exposure
  - Cumulative arsenic exposure estimated, based on:
    - Historic measurements of arsenic in well water
    - Duration of drinking well water in the village (from interviews)
- Outcome measure
  - Diabetes incidence (new diagnoses)
- Analysis
  - Multivariate analysis using Cox's proportional hazards model
  - Result: Relative risk of arsenic exposure from drinking water on incidence of diabetes mellitus
    - Results adjusted for the effects of age, sex, and body mass index

Arsenic and Diabetes: Results

Incidence rates (per 1,000 person-years) and relative risks for diabetes mellitus in subgroups of subjects living in arseniasis-hyperendemic villages in Taiwan

Variables	Total no.	Newly diagnosed DM cases (n)	Incidence rate	RR (95% CI)	ARR (95% CI)
Age (years)					
≥ 55	90	15	50.8	2.4 (1.3-4.5)*	1.6 (0.8-3.3)
< 55	356	26	21.6	1.0	1.0
Sex					
Male	223	24	31.5	1.3 (0.7-2.5)	1.1(0.6-2.1)
Female	223	17	23.1	1.0	1.0
BMI (kg/m^2)					
≥ 25	171	27	42.1	2.3 (1.2-4.3)*	2.3 (1.2-4.3)*
< 25	275	17	18.3	1.0	1.0
CAE (mg/L-years)					
≥ 17	132	21	47.6	2.5 (1.4-4.7)*	2.1 (1.1-4.2)*
< 17	314	20	18.9	1.0	1.0

Abbreviations: DM, diabetes mellitus; RR, relative risk (based on Cox models with each variable singly); ARR, adjusted relative risk (based on Cox model with all variables simultaneously).

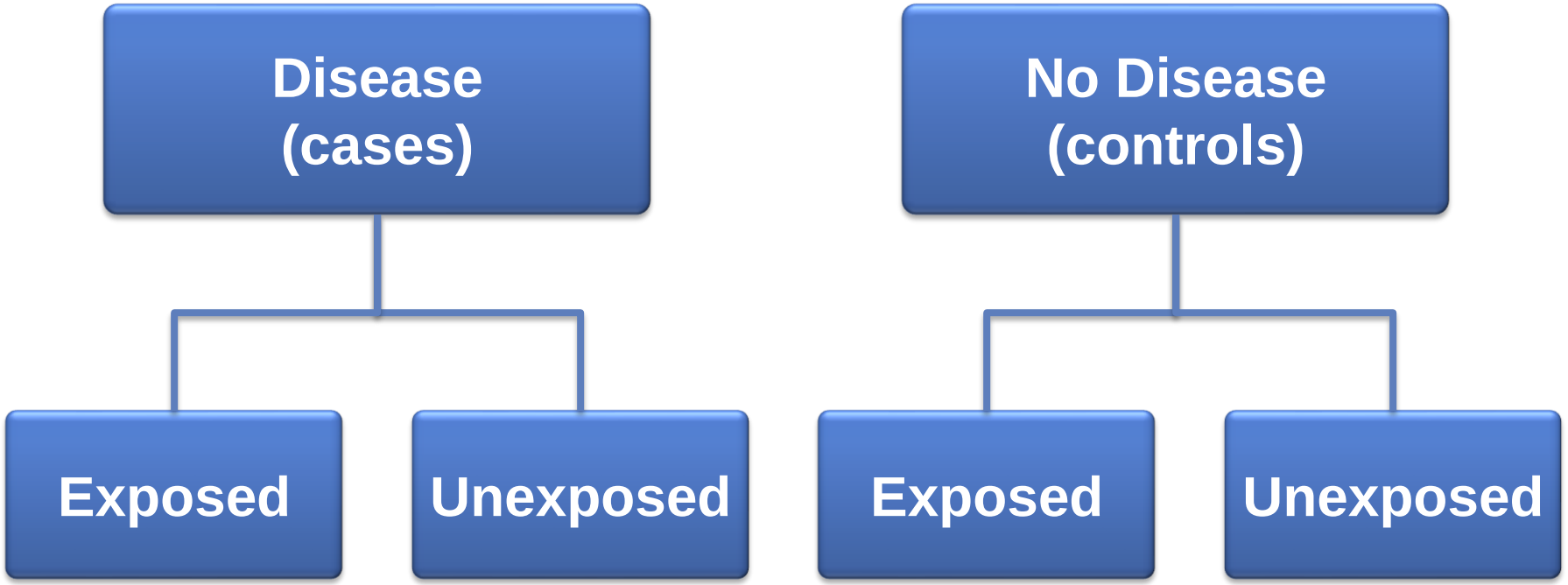
*p< 0.05

Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis-hyperendemic villages in Taiwan.

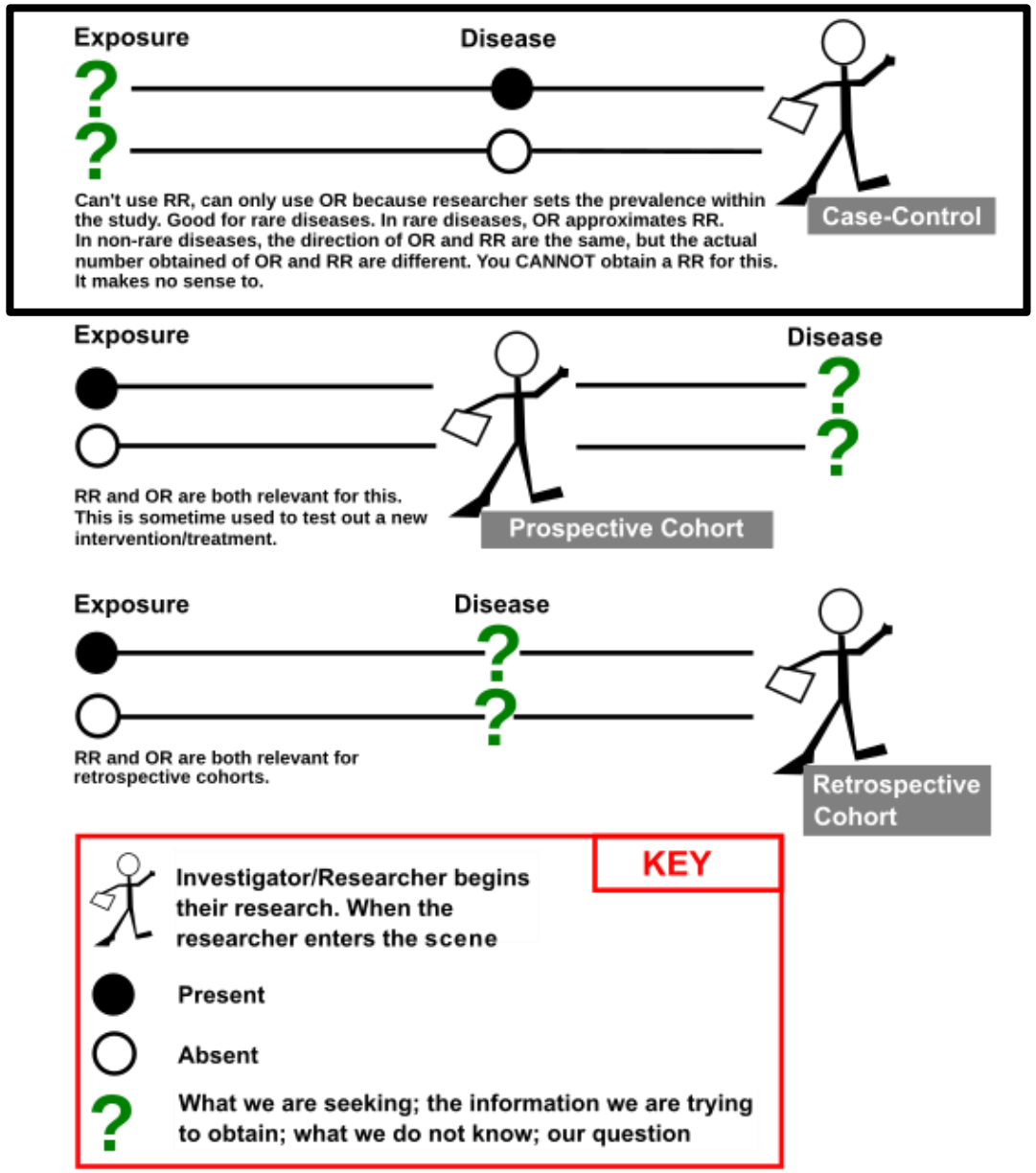
Tseng CH, Tai TY, Chong CK, Tseng CP, et.al. Environ Health Perspect. 2000 Sep;108(9):847-51.

Case-Control Studies

Case-control studies are defined by **disease status**



Observational Study Designs: Case Control vs Cohort



Considerations for Case-Control Studies

- Comparability of cases and controls
  - Controls should represent the “source population” of the cases – the population from which the cases came
    - Exclusion criteria should be the same for cases and controls
    - Matching can improve efficiency (cost) of a study, but is not necessary for validity
      - Group (frequency) matching; individual matching
- Ascertainment of exposure
  - Variety of methods available (e.g., job title, job exposure matrix, geographic information system-based, biomarkers)
  - Blinded to disease status
- Frequency of exposure
  - Uncommon exposures difficult to study

Common Measures of Association in Case-Control Studies

	Cases (Disease)	Controls (Disease Free)
Exposed	a	b
Unexposed	c	d
Total	a + c	b + d

What are the Odds?

$$\frac{\text{Pr (Event)}}{\text{(1 – Pr (Event))}}$$

80% chance of winning:

$$\frac{0.80}{(1-0.80)} = \frac{0.80}{0.20} = 4{:}1$$

Odds of Exposure

For cases:

$$\frac{\frac{a}{(a+c)}}{1-\frac{c}{(a+c)}} = \frac{a}{c}$$

Odds Ratio (Odds in Cases ÷ Odds in Controls)

$$\frac{\frac{a}{c}}{\frac{b}{d}} = \frac{ad}{bc}$$

Odds Ratio can be an estimate of the Risk Ratio

Case-Control Study: Non-Hodgkin Lymphoma (NHL) and Trichloroethylene (TCE) Exposure

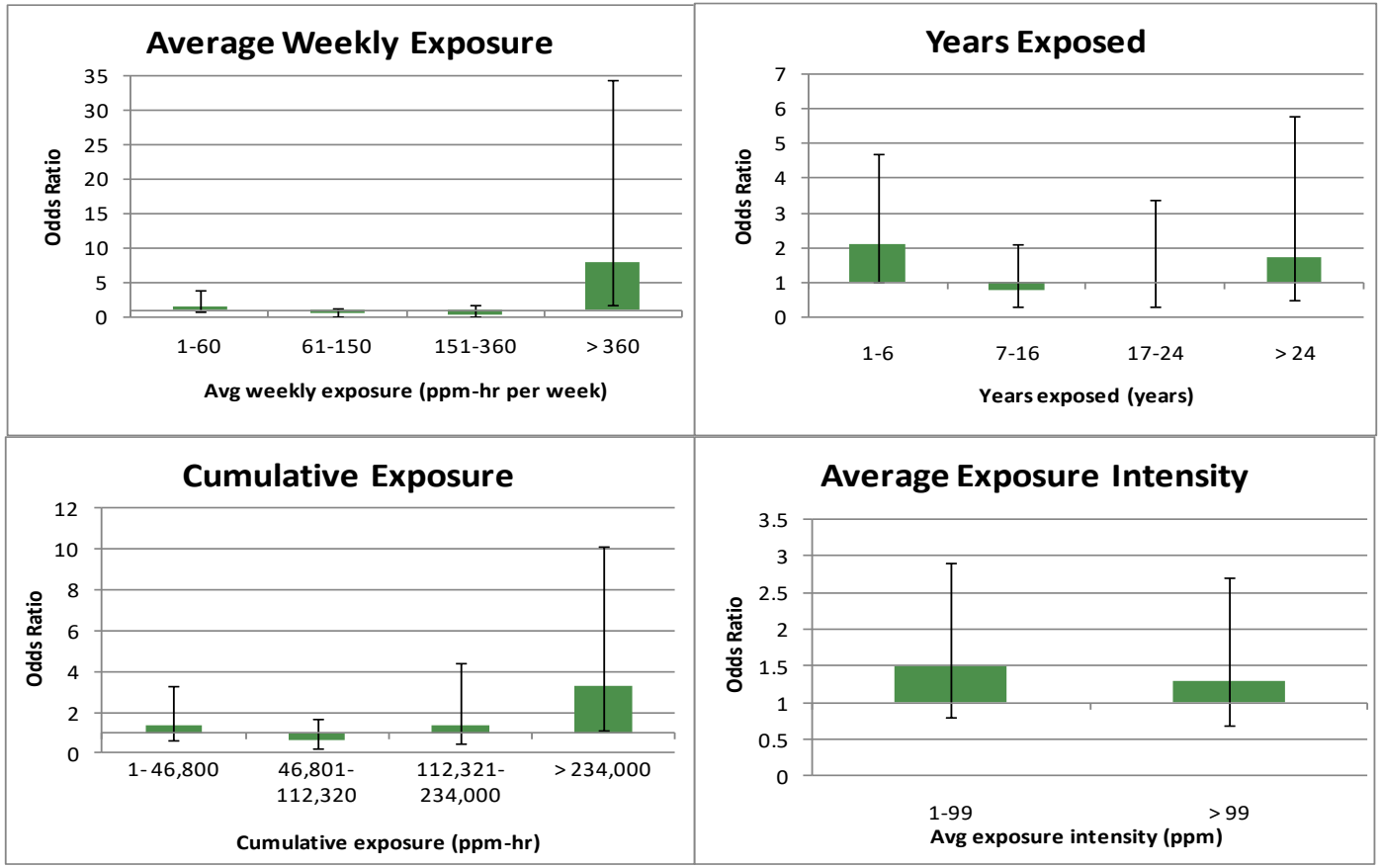
- Endpoint
  - NHL
- Design
  - Incident NHL **cases** in males and females, 20–74 years,1998–2000
    - 4 SEER (Surveillance, Epidemiology and End Results) reporting areas
    - 2,248 eligible cases with 1,321 cases selected/interviewed
  - Population **controls**: residents from same areas (1998–2000), no previous NHL diagnosis
    - Selected using random digit dialing (20–65 years) or from the Medicare files (65–74 years)
    - 2,409 eligible controls with 1,057 controls selected/interviewed

Non-Hodgkin Lymphoma and TCE: Exposures and Outcomes

- Exposure (occupation-based)
  - Industrial hygienist assessment of probability, frequency, and intensity of TCE exposure for jobs held for >1 yr since the age of 16 years based on detailed occupational survey and interview
  - Cases and controls classified into groups based on weekly average, years exposed, cumulative exposure, and average intensity exposure
- Outcome measure: Diagnosis of NHL
  - Based on definition of NHL found in the *International Classification of Disease Oncology*
- Analysis
  - Logistic regression
  - Adjusted for potential confounders (i.e., age, sex, race, education level, and SEER site)

NHL and Occupational TCE Exposure: Results

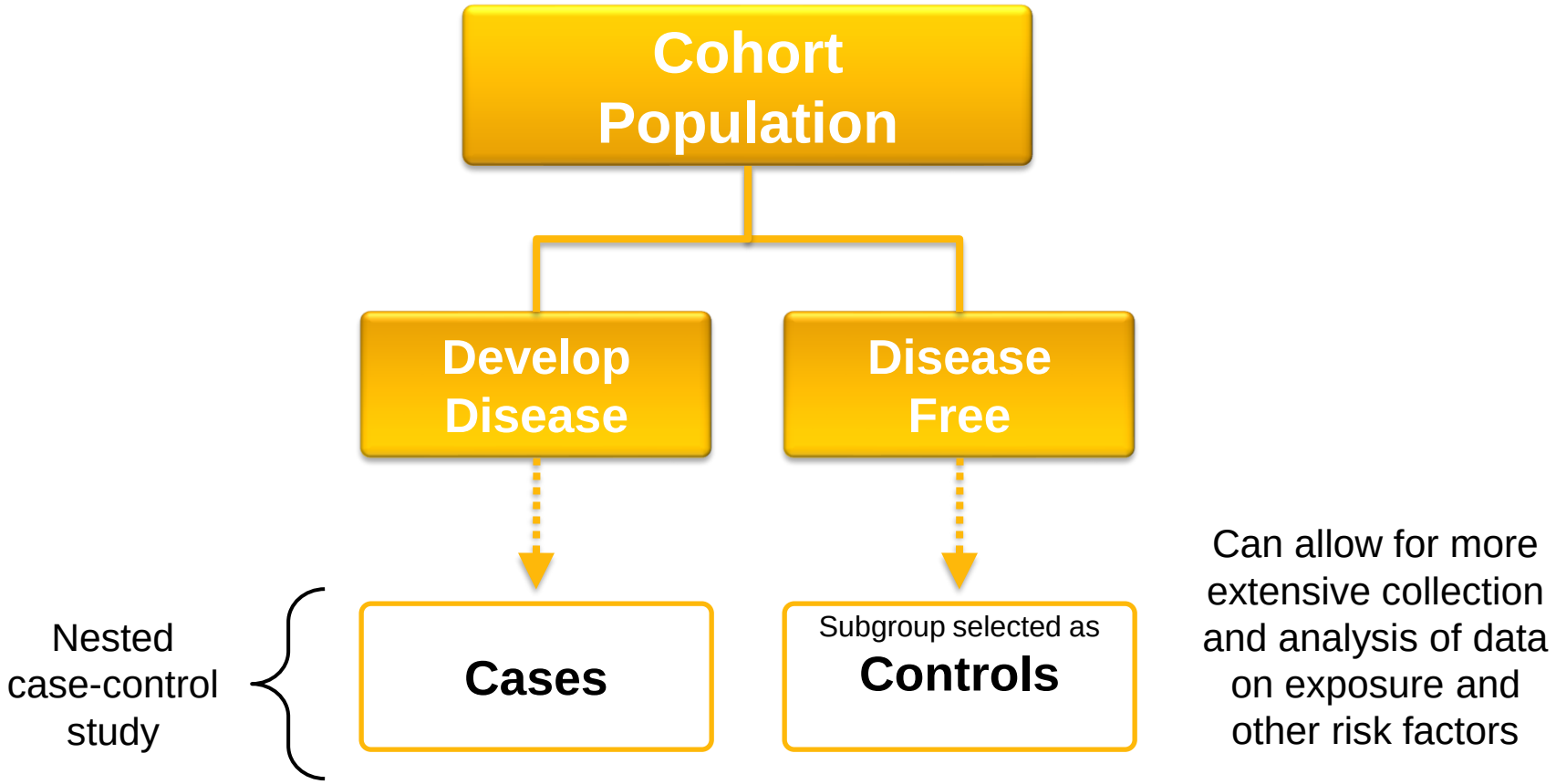
Odds ratios of exposure to TCE within the NCI-SEER study, 1998–2001



A case-control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma.
Purdue MP, Bakke B, Stewart P, De Roos AJ,et.al. Environ Health Perspect. 2011 Feb;119(2):232-8.

Nested Case-Control Studies

Case-control study **within a cohort**



Can allow for more extensive collection and analysis of data on exposure and other risk factors

Nested Case-Control Study: Angiosarcoma of the Liver (ASL) and Vinyl Chloride (VCM) Exposure

- Endpoint
  - Angiosarcoma of the liver (ASL), brain and lung cancer
- Setting: Large PVC/VCM polymerization plant
- Design
  - **Cohort**: employees who had worked at the plan between 1942-1974, before data collection
  - **Cases and controls**: selected from entire original cohort at risk (VCM-exposed and non-exposed)
    - **Cases:** deaths from ASL
    - **Controls**: Matched 5:1 to cases, by age
- Analysis
  - Conditional logistic regression, adjusted for potential confounders (i.e., age, year of first employment) and cumulative dose of VCM (as a measure of exposure)

ASL and Occupational VCM Exposure: Results

Cases and Control Subject from the Entire Cohort Ever Exposed to VCM and average values of cumulative exposure (duration x exposure level)

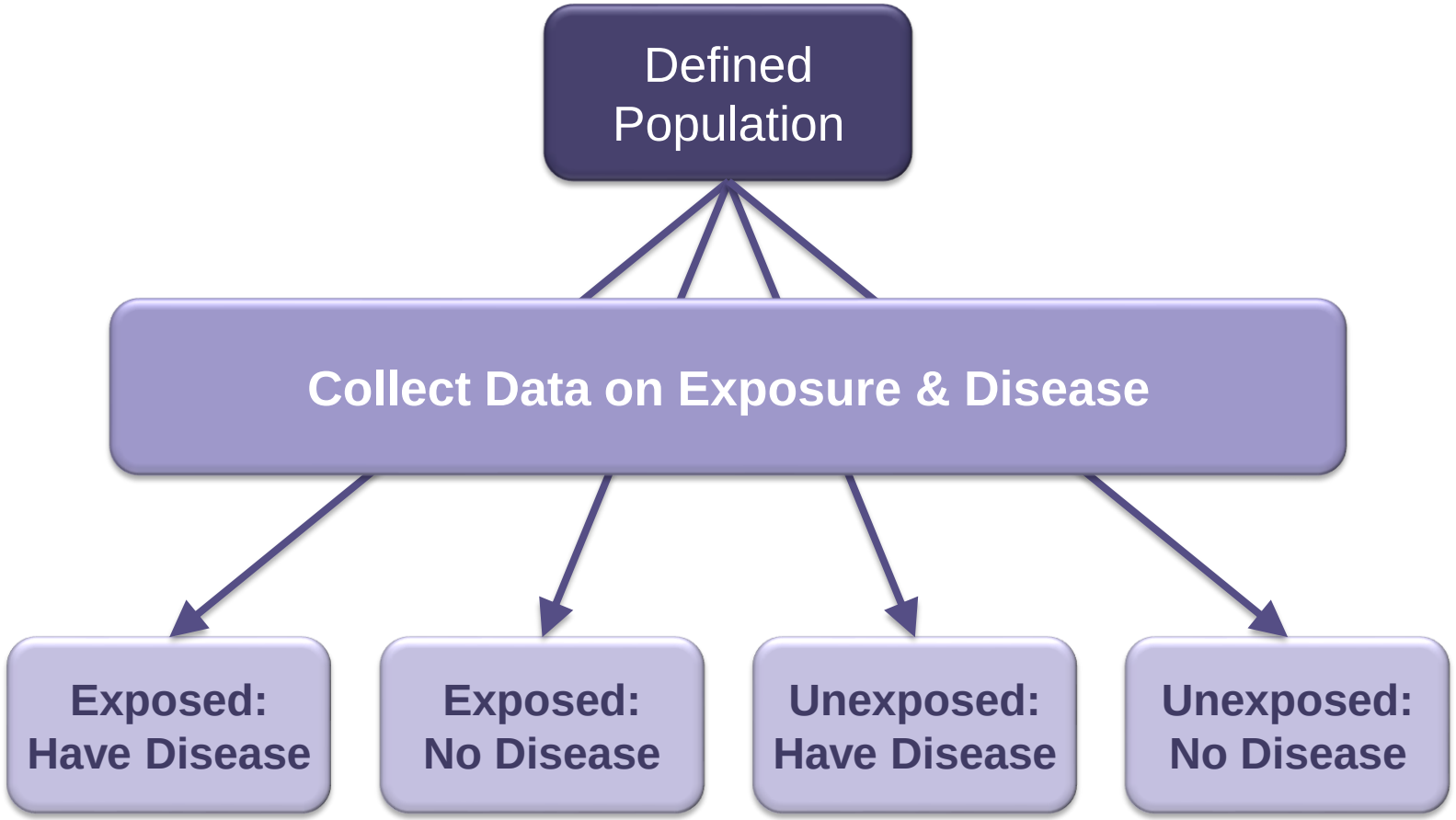
	Number (%) Exposed to VCM	Cumulative exposure to VCM
Liver cancer study		
Case subjects	16 (84%)	42,8
Control Subjects	74 (78%)	9.6
Brain cancer study		
Case subjects	13 (87%)	14.2
Control Subjects	63 (84%)	14.0
Lung cancer study		
Case subjects	96 (84%)	10.8
Control Subjects	745 (83%)	12.2

Coefficients and p-values for cumulative dose of VCM in the three case-control studies

	Coefficient	P-value
Liver cancer study		
VCM	.083	.002
Brain cancer study		
VCM	-.002	.908
Lung cancer study		
VCM	.000	.967

Cohort and case-control analyses of workers exposed to vinyl chloride: an update.
Wu W, Steenland, K, Brown, D, Wells, V,et.al. J Occupational Medicine, 1990 Jun;31(6):518-23.

Cross-Sectional Studies



Common Measures of Association in Cross-Sectional Studies

	Disease	No Disease
Exposed	a	b
Unexposed	c	d

	Disease	No Disease
Exposed	a	b
Unexposed	c	d

Prevalence Ratio

Prevalence of disease in exposed vs. unexposed	Prevalence of exposure in diseased vs. non-diseased
$\frac{a}{a+b}$ vs. $\frac{c}{c+d}$	$\frac{a}{a+c}$ vs. $\frac{b}{b+d}$

Cross-Sectional Study: Pesticide Exposure and ADHD

- Endpoint
  - ADHD among children exposed to organophosphate pesticides
    - ADHD: attention deficit syndrome and hyperactivity disorder
- Design
  - Cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) (2000–2004)
    - 1,139 children between 8 and 15 years of age included in this study
  - Exposure to pesticide by measurement of metabolites
    - Urinalysis for 6 metabolites of dialkyl phosphate (DAP), a common marker of organophosphate pesticide exposure
    - Specific analytes: 3 dimethyl and 3 diethyl alkylphosphates (DMAPs and DEAPs)
  - Outcome measure (ADHD) by individual survey
    - ADHD identified through diagnostic interviews (DISC-IV) and based on whether ADHD medication administered

Pesticide Exposure and ADHD: Data Collected and Analysis

- Outcome measure
  - 119 diagnosed with ADHD in study sample (12% prevalence rate)
- Exposure measurements

Concentrations of Urinary DAP Metabolites (N = 1,129)

			Urinary Metabolite Level, nmol/L			
Pesticide	N	Below Detection Limit, n (%)	Geometric Mean	Interquartile Range	Minimum	Maximum
DEAPs	1139	253 (22.2)	11.0	2.1-35.0	0.8	5,905
DMAPs	1139	209 (18.3)	41.3	10.1-130.7	4.5	10,068
Dimethyl thiophosphate	*1139*	*407 (35.7)*	*13.7*	*1.9-58.8*	*0.9*	*9,929*
Total DAPs	**1139**	**71 (6.2)**	**68.3**	**24.4-186.0**	**6.0**	**10,195**

- Analysis
  - DAP (metabolite) concentrations categorized
  - Logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for ADHD, per increases in total DAP, DMAP, and DEAP metabolite concentrations

Pesticide Exposure and ADHD: Results

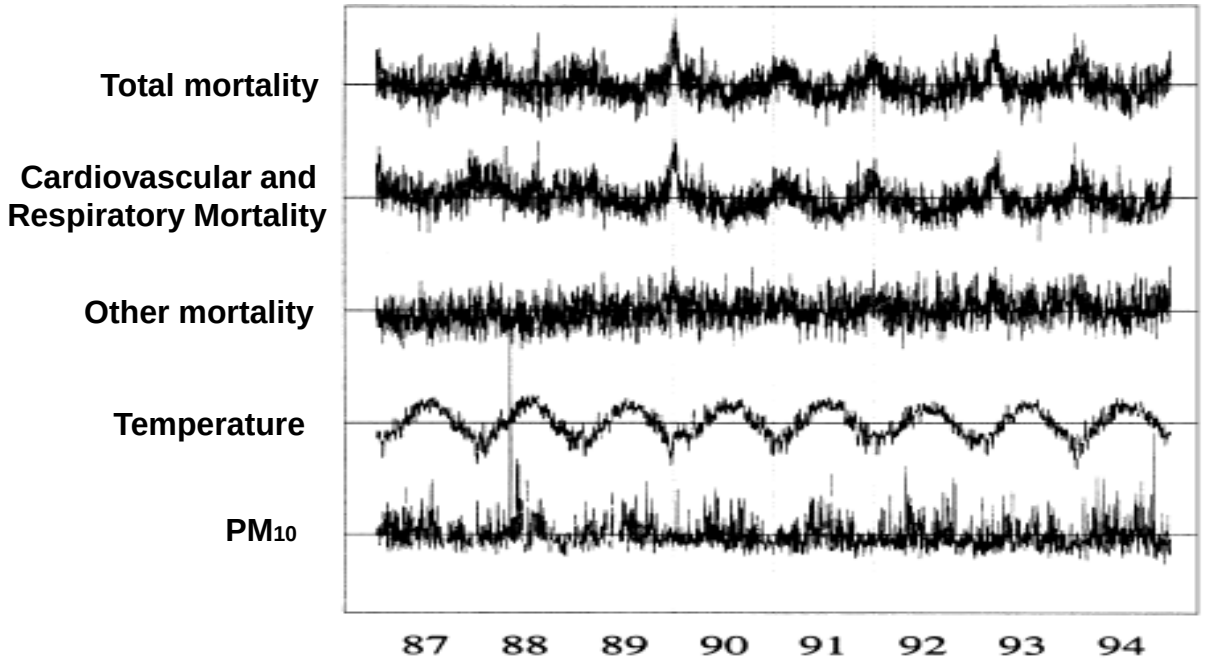
ORs for Any ADHD Subtype According to Creatinine Level-Adjusted Urinary Dimethyl Thiophosphate Concentration (N = 1,129)

	OR (95% CI)			
	Cases identified with DISC-IV (n = 119)		Cases identified with DISC-IV or ADHD Medication (n = 148)	
Dimethyl Thiophosphate Concentration	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Below detection limit (n = 407)	1.0 (reference)			
Lower than median (n = 366)[b]	1.11 (0.63 – 1.97)	1.05 (0.57 – 1.95)	1.36 (0.76 – 2.44)	1.22 (0.65 – 2.27)
Higher than median (n = 366)[c]	1.83 (1.18 – 2.82)	1.93 (1.23 – 3.02)	2.04 (1.30 – 3.22)	2.12 (1.32 – 3.41)

Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides.
Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG. Pediatrics. 2010 Jun;125(6):e1270-7.

Time-Series Studies

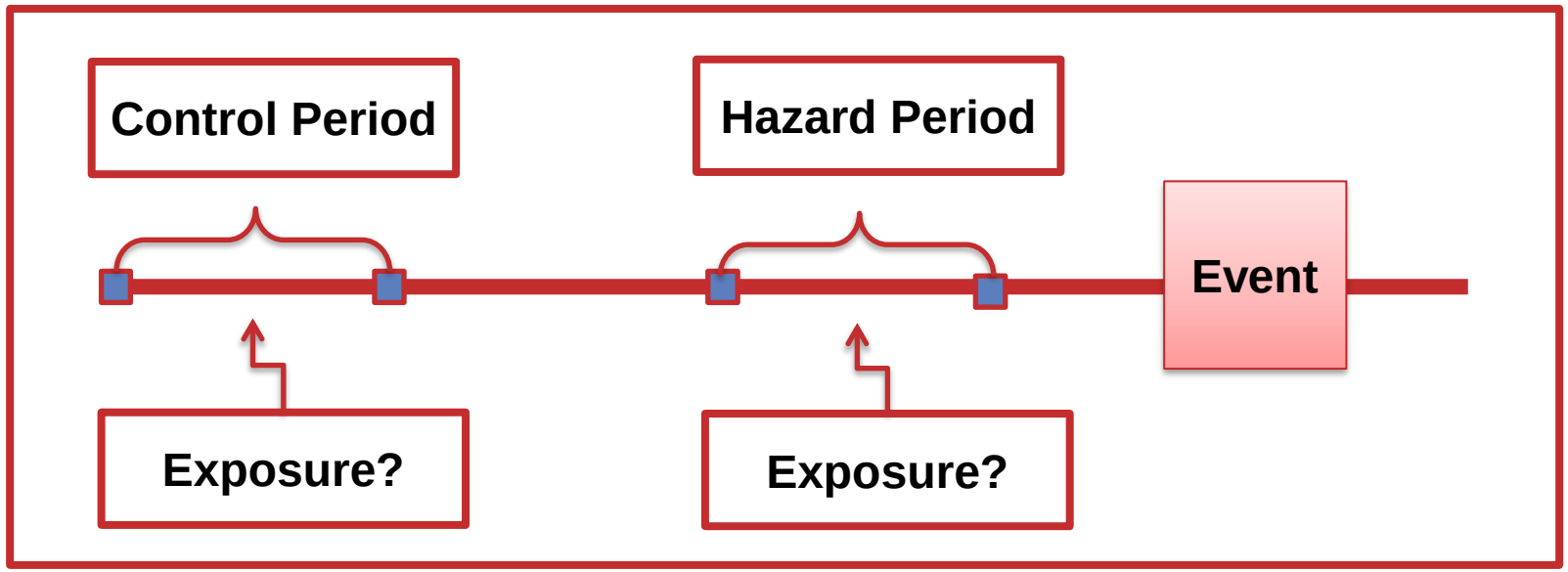
Time-series studies estimate association between short-term changes in air pollution levels and short-term changes in health outcomes



Chicago: Daily time series of mortality, temperature, and particulate matter, 1987-1994

Dominici et al. (2003) "Airborne Particulate Matter and Mortality: Timescale Effects in Four US Cities" *American Journal of Epidemiology*

Case-Crossover Studies



- Each person is their own control thereby controlling for all confounders that remain constant over short time periods
- Compares exposure to an agent during an interval when the event does not occur (control period) to an interval when the event occurs (hazard period)
- Generally limited to estimate acute effects

Ecologic Studies

- Study of group (area), rather than individual, characteristics
- Useful for hypothesis generation
- Ecologic (area-wide) measures:
  - Aggregate measures
    - Median income, sales data
  - Environmental measures
    - Mean air pollution level
  - Global measures
    - Health care system; population density

Be Aware of Ecologic Fallacy

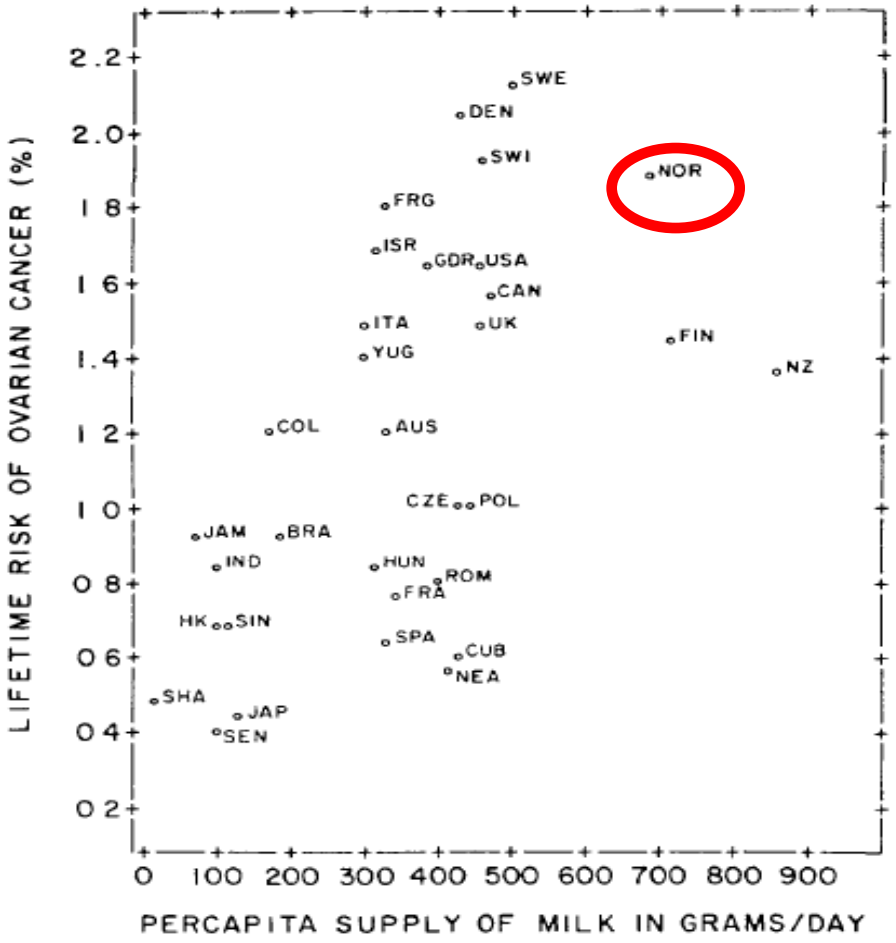
Failure of group level associations to correspond to associations at a different (e.g., individual) level

Ecologic Study: Milk Consumption and Ovarian Cancer

- Design
  - Comparison of ovarian cancer incidence, per capita milk consumption, and population estimates of lactase persistence (the ability to digest lactose after infancy) in 27 countries
- Analysis
  - Multiple regression models for milk consumption and cancer
- Results
  - Significant positive correlations
  - Lactase persistence showed stronger association in multiple regression models
  - For each 100-g increase in the daily per capita consumption of fluid milk, there is a net increase of 0.14 percent in the cumulative incidence of ovarian cancer

Ecologic Study: Milk Consumption and Ovarian Cancer

Correlation between ovarian cancer incidence and per capita milk consumption in 32 countries



- In Norway, there is both higher ovarian cancer incidence and higher milk consumption...

  However:

  We do not know whether the same individuals in whom ovarian cancer developed actually consumed a lot of milk

- **Ecological fallacy:** Assuming that individuals with ovarian cancer also consumed a lot of milk

Lactase persistence and milk consumption as determinants of ovarian cancer risk.
Cramer, DW. Am J Epidemiol 1988; 130(5): 994-910.

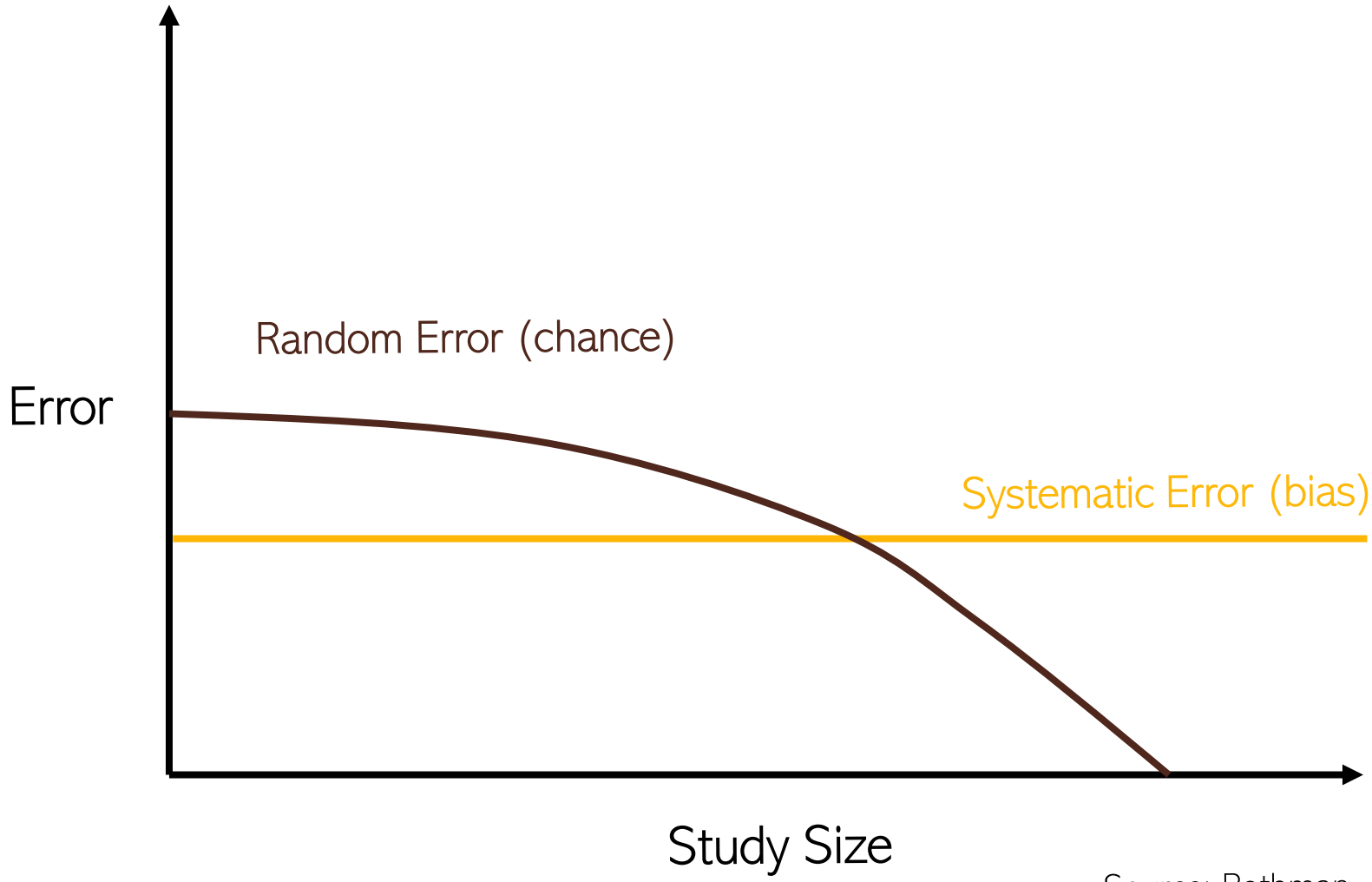
EPA United States Environmental Protection Agency

EVALUATION OF CHANCE, BIAS, AND CONFOUNDING

Why Do We Focus On These Elements?

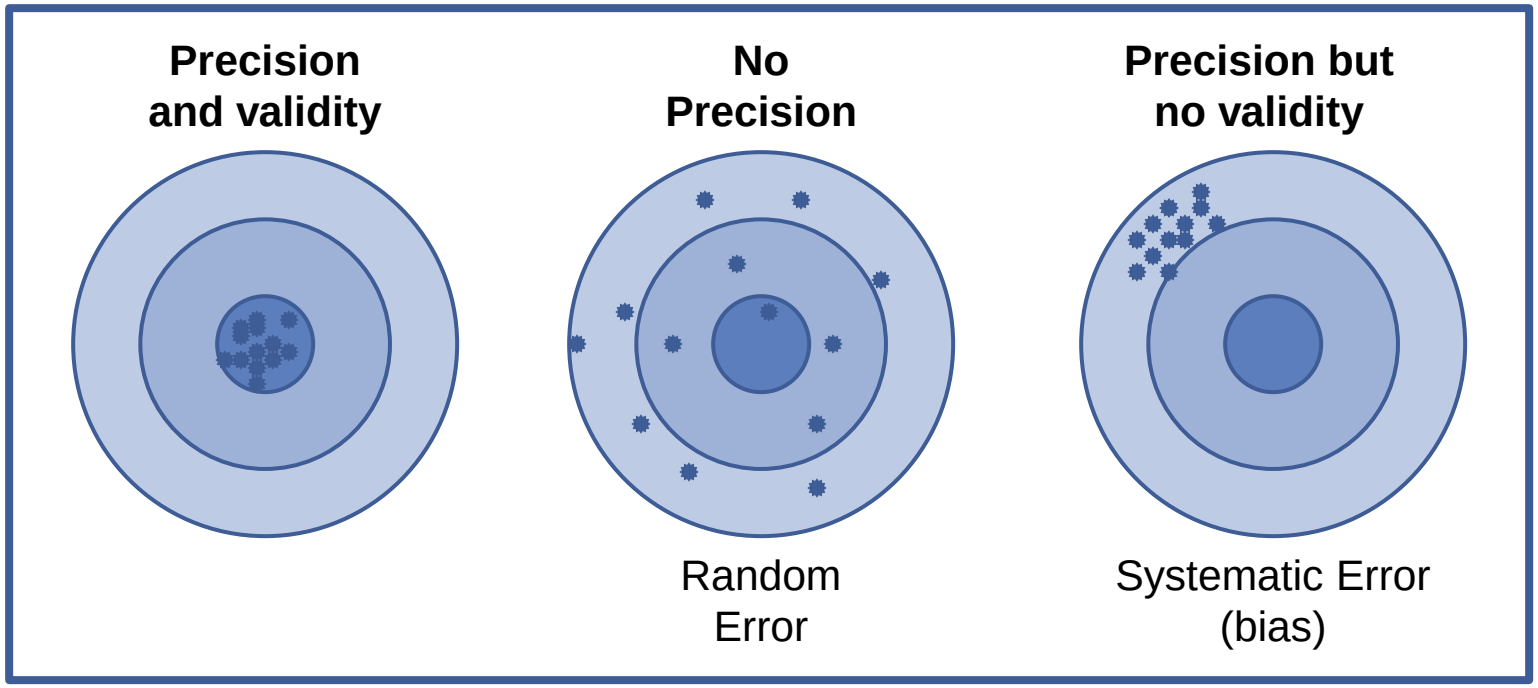
- Important for interpretation of study results
  - "Chance" reflects *precision* (or imprecision) of an estimate
  - Bias and confounding can affect the *validity* of an estimate
- Greater confidence in study results and causality if chance, bias, and confounding are minimized

Types of error in epidemiological studies



Source: Rothman, 2002

Precision and Validity in Epidemiology



- Random error (chance) → low precision
- Bias (systematic error) → low validity

Precision and Confidence Intervals

- Precision depends on number of observations and on sampling variability
  - Precision typically increases with larger sample size, longer follow-up, larger cohort, higher prevalence of exposure
- How is precision expressed in epidemiology studies?
  - Magnitude of the point estimate – effect size
  - Precision of the point estimate – p-value or confidence interval (CI)
- CI and p-value are related, but the CI can be more informative (move past “Significant vs. non-significant”)

Interpreting Confidence Intervals

- The confidence interval displays the range of values of the risk estimate that are supported by the data in a study
  - The point estimate is the best (most likely) estimate, while the extreme values of the confidence interval have the lowest probability of occurrence

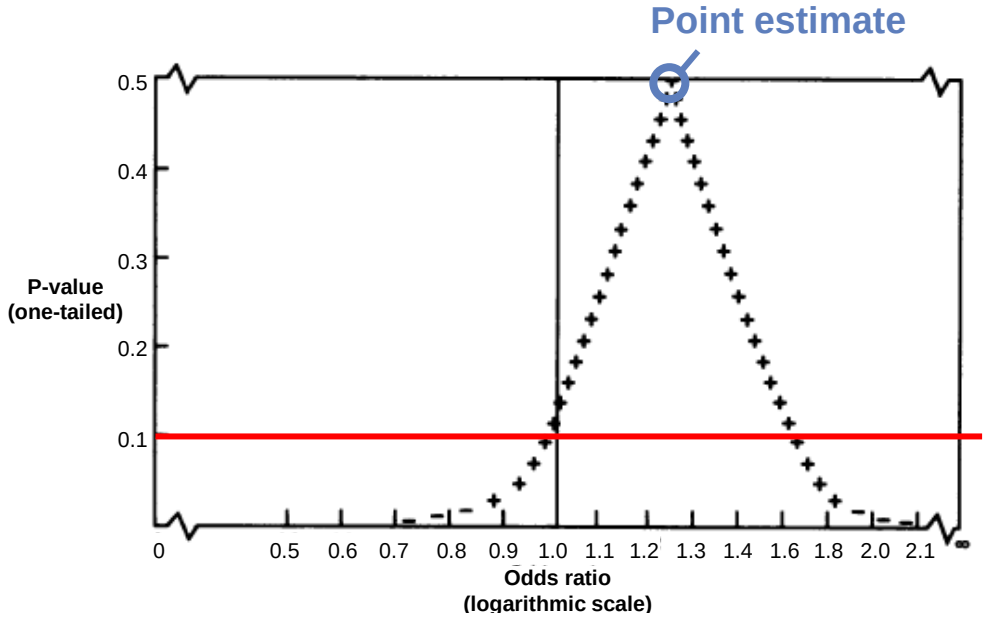
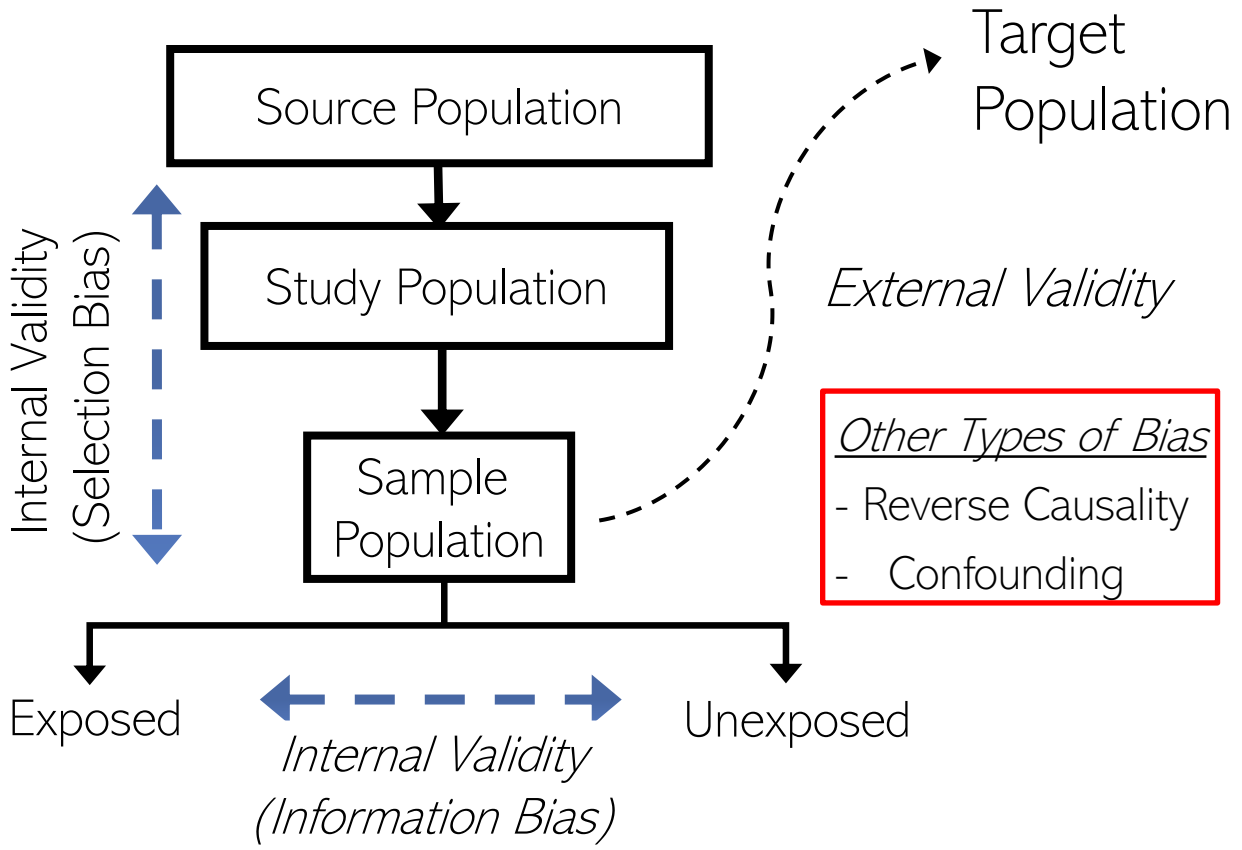


FIGURE 1 – P-value function for the odds ratio comparing the two control groups in Rothman's study of spermicides and Down syndrome.[3] Following Thompson,[4] parameter values inside the 95 percent confidence interval are represented by plus signs and values outside of the interval by minus signs.

Poole, C. Confidence Intervals exclude nothing. Am J Public Health (1987) 77:492-493. (Red line not in original graph.)

RR (95% CI)	Interpretation
1.8 (1.6–2.0)	Precise and statistically significant
2.7 (0.8–14.5)	Imprecise and not statistically significant

Validity of Epidemiological studies



Study Populations and Selection Bias

- **Selection bias** results from systematic (differential) error in identifying or selecting study participants
- Occurs when:
  - Cases and controls selected from different populations
  - The exposure of interest influences the participation depending on disease status
  - Non-comparability of groups (e.g., healthy worker effect)
- Can result in biased effect measure (i.e., affects validity)
- Selection bias is NOT related to generalizability of the results

Information Bias and Types of Misclassification

- **Information bias** results from a systematic error in measuring information on exposure or outcome.
- **Misclassification** occurs when an investigator incorrectly categorizes exposure or outcome status.
  - **Differential** – when measurement process and accuracy depend on which group you are studying:
    - Exposure assessment not blinded to disease status
    - Different disease assessment in exposed and unexposed groups
  - **Non-differential** (random error) – measurement process and accuracy are not related to the group you are studying:
    - Cause of death from death certificates
    - Uncalibrated stadiometer

Non-Differential Exposure Misclassification

- This figure shows the effect of non-differential exposure misclassification on the exposure-response curve
- (Note): It is common to see non-linear patterns in the exposure-response curve

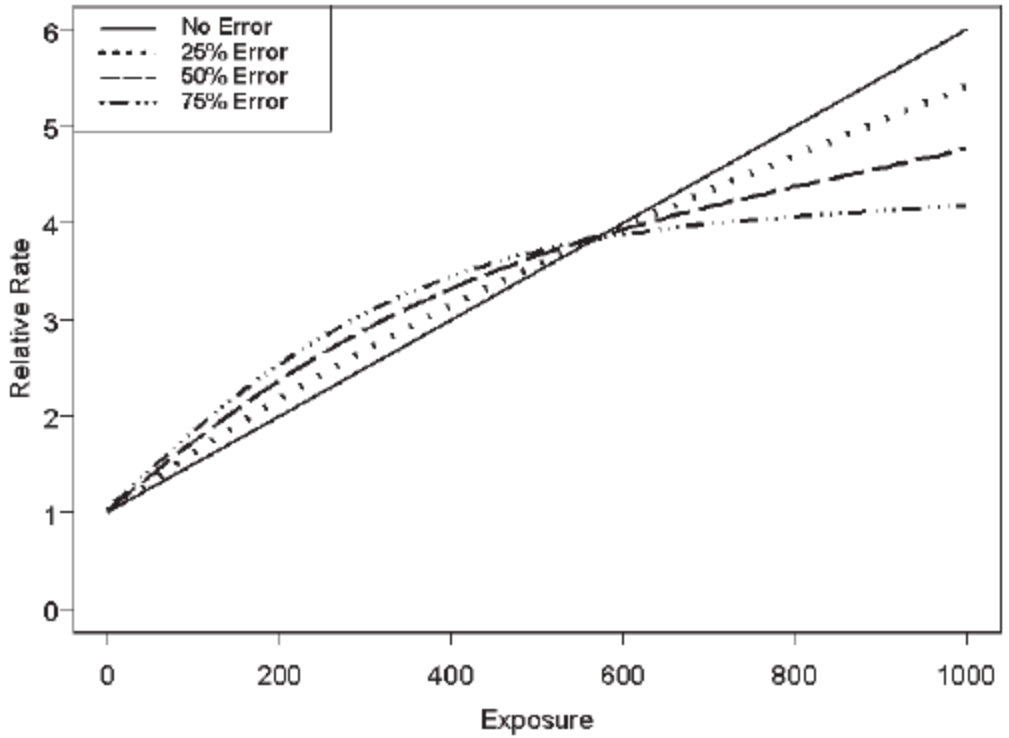


Figure 3. Results from a simulation study of the effect of random misclassification of exposures on a true linear exposure relationship.

Attenuation of exposure-response curves in occupational cohort studies at high exposure levels.
Stayner L. et al. *Scand J Work Environment Health*. 2003; 29: 317-324.

Non-Differential Exposure Misclassification

- Non-differential misclassification is a common phenomenon
  - Not expected to invalidate results, but may attenuate effects
  - Exceptions can occur (e.g., very small studies, >2 groups)

No Misclassification	Cases	Controls
Exposed	50	20
Unexposed	50	80

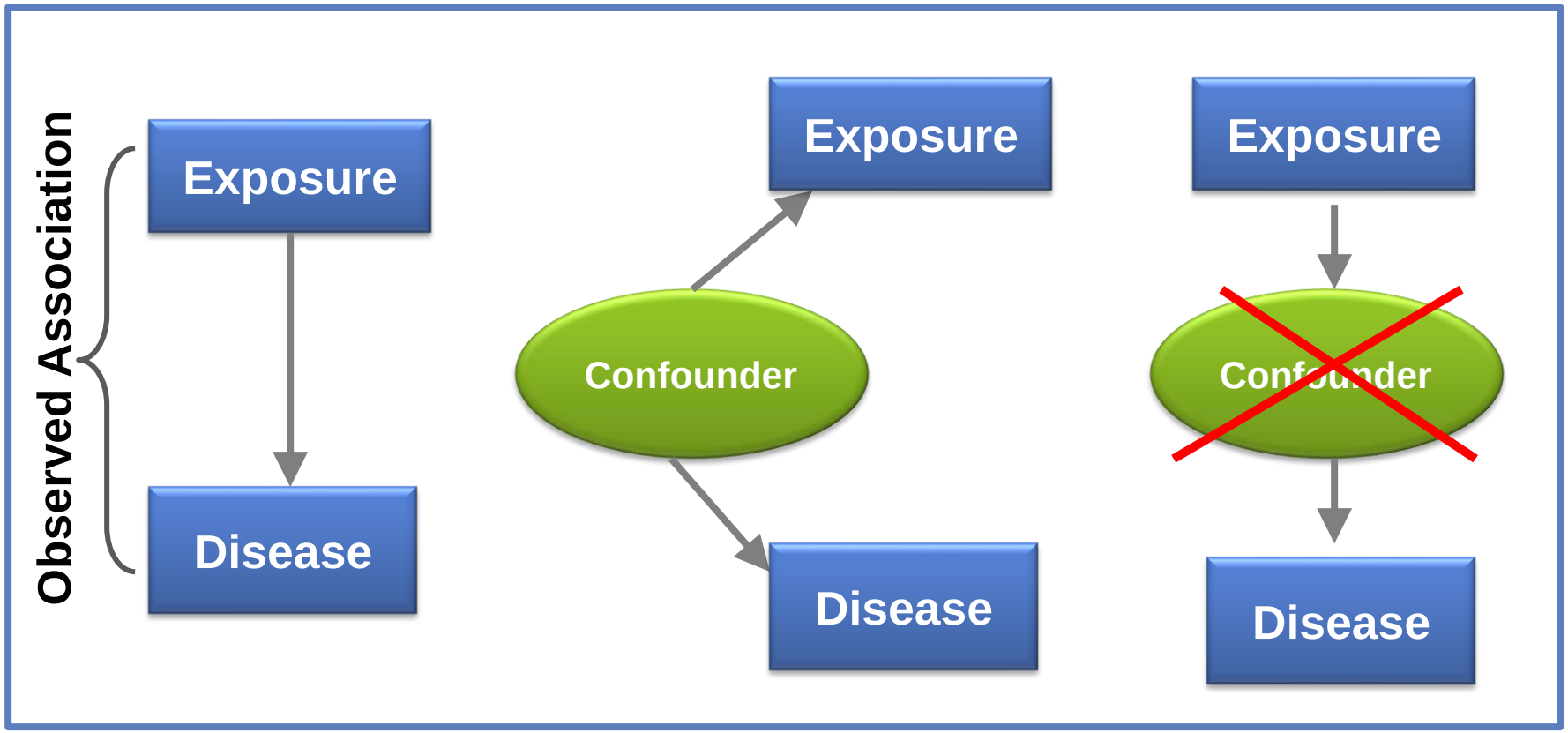
30% Exposure Misclassification	Cases	Controls
Exposed	50**-15**	20**-6**
Unexposed	50**+15**	80**+6**

$$OR = \frac{\left(\frac{50}{50}\right)}{\left(\frac{20}{80}\right)} = 4.0$$

$$OR = \frac{\left(\frac{35}{65}\right)}{\left(\frac{14}{86}\right)} = 3.3$$

Confounding in Epidemiologic Studies

Factor that affects both exposure and disease but does not lie along the causal pathway from exposure to disease



Example of Confounding: Sex and skin cancer

	Cases	Controls
Males	88	68
Females	62	82

"Crude" OR=1.71

Is work environment a confounder?

Mostly outdoor occupation	Cases	Controls
Males	53	15
Females	10	3

OR=1.06

Mostly indoor occupation	Cases	Controls
Males	35	53
Females	52	79

OR=1.00

Methods to Control Confounding

- **Study design:**
  - Randomization
  - Restriction
  - Matching
- **Study analysis:**
  - Direct and indirect standardization (e.g., age and sex standardized mortality rates)
  - Stratified analysis (examine exposure-disease in each strata of the potential confounder)
  - Multi-variable models (examine several confounders, and examine continuous measures as confounders)

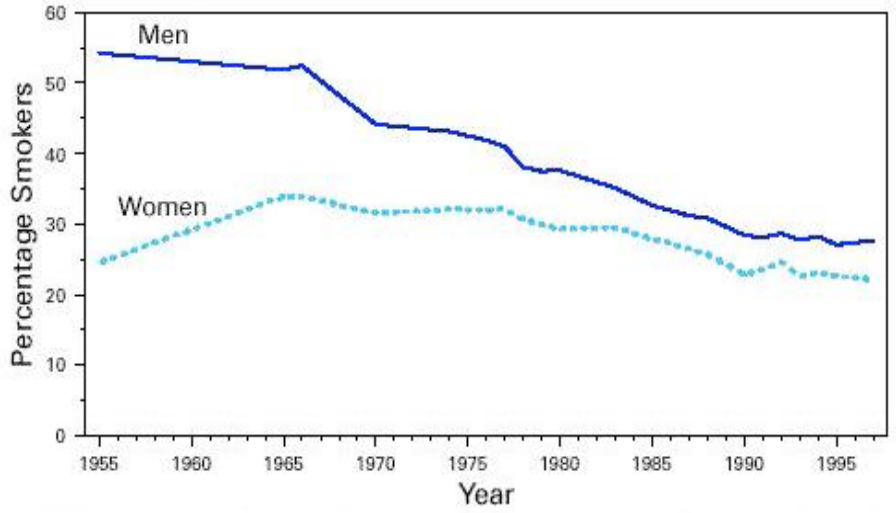
Evaluating the Presence and Impact of Confounding

- How **likely** is it that the (potential) confounder is associated with the disease? – and with the exposure?
  - Use diagrams (“causal pathways”)
- How **strongly** is the (potential) confounder associated with the disease? – and with the exposure?
  - Weak associations would not produce strong confounding
- **Compare** unadjusted and adjusted results
  - If there is little change, confounding unlikely
- Is there potential for **residual confounding**?
  - Inadequate measurement of strong confounder

What About Smoking?

- Smoking is strongly related to lung cancer (RR 10–20)
- Smoking is more weakly related to many other conditions (e.g., cardiovascular disease, bladder cancers; RR 2–3)
- But, it's not related to everything (e.g., not a risk factor for some kinds of lymphoma)
- Smoking is common

Trends in cigarette smoking* among persons aged ≥18 years, by sex — United States, 1955–1997



*Before 1992, current smokers were defined as persons who reported having smoked ≥100 cigarettes and who currently smoked. Since 1992, current smokers were defined as persons who reported having smoked ≥100 cigarettes during their lifetime and who reported now smoking every day or some days.

Sources: 1955 Current Population Survey; 1965–1997 National Health Interview Survey.

Evaluating Smoking As a Confounder

- **How likely/strongly is smoking associated with the exposure?**
  - Less of a concern when smoking rates were high
  - Smoking rarely has a large impact on RR estimates for exposure in occupational studies of lung or laryngeal cancer (less 40% impact on RR)
- **Look within and across studies to see if the exposure-disease patterns look like expected smoking-disease patterns**

Is Smoking a Confounder in Studies of Nickel and Lung Cancer?

- Workers exposed to nickel dust experience an increased lung cancer risk in several occupational cohort studies. Could this be due to confounding by smoking?
- If so, what would you expect to see in these same workers with respect to other smoking-related cancers?

Bladder Cancer Risk in Cohorts of Nickel Workers

Reference	Cohort	n	Relative Risk	95% C.I.
Andersen et al., 1996	Norway 1953 – 1993	33	0.9	(0.6, 1.3)
Grimsrud et al., 2003	Norway 1953 – 2000	61	1.1	(0.8, 1.4)
Anttila et al., 1998	Finland 1953 – 1995	2	0.57	(0.07, 2.0)
Easton et al., 1992	Wales 1931 – 1985	11	1.3	(0.02, 2.4)
Sorahan, 2005	Wales 1958 – 2000	1	0.49	(0.02, 2.4)
Pang et al., 1996	United Kingdom 1945 – 1993	1	1.0	(0.03, 5.7)
ICNCM, 1990	Canada 1950 – 1984	0	0	--

EPA United States Environmental Protection Agency

USING EPIDEMIOLOGIC STUDIES IN RISK ASSESSMENT

Evaluating Individual Studies: Chance, Bias, and Confounding

- Overall study design
  - What kind of study design was used?
  - What is the sample size?
- Exposure characterization
  - What are the comparison groups?
- Outcome
  - How were outcomes measured?
  - How likely were non-differential and differential misclassification?
  - Was follow-up sufficient?
- Analysis
  - Were relevant confounders assessed properly?
  - Did exposure precede disease?

Evaluating Individual Studies

- “Domains” are used to organize study evaluations and determine whether the extent to which study results might be affected by chance, bias and confounding.
  - Participant Selection
  - Exposure Measurement
  - Outcomes Ascertainment
  - Confounding
  - Analysis
  - Selective Reporting
  - Sensitivity
  - Overall Study Confidence

https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350086

Evaluating Individual Studies: Exposure-Response Data

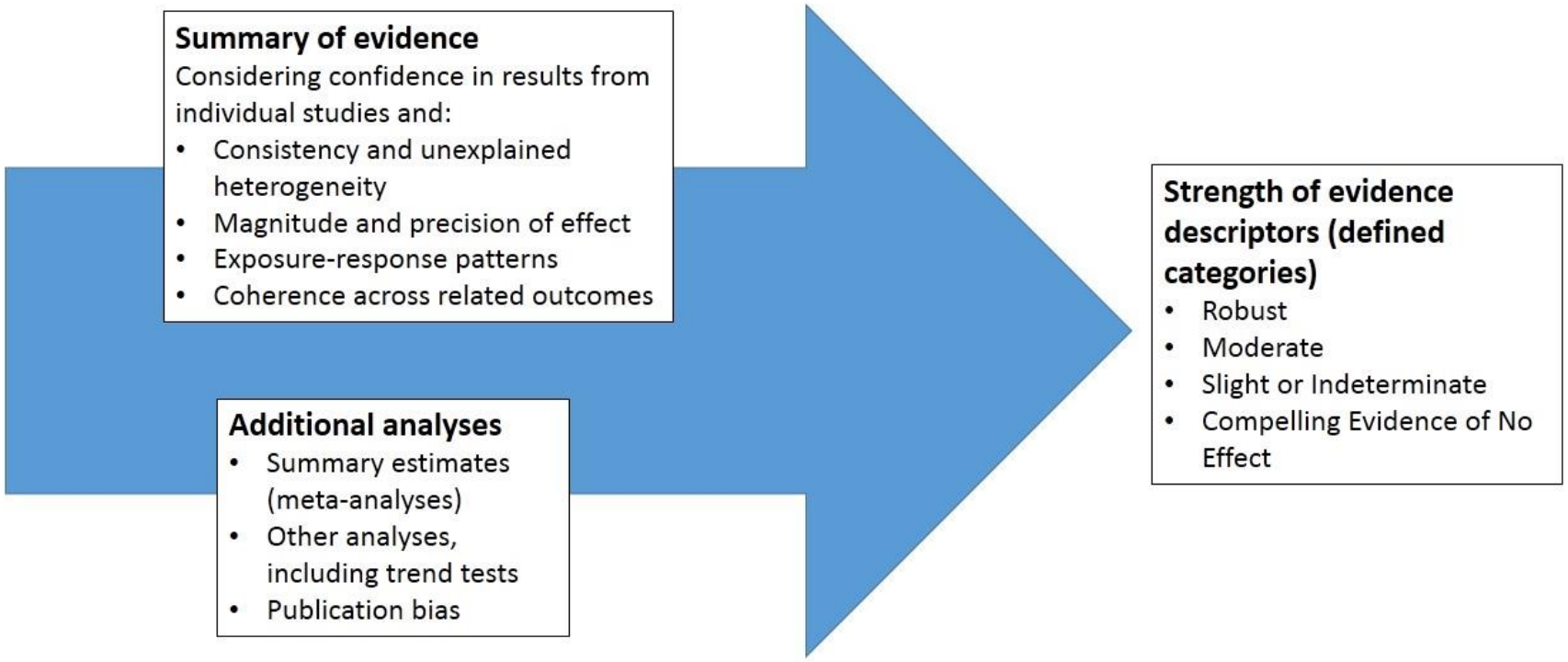
- Epidemiology studies provide varying types of information about exposure-response relationships
  - How is exposure used?
    - Continuous (often greater statistical power)
    - Categorical (can inform shape of exposure-response)
    - Binary (e.g., “ever-never” exposures)
    - Proxy measures (e.g., duration of work)

Evaluating Individual Studies: Summary

- Rare for one single study to provide sufficient evidence of a causal link

- More often:
  - Several relevant epidemiology studies available
  - Evaluate collection of studies from the perspective of hazard identification (does exposure cause disease?) and for exposure-response (how much exposure causes how much disease?)

Evaluating a Collection of Studies



Assessing Causality: Bradford Hill Guidelines

- **Considerations for epidemiology data**
  - Temporal relationship (exposure precedes disease)
  - Strength of association (considering units of exposure)
  - Exposure-response relationship
  - Consistency across studies
- **Considerations drawing in other data**
  - Plausibility and coherence
- **Considerations of low utility**
  - Specificity (single cause, single effect)

Hill AB. The environment and disease: association or causation? J R Soc Med. 2015 Jan;108:32-7.

Considerations for Synthesis Across Studies: Strength of association

Magnitude and precision of effect estimates:

- Magnitude can depend on the exposure units
- Do the effect estimates (of individual studies or a collection of studies) rule out chance as an explanation?
- Do the effect estimates show an expected pattern when sorted by factors such as:
    - quality evaluation
    - exposure range or levels

Considerations for Synthesis Across Studies: Consistency

- **Conflicting** results decrease confidence that observed effects reflect a causal association

BUT

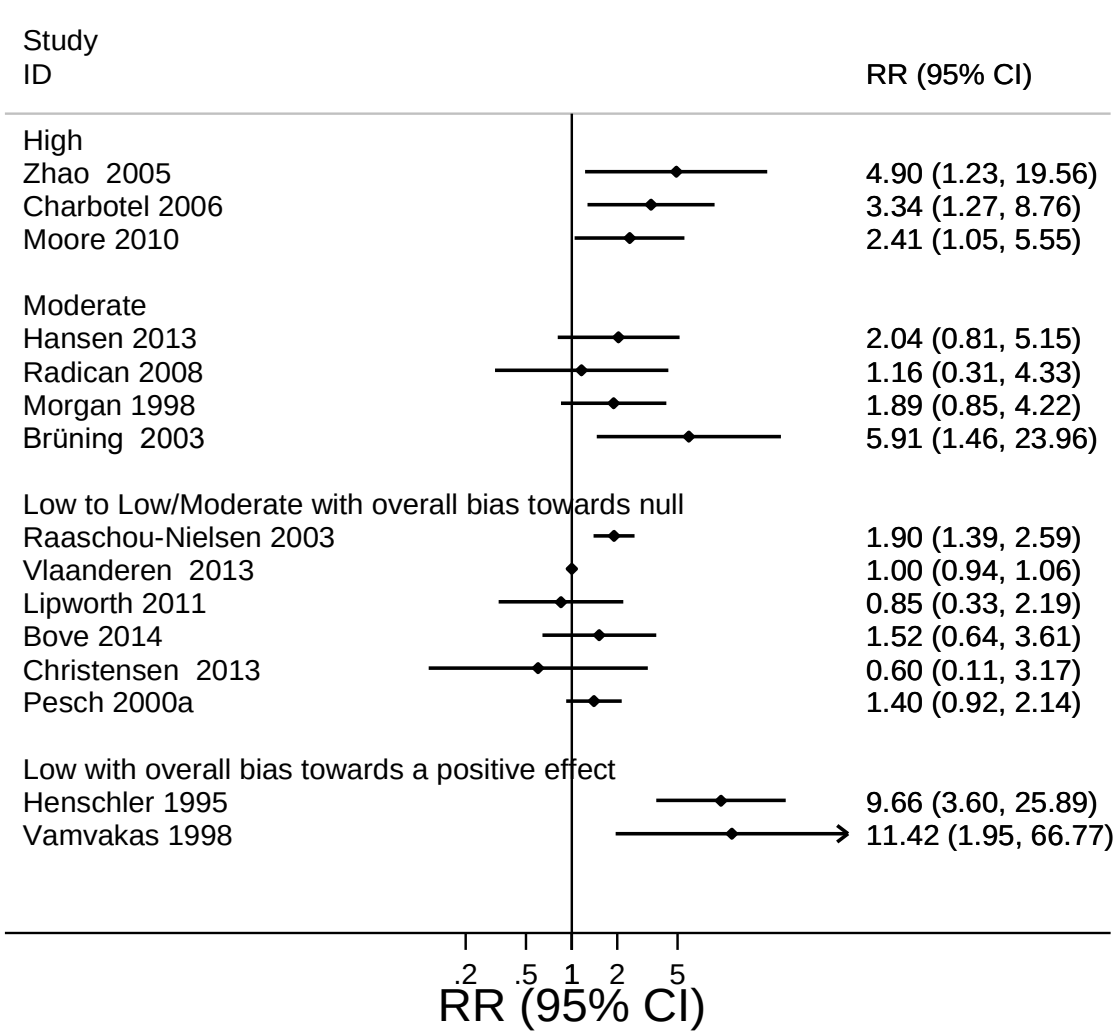
- Confidence is not decreased by **differing** results for which reasonable explanations for differences can be made.

- Consistency does *not* mean counting number of “positive” and “negative” studies

Considerations for Synthesis Across Studies: Consistency

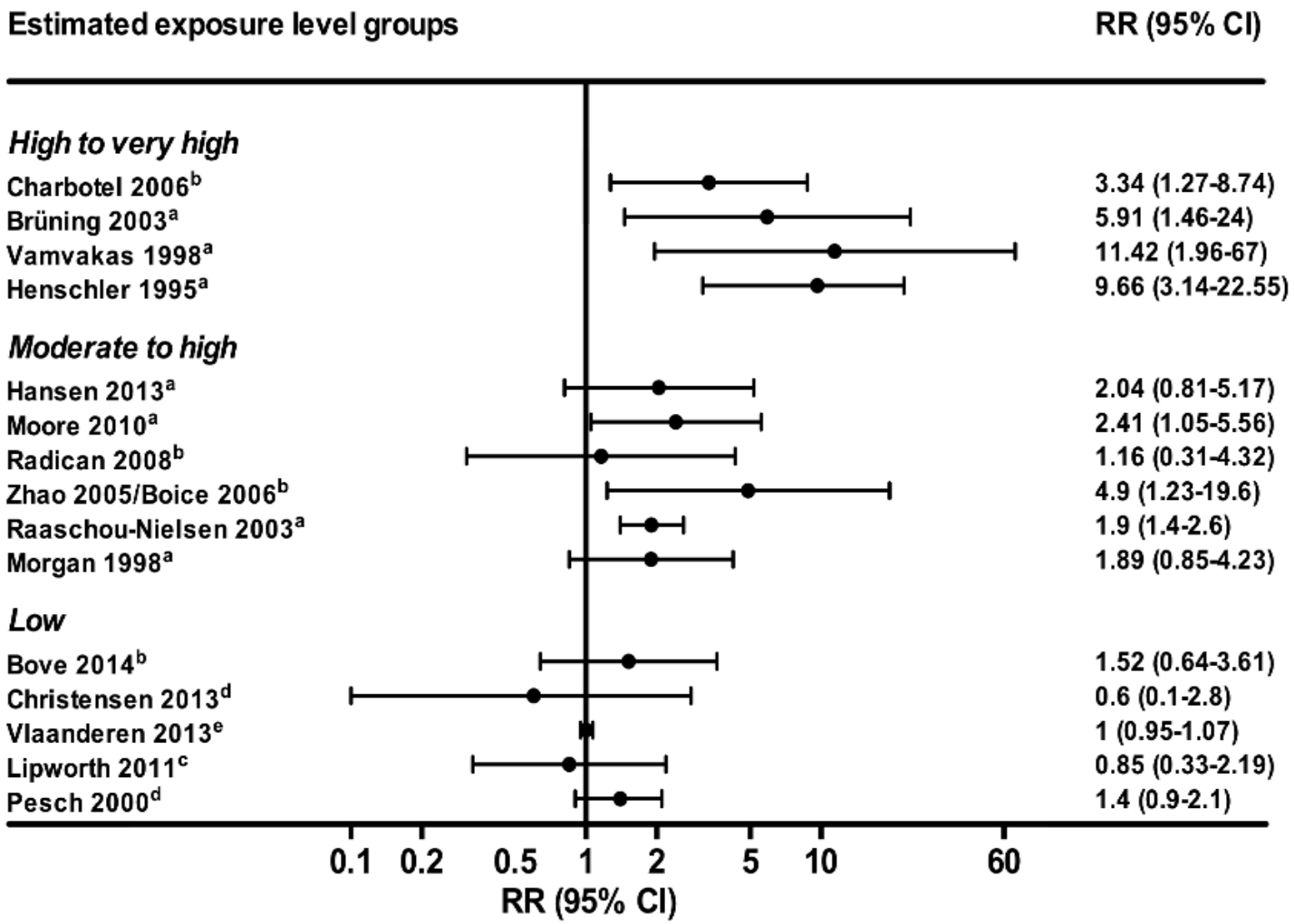
Is there consistency in results among studies with similarities with respect to:

- quality evaluation (confidence and direction of expected bias, based on bias and sensitivity domains)
- exposure range or level
- specific domains of bias or sensitivity (e.g., more robust or relevant exposure assessments, adjustment for key covariates and co-exposures, follow-up period, exposure settings)



TCE and Kidney Cancer: stratification of high exposure studies by study quality

NTP (National Toxicology Program). 2014. *Report on Carcinogens, Thirteenth Edition.* Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. http://ntp.niehs.nih.gov/pubhealth/roc/roc13/



TCE and Kidney Cancer: stratification by exposure level

Additional analyses: Meta-Analysis, Pooled Analysis, and Meta-Regression

- **Meta-analysis** – “the study of studies”
- **Pooled analysis** – combines data from multiple studies
- **Meta-regression** – regression analysis using study as unit

Why bother?

- Can increase precision
- Can evaluate effects of different aspects of study design (e.g., study populations, type of measurements)

Additional analyses: Meta-Analysis, Pooled Analysis, and Meta-Regression

- What could the analysis contribute to the synthesis of the evidence?
- What factors, if any, should be used to stratify a meta-analysis?
- How can you include results from studies that cannot be combined numerically (e.g., because of different measures or forms of the results), in the synthesis?

Meta-analysis: example

Forest plots of studies of TCE exposure and kidney cancer by highest exposure category with figure description from EPA's Toxicological Review of Trichloroethylene (U.S. EPA, 2011).

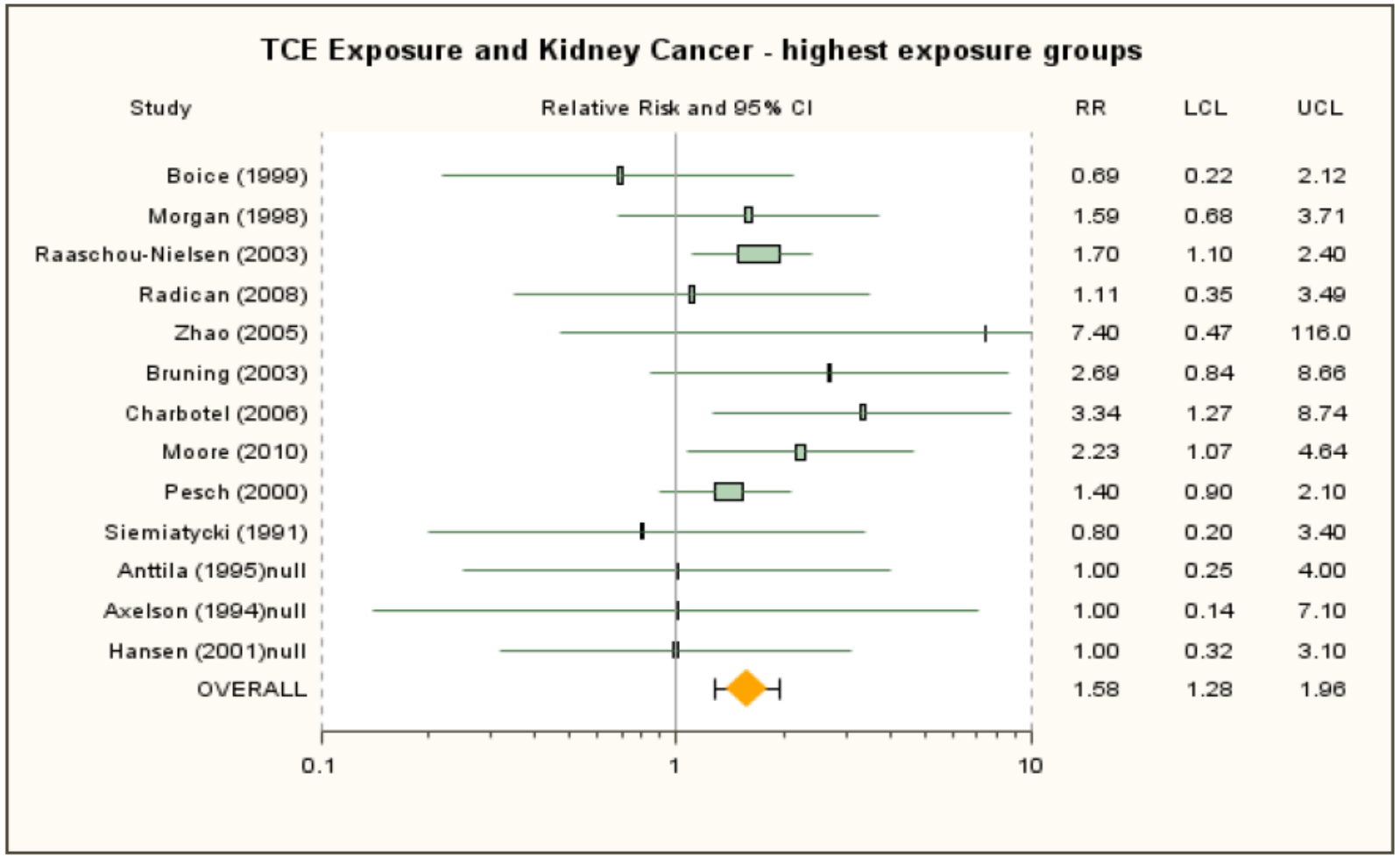


Figure C-7. Meta-analysis of kidney cancer and TCE exposure—highest exposure groups, with assumed null RR estimates for Anttila et al. (1995), Axelson et al. (1994), and Hansen et al. (2001) (see text). Random-effects model; fixed-effect model same. Rectangle sizes reflect relative weights of the individual studies. The summary estimate is in the bottom row, represented by the diamond.

Weight of Evidence: Examining Possible Explanations

- Similar to approach for individual studies, with a few more tools to use
  - Chance (precision)
    - Meta-analysis could improve precision
  - Bias
    - Examine effect of study attributes and/or domain ratings
      - For example, consider type of exposure assessment. Are stronger effects seen with methods that have less non-differential misclassification or better exposure contrasts?
  - Confounding
    - Could be evaluated and controlled for differently across studies

Weight of Evidence: Examining Possible Explanations

- Do analyses across different studies (e.g., different geographic areas, industries) provide evidence that increase or decrease confidence that confounding (or other biases) can be ruled out?

- Larger range of exposures among studies could reveal pattern not evident within a single study

- Is there an indication of publication bias (e.g., large positive effects only seen in small studies?)

Weight of Evidence: Examining Possible Explanations

Coherence across related outcomes:

- Do studies that evaluated related outcomes provide evidence that increases or decreases confidence in the interpretation of a causal association?
  - For example, associations with subclinical endpoints/ precursors to clinical disease

Example Framework for Classification of Evidence from Studies in Humans

Robust	Strong signal of effect with little residual uncertainty
Moderate	Signal of effect with some uncertainty
Slight	Signal of effect with large amount of uncertainty
Indeterminate	Signal cannot be determined for or against an effect
Compelling evidence of no effect	Strong signal for lack of an effect with little uncertainty

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Using Epidemiologic Data in Exposure-Response Assessment

- **Numerous examples:**
  - Cardiovascular disease (carbon monoxide)
  - Lung function (ozone, ammonia)
  - Neurological effects (toluene, manganese)
  - Lung cancer (asbestos, chromium)
  - Leukemia (benzene, 1,3-butadiene)
- **Primary considerations for choosing data to model:**
  - Chance, bias, and confounding ruled out or minimized
  - Quality of exposure measurements

Using Epidemiologic Data in Exposure-Response Assessment

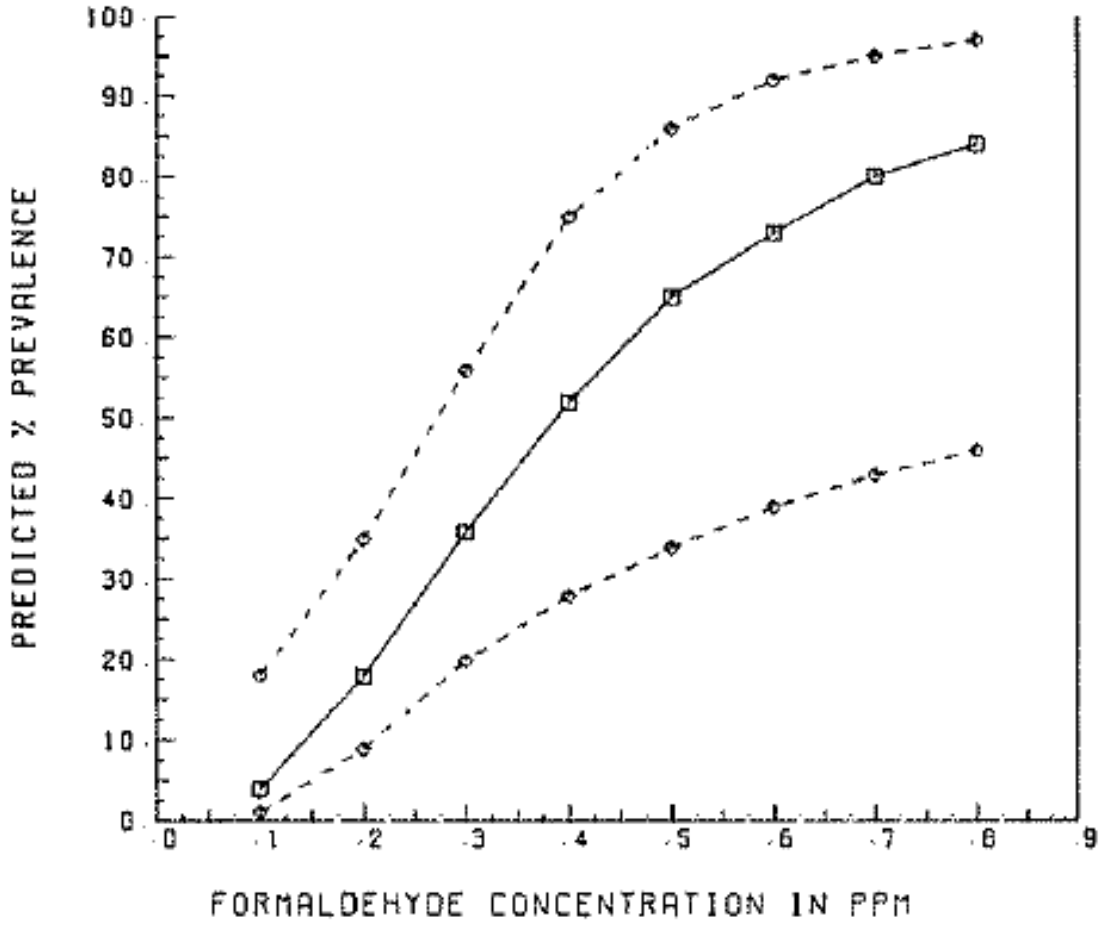

FIGURE 1—Burning Eyes Response at Mean Respondent Age of 48 Years with 95% confidence intervals

Hanrahan et al. (1984) Formaldehyde Vapor in Mobile Homes: A Cross-sectional Survey of Concentrations and Irritant Effects. AJPH 74:1026-1027.

EPA United States Environmental Protection Agency

SUMMARY

Summary

- Epidemiologic studies provide important information for hazard identification and exposure-response assessment
  - Epidemiologic data are from species and exposures of interest, and complement other types of data

Determinants of validity of epidemiological data for risk assessment purposes.

Proper study design
Adequate sample size (power, precision)
Representative sample (selection bias, generalizability)
Unbiased measures of exposure and outcomes
Control for confounding
Data analyzed using correct statistical model

Source: Mundt KA et al. 1998. Hum Ecol Risk Assess 4: 675-683

Summary

- Associations in epidemiologic studies are given greater weight when chance, bias, and confounding are minimized
  - Assess in individual studies
  - Assess in a collection of studies
- Exposure assessment approaches in some epidemiology studies enable their use in derivation of toxicity values