IOM

WORKING FOR A HEALTHIER FUTURE

Occupational Epidemiology Webinar

Prof. Damien McElvenny

Damien.McElvenny@iom-world.org

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What is epidemiology?

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- It's an observational, rather than experimental science

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So what is occupational epidemiology?

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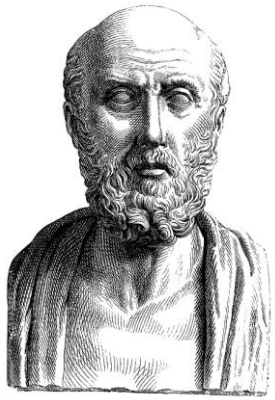
Historical Background

- Occupational hazards were known to Hippocrates (c460-370 BC)
  - Admonished physicians to explore patients' environmental, lifestyle and vocational backgrounds when diagnosing and treating diseases
- Bernadino Ramazzini (often acknowledged as the father of occupational medicine)
  - Described occupationally related diseases in his book *De Morbis Artificum* (1700)



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What were the earliest recognised occupational diseases?

Early Examples of Occupational Diseases

- Respiratory impairment (silicosis) in stonemasons
- Ocular disorders in glassblowers
- Neurological toxicity among tradesmen exposed to mercury

- The recognition of many well-known occupational hazards can be traced to astute physicians or to workers themselves

Early Examples of Occupational Diseases

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Development of Methods

- Many occupational health risks initially identified by case series or clusters, for example:
  - Ludwig Rehn in 1895 observed 3 cases of bladder cancer in workers exposed to aromatic amines in a fuschin dye factory
  - Rare tumour of the blood vessels in the liver, angiosarcoma, among workers exposed to vinyl chloride

Types of epidemiological approach

Descriptive epidemiology

- Describing patterns and trends in health and disease in populations
- Good for generating hypotheses

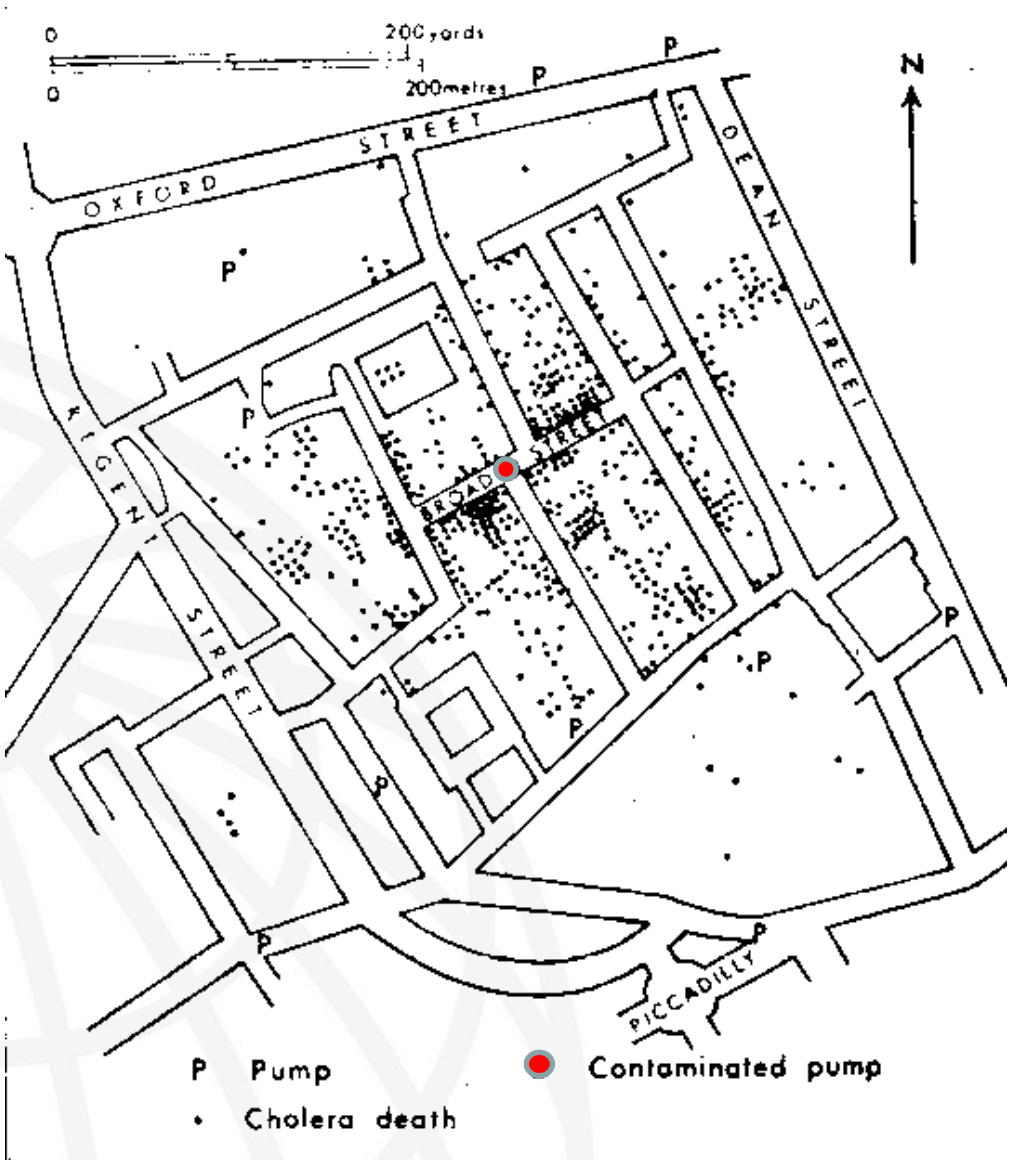
The 5W's of descriptive epidemiology:

What = health issue of concern
Who = person
Where = place
When = time
Why/how = causes, risk factors, modes of transmission

John Snow – cholera outbreak

Analysis by place

- Mapped the cases – most were near Broad Street
- Thus outbreak was traced to the Broad Street water pump



Types of epidemiological approach

Analytical epidemiology – observational studies

- To test hypothesis (e.g. generated by descriptive epidemiology) - is exposure ‘x’ associated with disease ‘y’
- Key feature of analytic epidemiology is a **comparison group**
- Comparison of exposed and unexposed groups, or comparison of low exposure, medium exposure and high exposure groups
  - comparison of those with and without disease

Types of analytical studies

- Cross-sectional studies
- Case-control studies
- Cohort studies

Short-term (acute) health effects

Longer-term (chronic) health effects

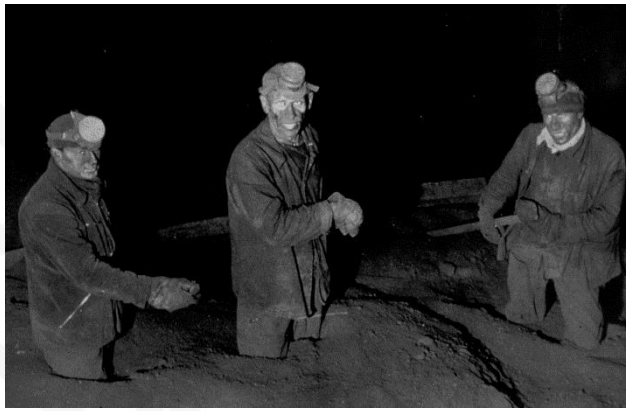
Cross-sectional studies

- Information on health and exposure is collected from each subject in a population at one point in time

- Statistical tests of association between exposure and health outcome

Example – Carbon Black

- European cross-sectional study
- Total population approx. 2500
- Workers in carbon black manufacturing industry
- Exposure to dust and respiratory symptoms
- Lung function measurements
- Respiratory symptoms questionnaire
- Chest radiographs
- Personal dust measurements



Carbon black is mainly used as a reinforcing filler in tyres and other rubber products. In plastics, paints, and inks, carbon black is used as a colour pigment.

Results Carbon Black study

	Current	
	OR	95% CI
Cough		
Ex-smoker	1.3	0.8-2.2
≤ 250 cig.yrs	**2.7**	**1.6-4.5**
251-500 cig.yrs	**4.0**	**2.5-6.6**
> 500 cig.yrs	**11.0**	**6.8-17.7**
CB Exposure	**1.4**	**1.2-1.8**

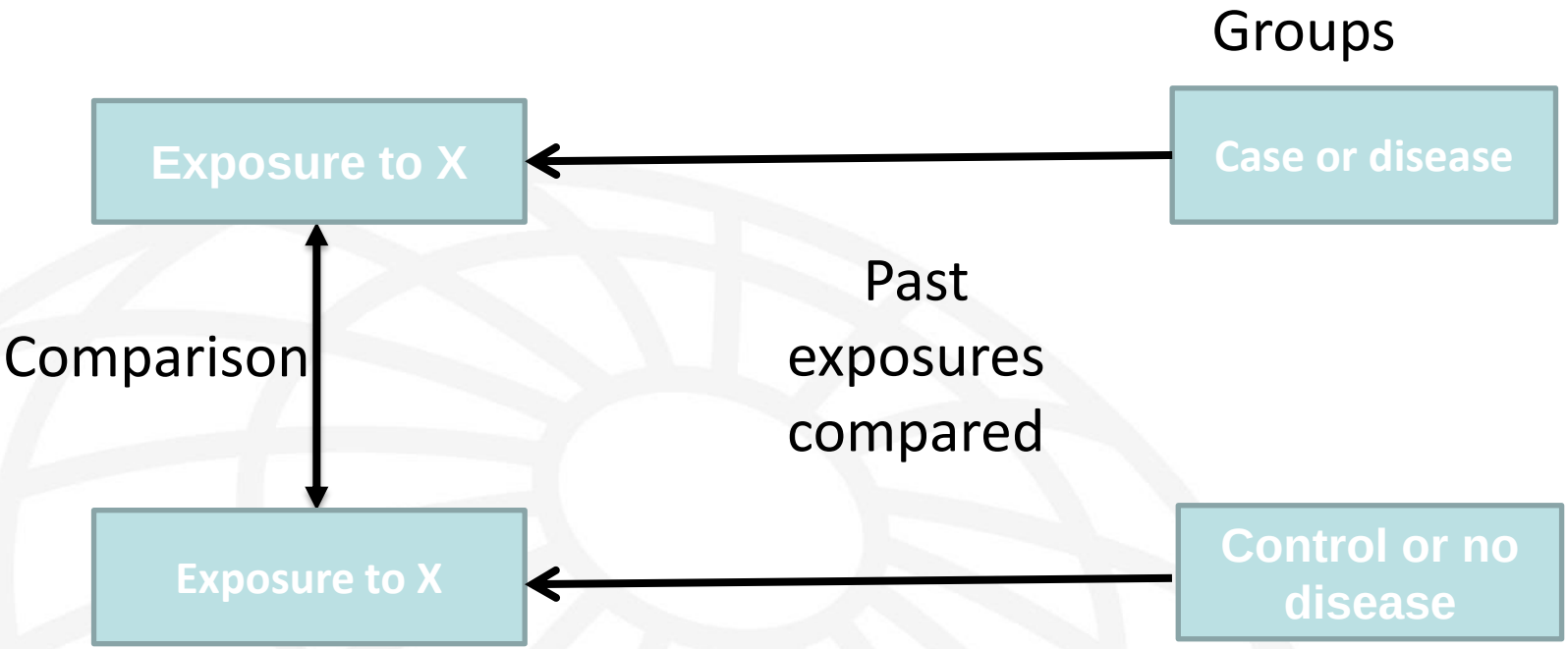
	Current	
	β	95% CI
FEV_1		
Ex-smoker	-0.01	-0.07, 0.06
≤ 250 cig.yrs	-0.06	-0.13, 0.01
251-500 cig.yrs	**-0.15**	**-0.23, -0.08**
> 500 cig.yrs	**-0.34**	**-0.42, -0.27**
CB Exposure[a]	**-0.07**	**-0.11, -0.03**

Case-control studies

- Compares people with a condition (cases) to a similar group of people without the condition (controls)

- The aim is to try and identify the risk factors which may have caused the cases to get the condition in the first place

Case – Control design



Is Exposure in cases greater than in controls?

The INTEROCC case-control study: risk of meningioma and occupational exposure to selected combustion products, dusts and other chemical agents

Damien M McElvenny,[1] Martie van Tongeren,[1,2] Michelle C Turner,[3,4,5,6] Geza Benke,[7] Jordi Figuerola,[3,4,5] Sarah Fleming,[8] Martine Hours,[9] Laurel Kincl,[10] Daniel Krewski,[6,11] Dave McLean,[12] Marie-Élise Parent,[13] Lesley Richardson,[14] Brigitte Schlehofer,[15] Klaus Schlaefer,[15] Siegal Sadetzki,[16,17] Joachim Schüz,[18] Jack Siemiatycki,[14] Elisabeth Cardis[3,4,5]

ABSTRACT

Background Little is known about occupational risk factors for meningioma.

Objectives To study whether risk of meningioma is associated with several occupational exposures, including selected combustion products, dusts and other chemical agents.

Methods The INTEROCC study was an international case-control study of brain cancer conducted in seven countries. Data collection by interview included lifetime occupational histories. A job exposure matrix was used to derive estimates of exposure for the 12 agents. ORs for ever versus never exposed and for exposure-response using duration of exposure and cumulative exposure were derived using conditional logistic regression stratified by sex, age group, country/region, adjusted for education.

Results These analyses included 1906 cases and 5565 controls. For 11 of the 12 agents, no excess risk was found for ever exposed. For ever exposure to oil mists, an elevated OR of 1.57 (95% CI 1.10 to 2.22, 51 exposed cases) was found. Statistically significant exposure-response relationships were observed with cumulative exposure (p=0.01) and duration of exposure (p=0.04). Among women, there were also significant trends for cumulative and duration of exposure to asbestos and excesses in the highest exposure categories for formaldehyde.

Conclusions Most agents examined did not provoke excess risks of meningioma. The main finding from this study is that it is the first study to identify a statistical association between exposure to oil mists and meningioma. This may be a chance finding or could be due to confounding with iron exposure and further research is required to understand whether the relationship is causal.

What this paper adds

- Little is known about occupational risk factors for meningioma.
- The INTEROCC study is the largest case-control study of meningioma and occupational risk factors, with data collected from seven countries.
- Occupational exposure to mineral oil appeared to be associated with elevated risk of meningioma.
- Among women, there was also some indication of exposure-response for asbestos and some indication of excess risks from formaldehyde in the highest exposure categories.
- No association was observed with other occupational substances investigated in this paper, which included combustion products, mineral and organic dusts and other chemical agents.

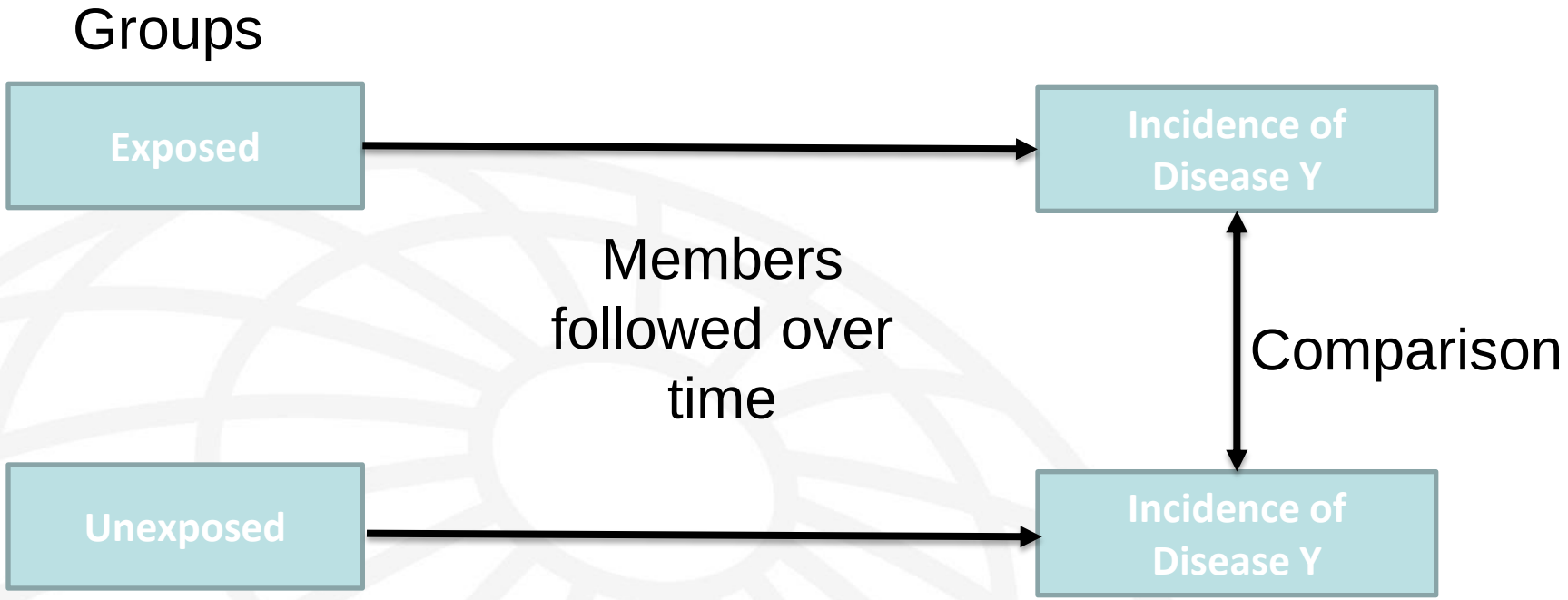
is rising in some countries, but remains stable in others.[2] Differences in cancer registration practices between countries mean that incidence rates differ considerably between countries. Meningiomas exhibit a range of morphological appearances, with WHO suggesting there are up to 15 histopathological variants.[2] Five-year survival has been reported as 55% and 3-year survival at over 85%.[2] The incidence rate increases rapidly with age and is twice as high in females as in males.[2]

The only established environmental risk factor for meningioma is exposure to ionising radiation, with some doubt as to the dose required to trigger excess risk.[1] Results from other epidemiological

Cohort studies

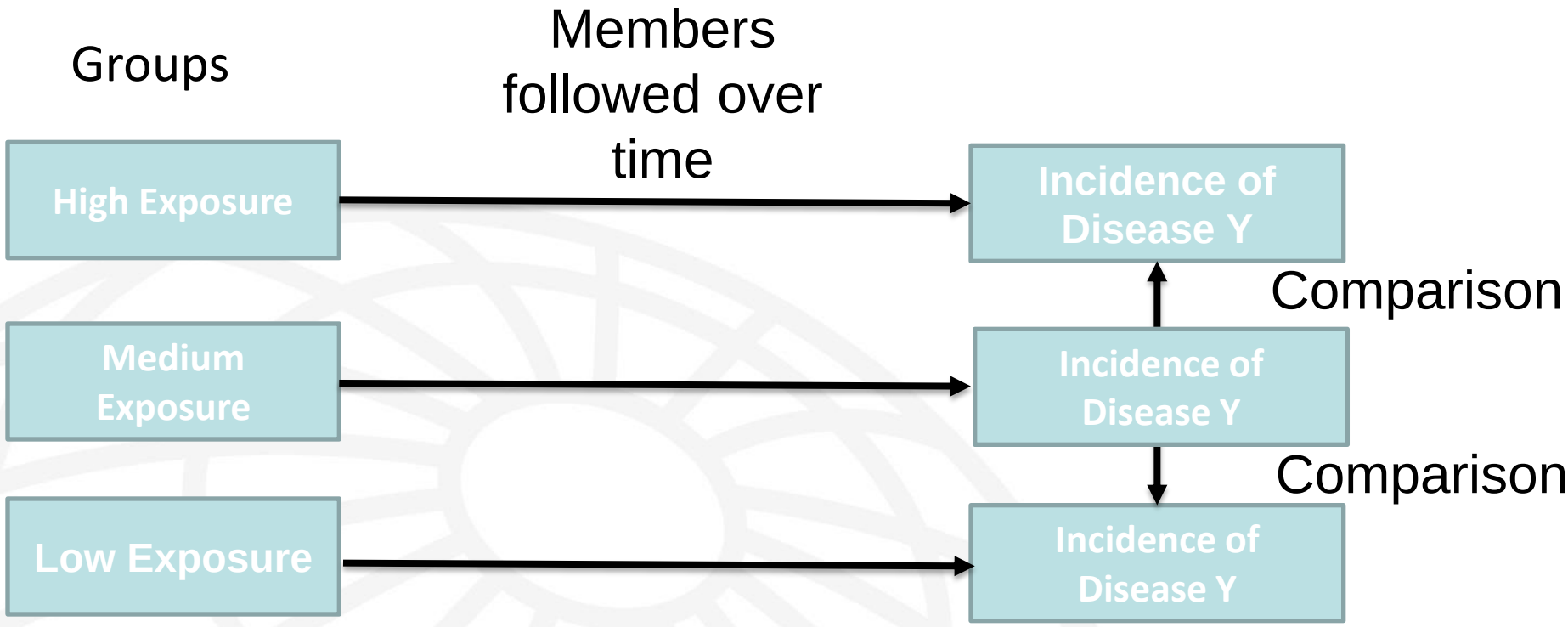
- Follow up one or more groups people over time and compare the occurrence (incidence) of disease
- Longitudinal – repeated measurements over time
- One group has been exposed to a possible risk factor for the disease, while the other has not
- Prospective, retrospective

Cohort study design



Is Incidence in Exposed greater than in Unexposed?

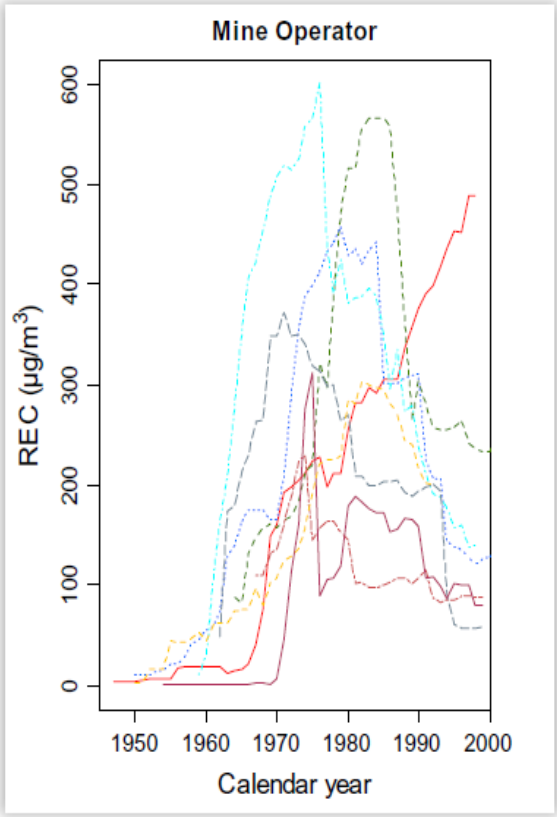
Cohort study design



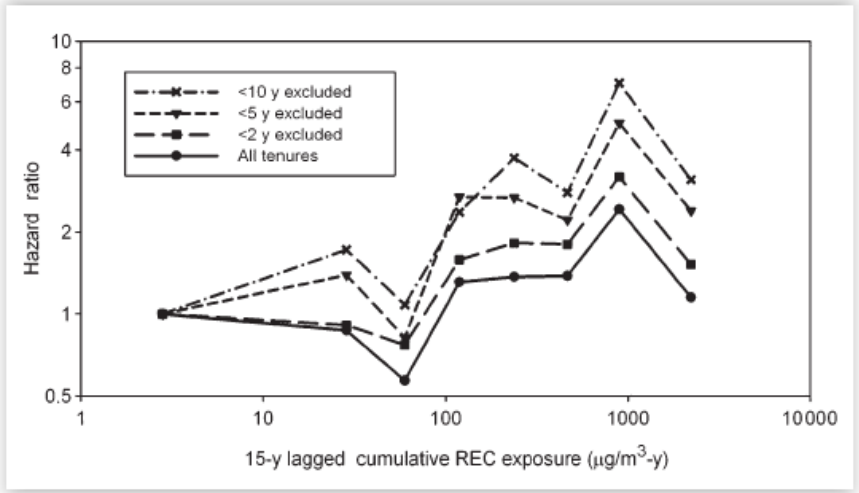
Does Incidence increase with increasing exposure?

Example Cohort study

- DEMS: Exposure to diesel engine exhaust in miners and risk of developing lung cancer
- Retrospective cohort study of 12315 workers in 8 non-metal mines
- Exposure to respirable elemental carbon (REC) was assessed retrospectively
- Vital status assessed end 1997 and causes of death obtained from national statistics



Vermeulen et al 2010



Attfield et al 2011

Mortality From Solid Tumors Among Workers in Formaldehyde Industries: An Update of the NCI Cohort

Laura E. Beane Freeman, PhD,[1]* Aaron Blair, PhD, MPH,[1] Jay H. Lubin, PhD,[2] Patricia A. Stewart, PhD,[3] Richard B. Hayes, DDS, PhD, MPH,[4] Robert N. Hoover, MD, ScD,[5] and Michael Hauptmann, PhD[6]

Background *Formaldehyde, a widely used chemical, is considered a human carcinogen.*
Methods *We extended follow-up of the largest industrial cohort of workers in formaldehyde industries (n = 25,619) by 10 years through 2004. Standardized mortality ratios (SMRs) and rate ratios (RRs) were calculated for deaths from solid tumors using quantitative formaldehyde exposure estimates.*
Results *During 998,239 person-years, 13,951 deaths occurred. With one additional death, previously observed excesses for nasopharyngeal cancer (n = 10) persisted for peak, average intensity and cumulative exposure; RRs in the highest exposure categories were 7.66 (95% CI: 0.94, 62.34), P-trend = 0.005, 11.54 (95% CI: 1.38, 96.81), P-trend = 0.09, and 2.94 (95% CI: 0.65, 13.28), P-trend = 0.06, respectively. For all cancer, solid tumors and lung cancer, SMRs among exposed workers were elevated, but internal analyses revealed no positive associations with formaldehyde exposure.*
Conclusions *Consistent with previous analyses of this cohort, this update continues to suggest a link between formaldehyde exposure and nasopharyngeal cancer.* Am. J. Ind. Med. 56:1015–1026, 2013.

Advantages and disadvantages?

Study design	Advantages	Disadvantages
Cross-sectional	Relatively cheap and quick Can look at multiple outcomes	Can't determine cause and effect Timing of the snapshot not guaranteed to be representative
Case-control	Good for rare diseases or diseases with a long latency period	Not good for rare exposures Can only look at single outcome
Cohort	Clearer indication of cause and effect Can look at multiple outcomes	Can be expensive and time consuming Not good for rare diseases

(Mis)Classification of exposure?

Exposure measures (occupational)

- Occupation, job, industry
  - Ever / Never
  - Duration of employment
- Intensity of agent
  - Exposure level (e.g. mg/m^3)
  - Duration of exposure (e.g. years)
  - Cumulative exposure (e.g. mg/m^3 – years)

Relative Risk

- The ratio of the probability of a disease occurring in an exposed group to the probability of the same event occurring in a comparison, unexposed group
- Cohort studies
  - Standardised mortality/morbidity ratio
  - Standardised rate ratio
- Case-control studies
  - Odds ratio
- A RR>1 indicates increased risk of disease in exposed (need to consider – usually 95% CIs - as measures of uncertainty)

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Measures of disease frequency

Two main measures

- **Incidence** - number of **NEW CASES** of disease that develop in a population during a specified time period

- **Prevalence** - total number of cases of disease in a population at one point in time

- Usually expressed as **rates** (which have a numerator and a denominator)

Incidence

Usually expressed as the number of new cases per 100,000 population per year.

For example: Incidence rate of asthma in England in 2012:

Number of new cases of asthma during 2012 = 146,000

England population in 2012 (mid-year estimate) = 53,490,000

Incidence rate = (146,000/53,490,000) x 100,000

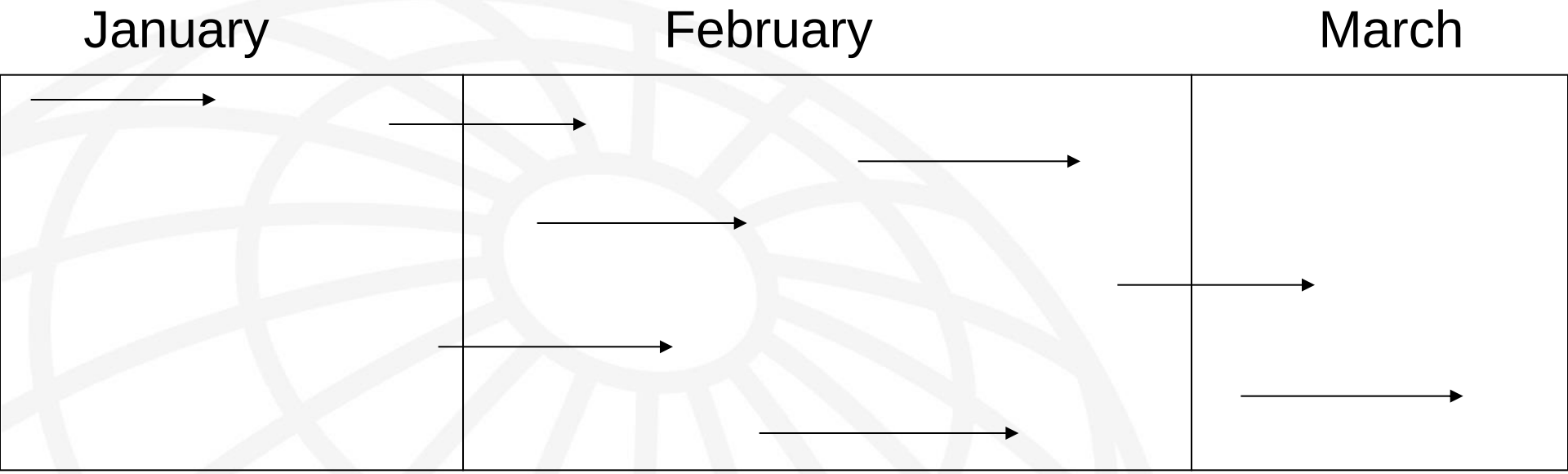
Incidence rate = 273 cases of asthma per 100,000 during 2012.

Prevalence

- Prevalence is the total number of cases of disease in a population at one point in time, taken as a proportion of the total number of persons in that population.
- Also referred to as “point prevalence”
- Period prevalence is a variation which represents the number of persons who were a case at any time during a specified (short) period as a proportion of the total number of persons in that population.

Example – incidence and prevalence

Cases of cold infections in students. Class size = 20



What is the incidence in February?

What is the point prevalence on the last day in February?

What is the period prevalence during February?

What issues might we encounter when calculating disease incidence rates?

Numerator (case)?

- How do you define your case?
  - Misclassification of disease
  - Under/over-reporting

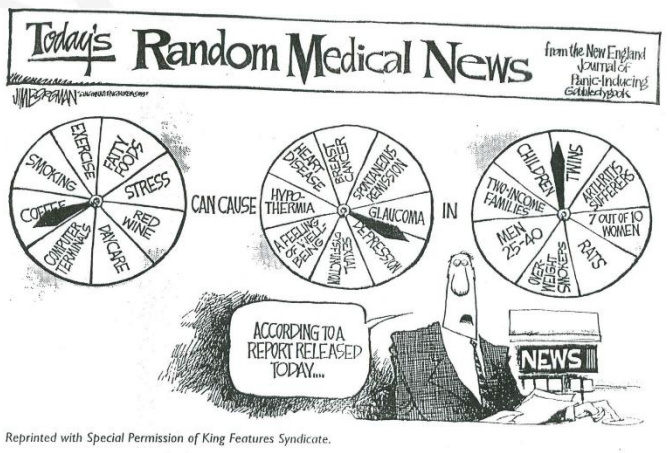
Denominator (population)?

- How do you define your population at risk?
  - e.g. the population at risk at the beginning, or the mid-point of the year, or the total person-time at risk.
  - Lag periods – long latency diseases

Suppose we observe a difference in incidence of disease between exposed and unexposed groups.

Possible explanations

Exposure is a cause of disease
Confounding (a type of bias)
Other biases in design
Chance association



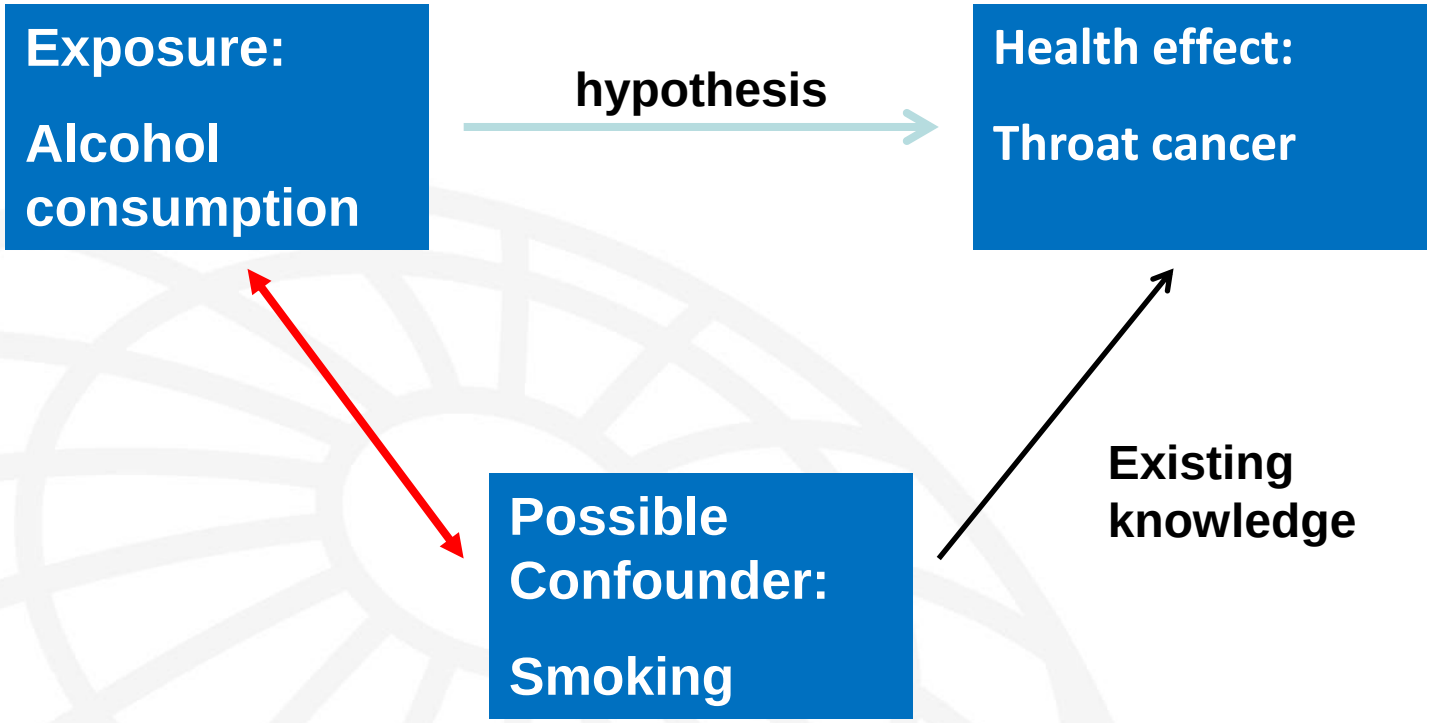
Bias, confounding and effect modification

- **Bias:** Systematic error in design, recruitment, data collection or analysis that results in mistaken estimation of true effect.

- **Confounding:** A situation in which the effect or association between an exposure and outcome is distorted by the presence of another variable.

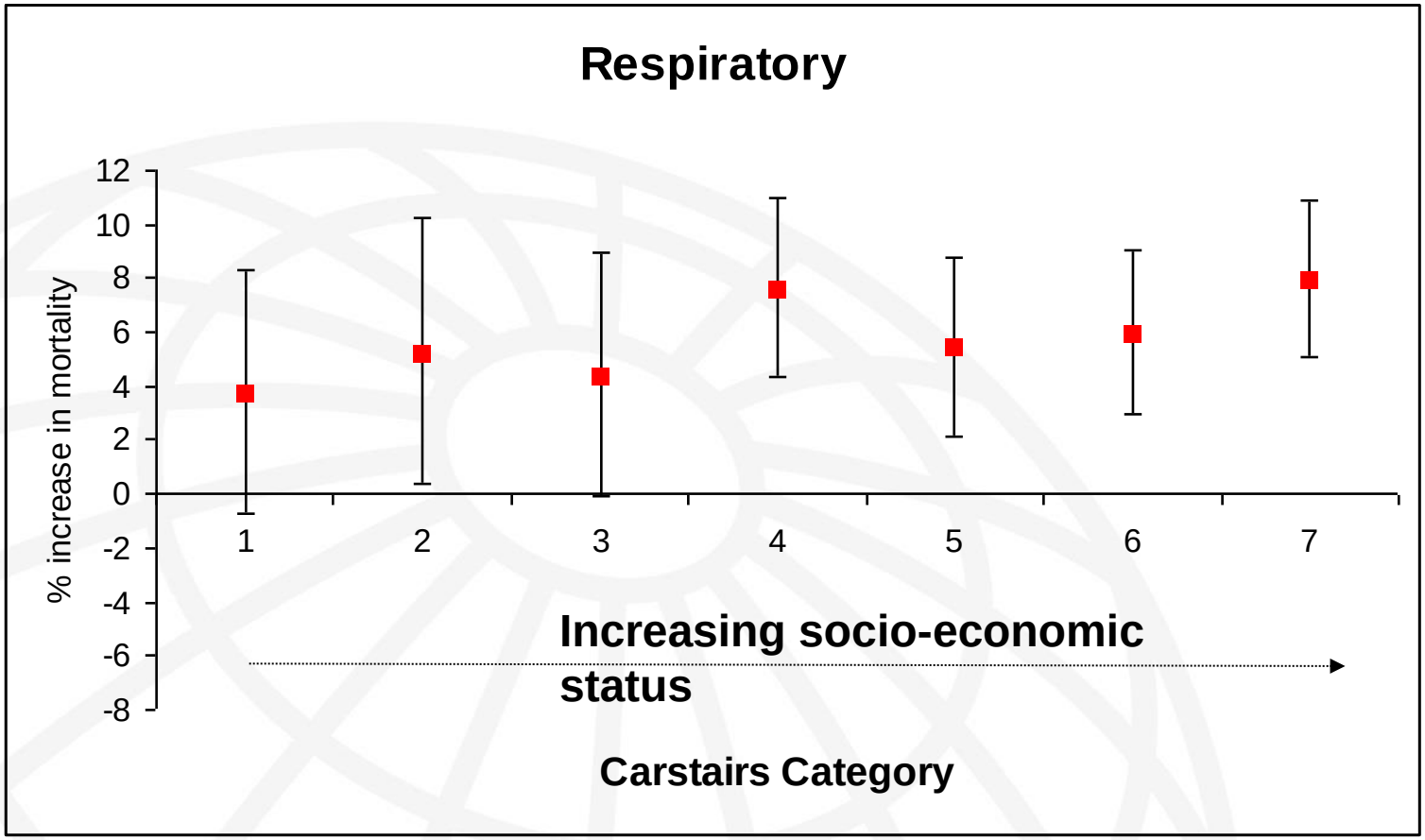
- **Effect modification:** a variable that differentially (positively and negatively) modifies the observed effect. Different groups have different risk estimates when effect modification is present.

Confounding - example



To be a confounder the variable (smoking) must influence/be associated with both the dependent variable (throat cancer) and the independent variable (alcohol consumption)

Estimated percentage increase in mortality over the ensuing one-month period associated with a 10μgm^{-3} increase in the mean black smoke concentration on any given day, at each Carstairs Category



Socio-economic status is modifying the effect of black smoke on respiratory mortality

Bradford-Hill considerations

- **Strength**: A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.
- **Consistency**: Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.
- **Specificity**: Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.
- **Temporality**: The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).
- **Biological gradient**: Greater exposure should generally lead to greater incidence of the effect.
- **Plausibility**: A plausible mechanism between cause and effect is helpful
- **Coherence**: Coherence between epidemiological and laboratory findings increases the likelihood of an effect.
- **Experiment**: "Occasionally it is possible to appeal to experimental evidence".
- **Analogy**: The effect of similar factors may be considered.

Future of Occupational Epidemiology

- New substances/agents to study
- Having to identify smaller and smaller risks
- Mixtures remain a problem
- Molecular approaches for exposure and disease markers
- Exposome (conception to grave exposures)
- Analysis of workplace inteventions

Thanks for your attention!

Happy to take questions!

Reserve Slides

How many people suffer from a work-related disease in GB?


1.3 million!

What are the most common occupational diseases in the UK?

Most common occupational diseases

Disease	Estimate	Comment
Musculoskeletal disorders	539,000	80% of the total
Stress, anxiety and depression	488,000	
Cancer	13,500	Not necessarily fatal
Non-malignant asbestos-related lung diseases	2,000	Deaths, larger number of non-fatal cases
Chronic obstructive pulmonary disease	4,000	Deaths, larger number of non-fatal cases
Other lung diseases	2,000	Deaths, larger number of non-fatal cases
Skin problems	6,000	New cases
Noise-induced hearing loss	20,000	
Hand-arm vibration/carpal tunnel syndrome	1,200	Likely to be an underestimate

Occupational Diseases

- Can't always be counted and so often have to be estimated from population surveys or epidemiological studies (using attributable fraction approach)
- Some haven't been well quantified, for example
  - Reproductive effects
  - Neurological effects
  - Cardiovascular disease

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What are results used for?

- Ultimately to limit exposures to workers by banning substances or limiting occupational exposures
- Hierarchy of control
  - Elimination
  - Substitution
  - Engineering controls
  - Signage/warnings and/or administrative controls
  - Personal protective equipment

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Study interpretation

- Does the exposure cause the disease?
- In some cases (see earlier examples) it can be obvious, for example
  - Acute disease occurring in temporal/physical proximity to occupational hazard
  - Some conditions e.g. pneumoconiosis can only be defined by occupational exposure (to dust)
- Much of occupational epidemiology research addresses the relative contributions of workplace exposures on health outcomes that have occupational and non-occupational causes

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Systematic Review/Meta-analysis

- A systematic review collects and critically analyses results of all studies addressing a particular research question. A systematic methodology is applied to prevent (sub)conscious bias.
- Meta-analysis is a statistical procedure used to explore why different studies produce a different relative risk
  - Some think it's a means of estimating a single overall measure of effect
    - This is too simplistic and can be misleading

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IOM

Formaldehyde and cancer risk: a quantitative review of cohort studies through 2006

C. Bosetti[1]*, J. K. McLaughlin[2,3], R. E. Tarone[2,3], E. Pira[4] & C. La Vecchia[1,3,5]

[1]*Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy;* [2]*International Epidemiology Institute, Rockville, MD;* [3]*Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA;* [4]*Dipartimento di Traumatologia, Ortopedia e Medicina del Lavoro, Università di Torino, Turin;* [5]*Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy*

Received 9 November 2006; revised 29 March 2007; accepted 18 April 2007

Background: Occupational exposure to formaldehyde has been associated with excess risk of nasopharyngeal and selected other cancers.

Patients and methods: We reviewed and pooled the results of cohort studies published through February 2007.

Results: There were 5651 deaths from all cancers observed in six cohorts of industry workers and six of professionals, with a pooled relative risk (RR) of 0.95 for industry workers and of 0.87 for professionals. Nine deaths from nasopharyngeal cancer in three cohorts of industry workers yielded a pooled RR of 1.33, which declined to 0.49 after excluding six cases from one US plant. The pooled RR for lung cancer was 1.06 in industry workers and 0.63 in professionals. Corresponding values were 1.09 and 0.96 for oral and pharyngeal, 0.92 and 1.56 for brain, 0.85 and 1.31 for all lymphatic and hematopoietic cancers, and 0.90 and 1.39 for leukemia.

Conclusions: Comprehensive review of cancer in industry workers and professionals exposed to formaldehyde shows no appreciable excess risk for oral and pharyngeal, sinonasal or lung cancers. A non-significantly increased RR for nasopharyngeal cancer among industry workers is attributable to a cluster of deaths in a single plant. For brain cancer and lymphohematopoietic neoplasms there were modestly elevated risks in professionals, but not industry workers.

Key words: formaldehyde, neoplasm, occupational exposure, review, risk assessment