MONASH University
Medicine, Nursing and Health Sciences

Exposure Assessment for Epidemiology

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Outline

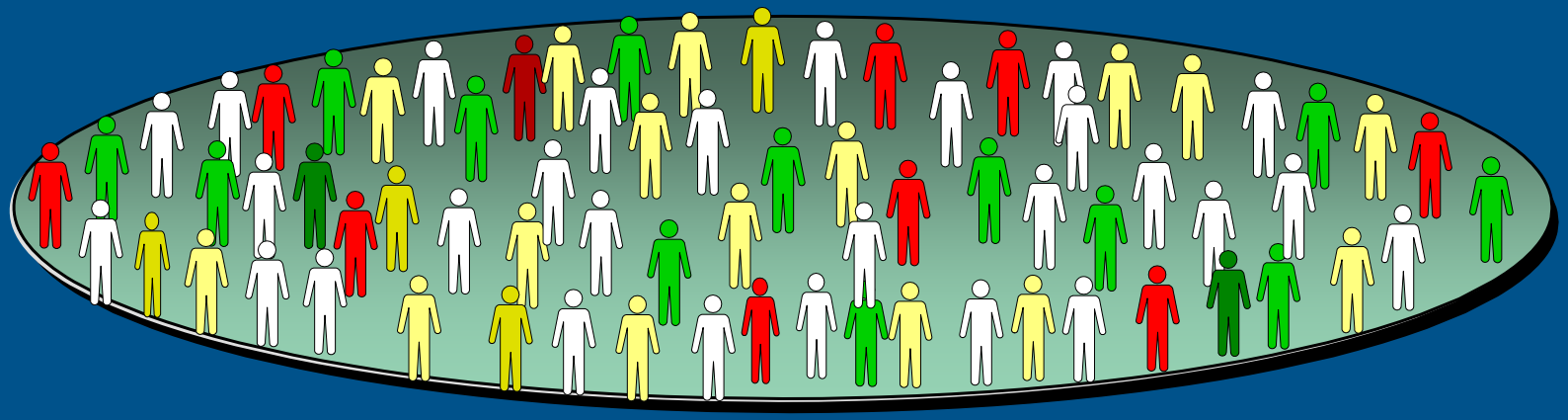
- Exposure assessment for epidemiology
- Exposure indices – factors to consider
- Exposure misclassification
- Exposure assessment in general population and Industry specific studies
- Case studies
  - Organochlorine compounds
  - Prostate cancer and occupational exposures
  - Benzene and leukaemia

Exposure Assessment

- Important part of epi studies for hazard identification
- Historically, considerably less well done than disease definition and measurement
- Over past 5-10 years has developed as a major scientific discipline within epidemiology
- Objective - better definitions of exposure and hence of risk

Purpose of Exposure Assessment

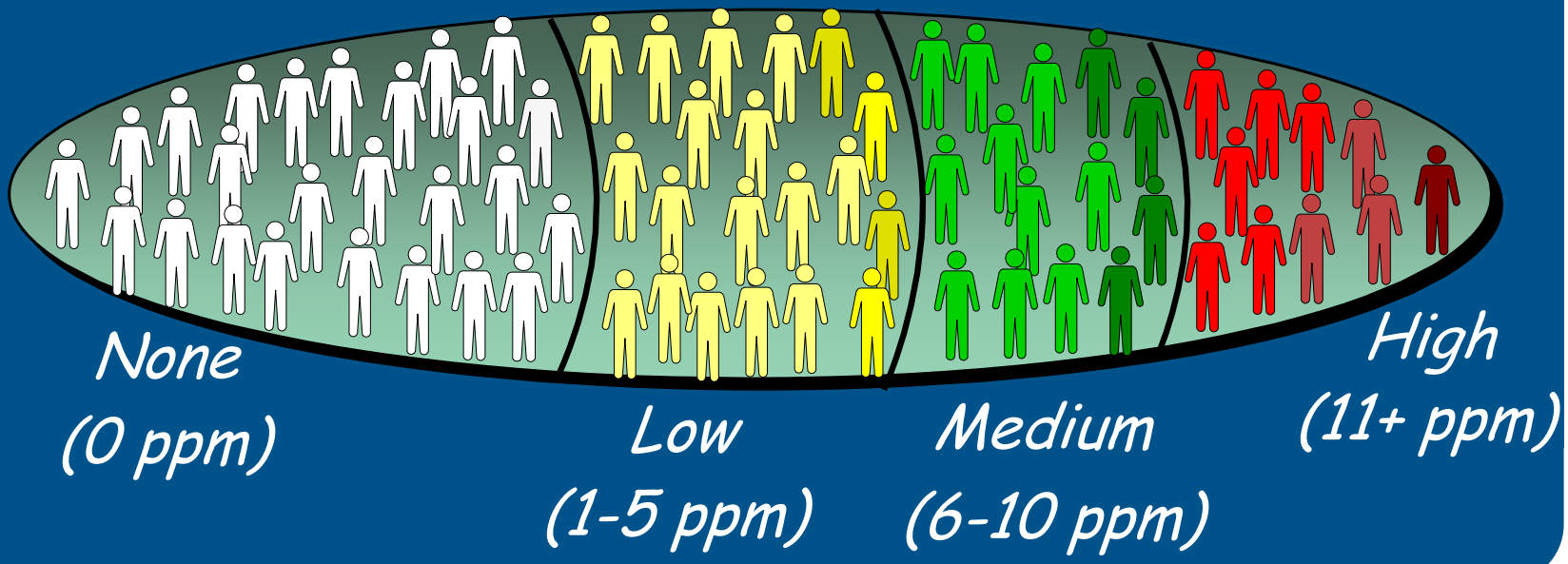
To identify the determinants of exposure variability within the study population



(0 ppm) Low (1 - 4 ppm) Medium (5-19 ppm) High (20+ ppm)

Purpose of exposure assessment

To classify subjects accurately with respect to exposure variability



Purpose of exposure assessment

To identify the average exposure and determinants of exposure variability within the study population

and

To classify subjects accurately with respect to exposure variability

Exposure measures

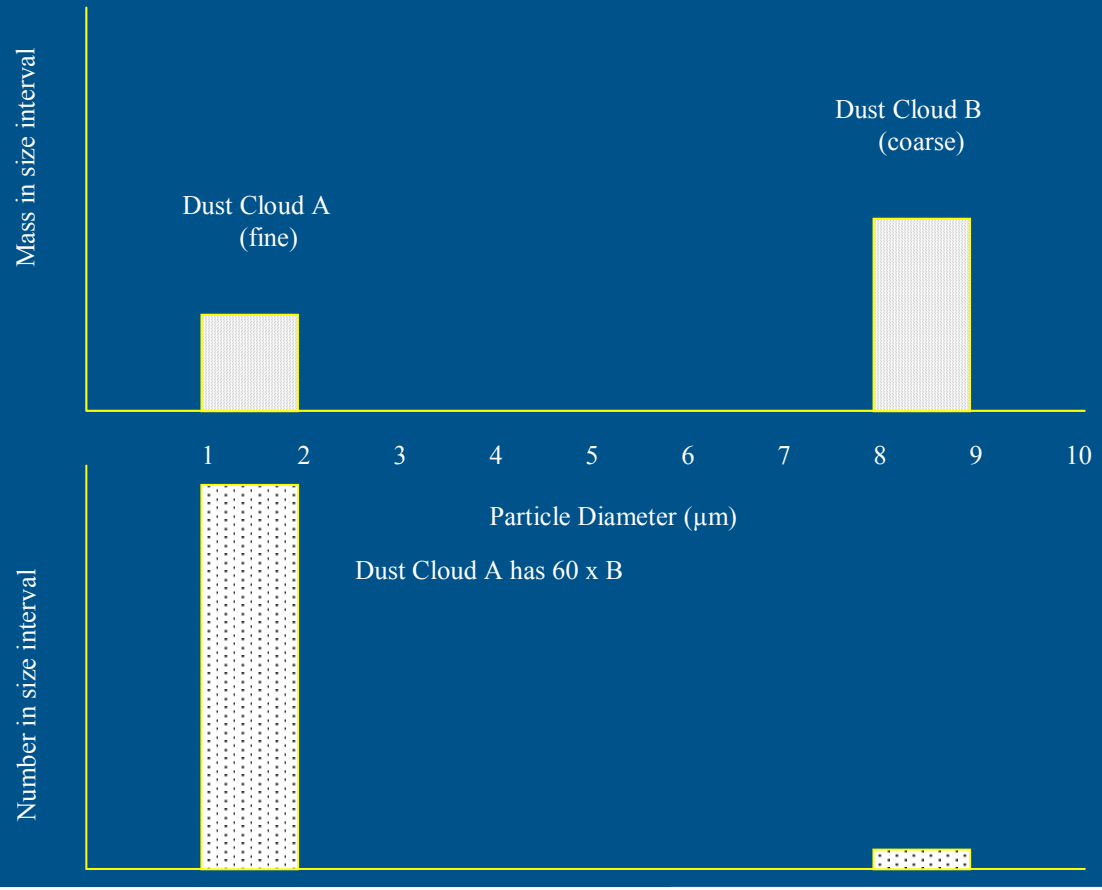
- Aim to measure exposure as close to the biological response as possible
- Need to understand nature of the exposure, form of the compound, exposure patterns
  - eg physical agents, chemicals, dust, vapour, mixtures
- Need to understand variability in exposure
  - Between individuals and over time

Mass or particle counts?

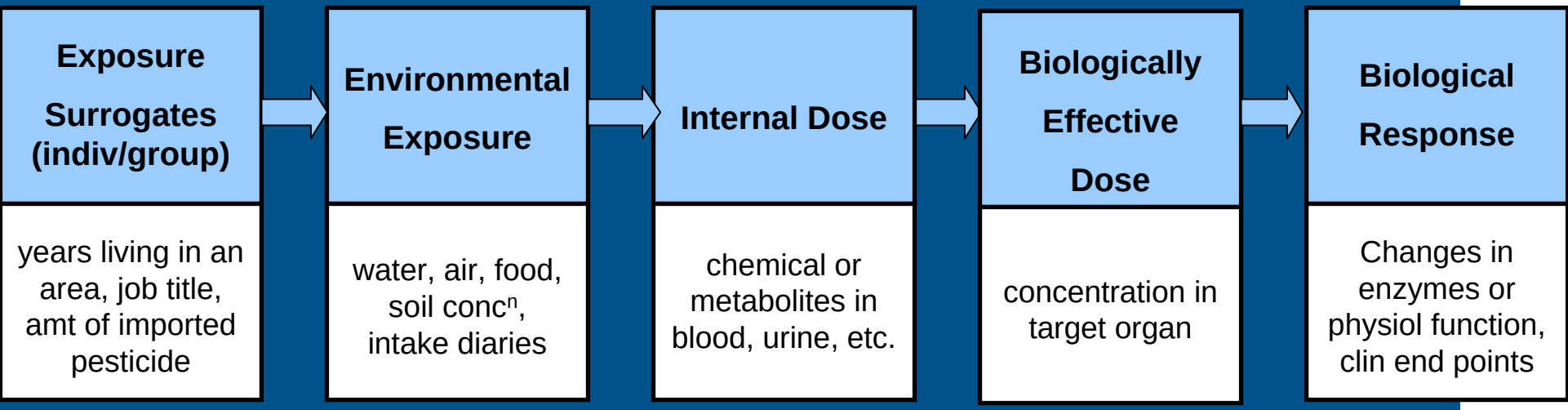
Dust

- Can count particles
- Measure surface area
- Weigh mg/m^3

Diameter vs mass of dust



Human exposure pathways



Biological markers of exposure

- Examples are blood, urine, breast milk, exhaled air, fat biopsies, etc
- Can measure compound itself or a metabolite
- Make sure relates to time period of relevance
- Require good knowledge of kinetics of the compound, such as half life in the body - if don't understand this, can lead to underestimates of exposure
- Need reliable lab and assays - low limit of detection to minimise non-detects, split sample reliability
- Can be invasive, therefore possible ethical concerns
- Expensive, eg dioxins
- Problems of storage, transport etc

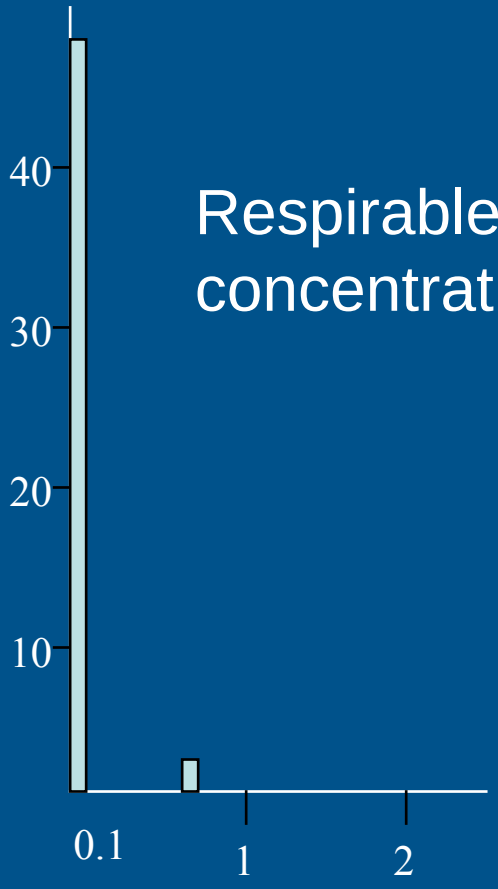
Other measures of exposure

- Occupational exposure measurements
  - ie concentration in ambient or indoor air
- ?All routes of exposure (smoking, drinking water, soil)
- Other exposure measures, such as self-report, commonly used in epi studies, but often little use in risk assessment, as low validity

Occupational exposure measurement

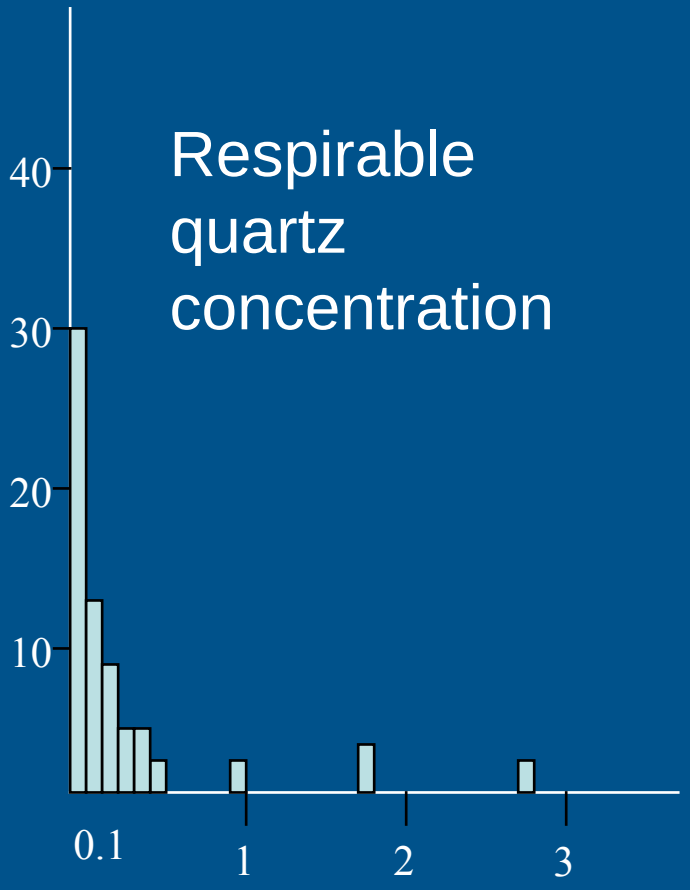
- Normal production, maintenance & cleaning
- Static samples versus personal samples
- Inhalation and skin
- Need good lab for analyses
- Need to take into account duration of exposure
- Historical data can be useful, eg monitoring records

Foundry Dust Static Sampling



Respirable quartz concentration

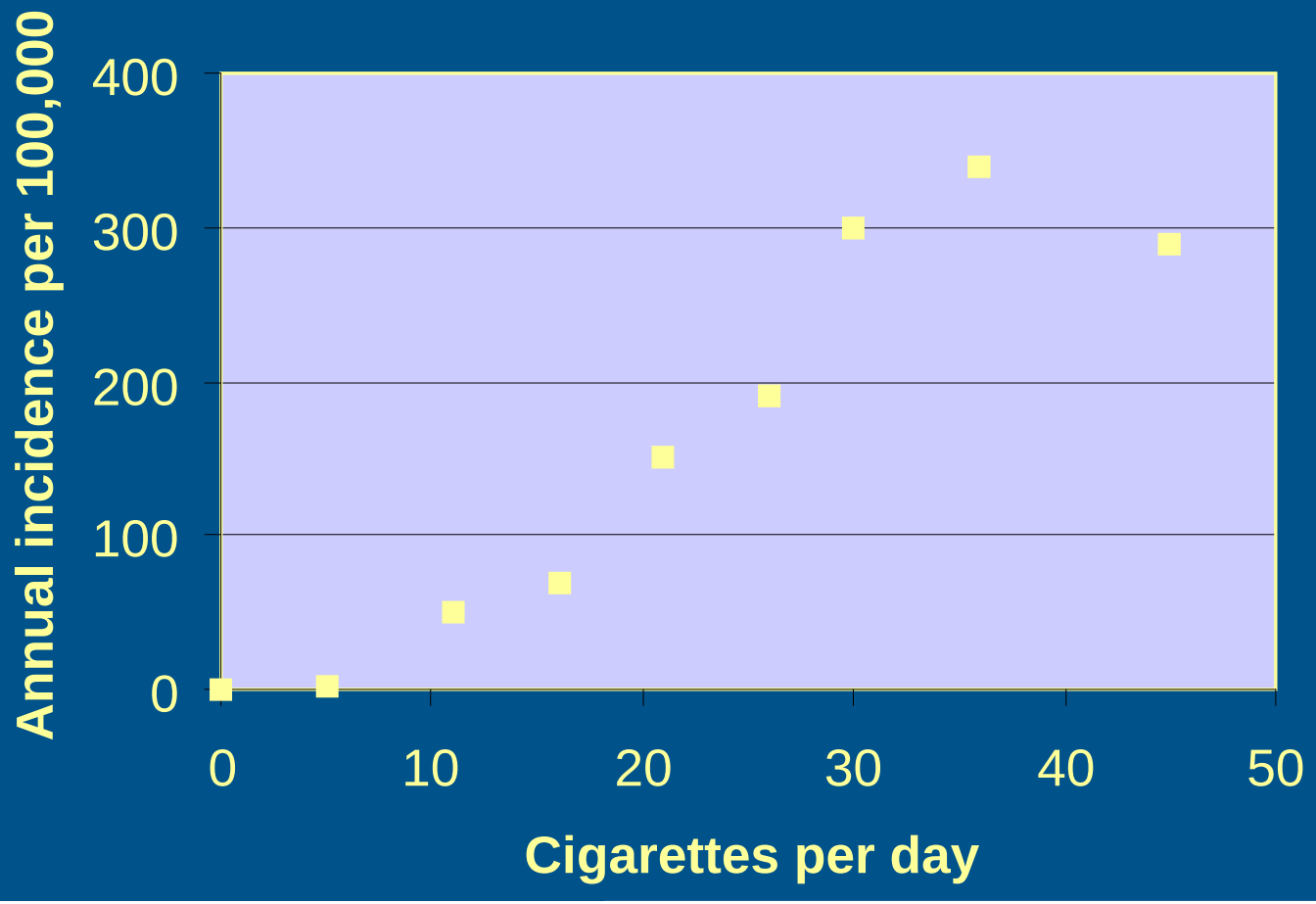
Foundry Dust Personal Sampling



Range of exposures

- The best studies include subjects with a large range of exposure – epi not good at identifying small differences
- Good to have large unexposed reference group
- Best if can examine dose-response relationship

Lung cancer incidence



Exposure assessment

- Must be unbiassed assessment
- Qualitative (eg yes/no or high/low)
- Quantitative more useful in risk assessment, but not always possible

Quantified exposure measures

Exposure intensity or concentration:

Amount of the substance per unit of environmental medium (milligrams per cubic meter of air, mg/m3)

Cumulative exposure:

Summations of concentrations over time

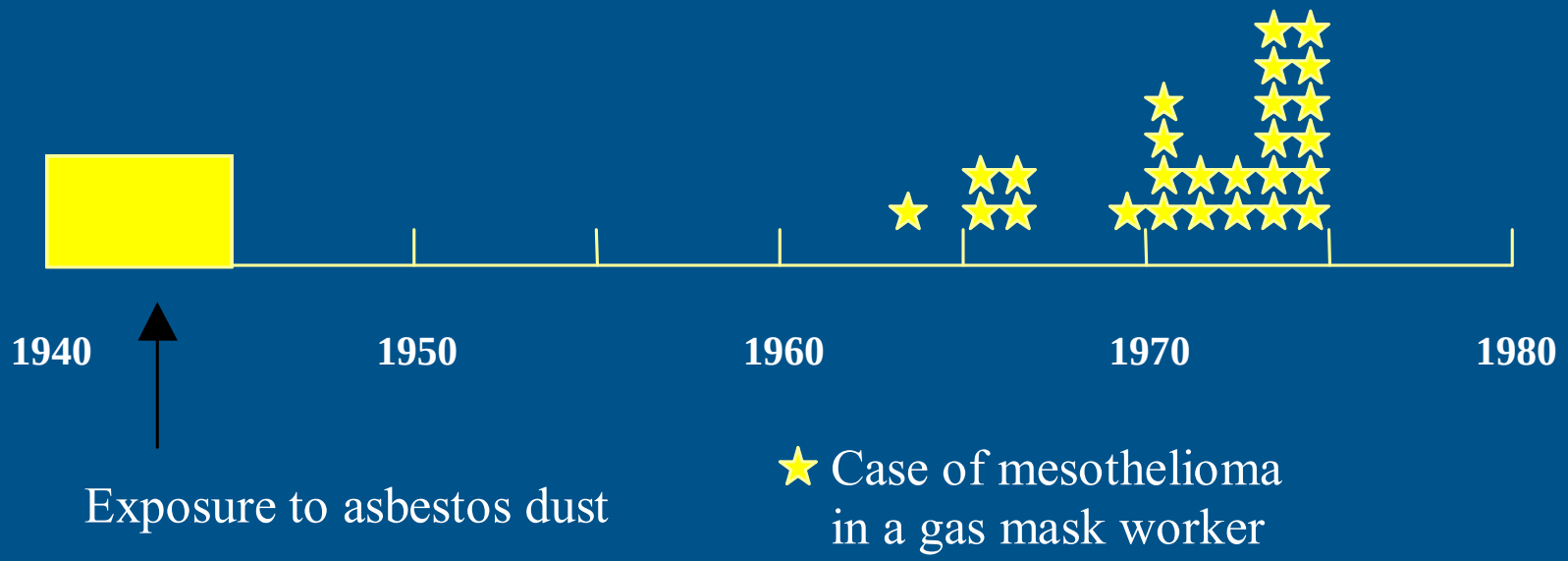
(mg/m3 x years or ppm x years)

Relevant averaging time and exposure period

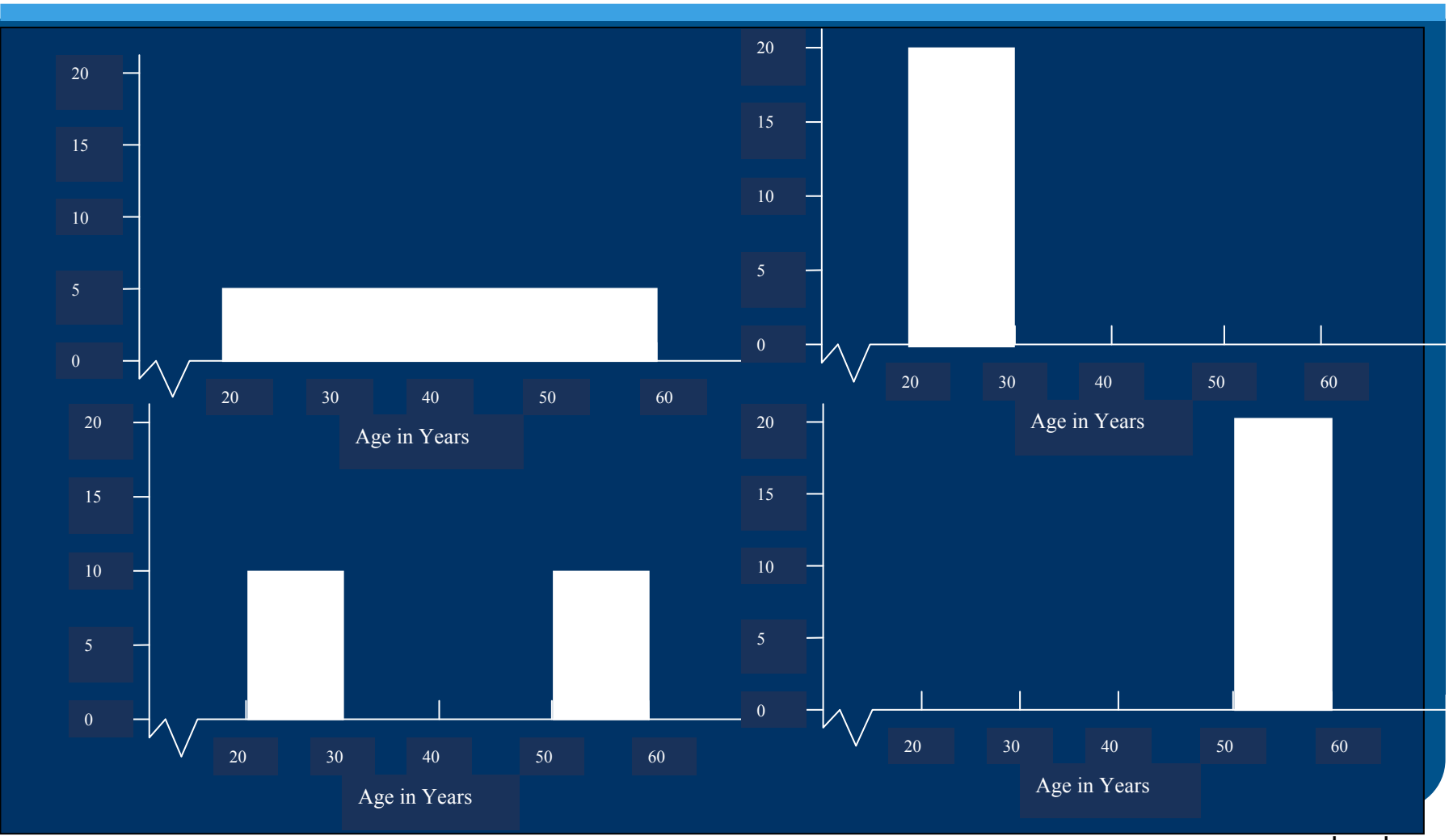
Exposure measure should relate to the time period of relevance to the natural history of the disease

- Long term exposure- pneumoconioses
  - cumulative average daily exposure
- Short term exposure- asthma
  - frequency of peak exposures
- Latent period
  - E.g. benzene exposure more than 10 years before diagnosis

Latency


1940
1950
1960
1970
1980
Exposure to asbestos dust
Case of mesothelioma
in a gas mask worker

When did exposure occur?



Exposure misclassification

- Exposed subjects classified as non-exposed and *vice versa* or level of exposure misclassified
- If differential, effect on risk estimates difficult to predict e.g. recall bias in case control studies
- If non-differential, tends to bias epidemiological risk estimates towards the null
- Reduces statistical power to find associations
- May make it more difficult to identify dose-response relationships

Differential misclassification

10% unexposed cases wrongly classified as exposed

	Cases	Controls	Total
Exposed	80	50	130
Not exp	120	150	270
Total	**200**	**200**	**400**

OR = ad/bc = 2.0

	Cases	Controls	Total
Exposed	92	50	144
Not exp	108	150	256
Total	**200**	**200**	**400**

OR = ad/bc = 2.5

Nondifferential misclassification

!0% of cases and controls wrongly classified

	Cases	Controls	Total
Exposed	80	50	130
Not exp	120	150	270
Total	**200**	**200**	**400**

OR = ad/bc = 2.0

	Cases	Controls	Total
Exposed	84	60	144
Not exp	116	140	256
Total	**200**	**200**	**400**

OR = ad/bc = 1.7

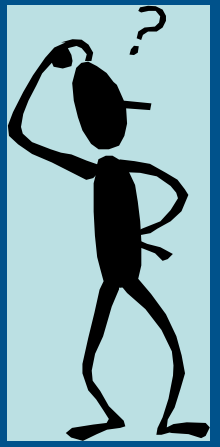
Lung cancer risks from smoking & asbestos exposure

Non-smokers	1 in 200
Non-smoking asbestos workers	1 in 100
Smokers	1 in 10
Smoking asbestos workers	1 in 5

Peto 1998

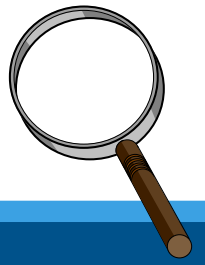
Research question must be clear

- Who are you interested in?
- What type of study will it be?
- Which exposures are you interested in?
- What exposure information do you have?



Questions?

Case-control study



Case-control study in general community

- Association between industry sector and risk
- Recall of specific exposures often poor
- Self reported exposure vulnerable to recall bias

Sources of exposure data in community-based studies

1. Personal interviews
2. Hospital records
3. Disease registry records
4. Death certificates
5. Census data

Expert exposure assessment

Doll & Hill Case-Control Study

		Lung Cancer	
		Case	Control
Smoker (Exposure)	Yes	688	650
	No	21	59
	Total	709	709

Odds ratio 2.97

Occupation, Job or Industry title

- Subject's job or industry title recorded from death certificate or company records
- Commonly used for cancer or mortality studies
- Crude surrogate for exposure
- E.g. Carpenters found to have elevated rates of nasal cancer etc. job used as surrogate for wood dust exposure

Job Exposure Matrices

- Cross-tabulation of Occupations and exposure(s) (may also have a time axis)
- May be for an industry, company or community-based
- Relatively low cost to construct
- Free from differential misclassification
- Suffer from non-differential misclassification
- Best for large studies >1,000 subjects
- Geographically dependent (?)

Data sources for developing JEMs

1. Industrial hygiene or health physics data
2. Process descriptions and flowcharts
3. Plant production records
4. Inspection and accident reports
5. Engineering controls and PPE info
6. Biological monitoring results

FINJEM

- FINJEM is a Job Exposure Matrix developed by the Finnish Institute of Occupational Health
- Excel database, provides proportions and mean level of exposure to workers to chemical agents in each occupation
- Based on Finnish Occupation Codes (Ocode)
- Applicability under Australian conditions has been previously reported (Benke et al, 2001)

FINJEM Laundry Workers

	%exposed/level		
	<1985	1985-1994	>1994
Aliphatic HCs	0	10/20	10/20
Aromatic HCs	0	10/20	10/20
Chlorinated HCs	40/20	25/20	25/20
Detergents	-	100/50	100/50
Textile Dust	6/0.2	6/0.2	6/0.2

Expert assessment

- Expert examines job title and/or industry then ra exposure(s) for agent of interest
- Expensive
- Panels usually used
- Experts normally occupational hygienists, engineers or physicians
- Used in industry or community-based studies
- Agreement good in industry studies, poor in community-based studies

Job Specific Modules and Expert assessment

- Job specific module (questionnaire) is elicited from subject then exposure assessed by expert, based on answers in module
- Expensive
- Highly sensitive for exposure probability
- Experts normally occupational hygienists
- Good for community-based case-control studies

Expert exposure assessment

- Experts examine individual job history
  – history needs careful collection
- Must be case-blind to avoid bias
- http://www.occideas.com/OccIDEASHome/index.jsp
- How expert are your experts?

Cohort study

- Cohort in specific industry
  - Mortality and cancer incidence in petroleum industry
  - Incidence of asthma in aluminium industry

Types of exposure data in industry studies

	Type of data	Approx. to dose
1.	Quantified personal measurements	Best
2.	Quantified area or job-specific data	↑
3.	Ordinally ranked job groups	
4.	Duration of employment in industry	↓
5.	Ever employed in the industry	Poorest

Quantified exposure for epidemiology

- Nested case-control study
  - Quantified benzene exposure and risk of leukaemia
  - Job history
  - Time on different activities
- Intensity (average daily ppm)
  - Highest or longest job
- Cumulative exposure (ppm-years)

Job-Exposure Matrix

Job	Fuel Oil	Vanadium	Carbon Monoxide (% of OEL)
Storeman	Low	No	10%
Foreman	Medium	Yes	30%
Furnace Attendant	High	Yes	90%
Cleaner	No	Yes	20%
Clerk	No	No	0%

Exposure matrix development

Matrix of exposure against time

- Include all subjects
- Group subjects
- Cover period of interest
- Need data for each cell

Completing missing cells

- Homogenous exposure groups
- Extrapolation and interpolation for missing periods
- Multipliers on known data
- Stepwise changes based on known data
- Recreation of historical process
- Statistical modeling

Healthwise study

- Cancer and respiratory disease in aluminium industry
- TEM: Site, Operating center, Dept.,Job title, Task
- 38 chemical exposures
- 2,700 tasks
- 12,000 subjects

Exposure to BaP

Worker 1

- 1955-1959 Labourer in Casting
- 1960-1964 Setter in Soderberg
- 1965-1974 Potman worked in the Soderberg
- 1975-1979 Potman worked in the Prebake
- 1980-1989 Crane Driver

Subject specific monitoring

- Monitoring data collected at the individual level that may be air, bio or health physics data
- May be single sample or continuous monitoring data i.e. radiation exposure by TLD
- Limited availability and seldom available for large studies
- Provides best approximation of biologically effective dose
- Expensive
- Can capture variability, within- between-worker and within- between-groups

Organochlorine Compounds

- Some evidence for endocrine disruption
- Subject knowledge about exposure usually poor
- Often incomplete data on environmental concentrations
- Persistent, lipophilic
- Long half life in body
- Good biological measures:
  - Breast milk lipid concentration good long term measure, but only available for restricted subgroup of population
  - Need to take into account maternal factors influencing levels, eg age, BMI, parity, lactation period
  - Measure in serum or adipose tissue, but invasive

Organochlorine Compounds 2

- Can measure in fat component of foods, such as meat
- Fingerprinting, such as using PCB congenors, can identify point sources
- Longitudinal population monitoring studies need epi input - appropriate sampling frame

Prostate cancer, BPH & occupational exposure

- 871 Cases and controls - community based
- Take brief job history
- Job specific modules to gather data on tasks and products
  - carpenter, driver, electrician, plumber, forestry worker, farmer, labourer, machinist, mechanic, miner, fisherman, painter, railway worker, welder
- Modules administered by CATI

Prostate cancer, BPH & occupational exposure

- 24 exposures of *a priori* interest
- 12,775 Job lines, average 14 jobs per person
- Each job rated possible, probable or no exposure
- Each exposure rated high, medium or low
- Half a million decisions

Farmer module: Prostate study

- *PU7. I'm now going to ask about your pesticide use. Please say yes if you did this yourself, but say no if someone else did it for you, whether that person was a family member, someone who lived on the farm, or was hired from off the farm. (READ ITALICS TO GF ONLY)*
- *a. Did you apply herbicides or weed killers?*
  - YES, NO. DK
- *b. Did you mix or load any herbicides or weed killers?*
  - YES, NO,DK
- IF PU7a = YES or PU7b = YES, ASK PU7c. ELSE, GO TO PU8
- *c. On how many weeks of the year did you mix or apply herbicides or weed killers?*
- *And, on average, how many hours on one of those weeks?*

Expert exposure assessment

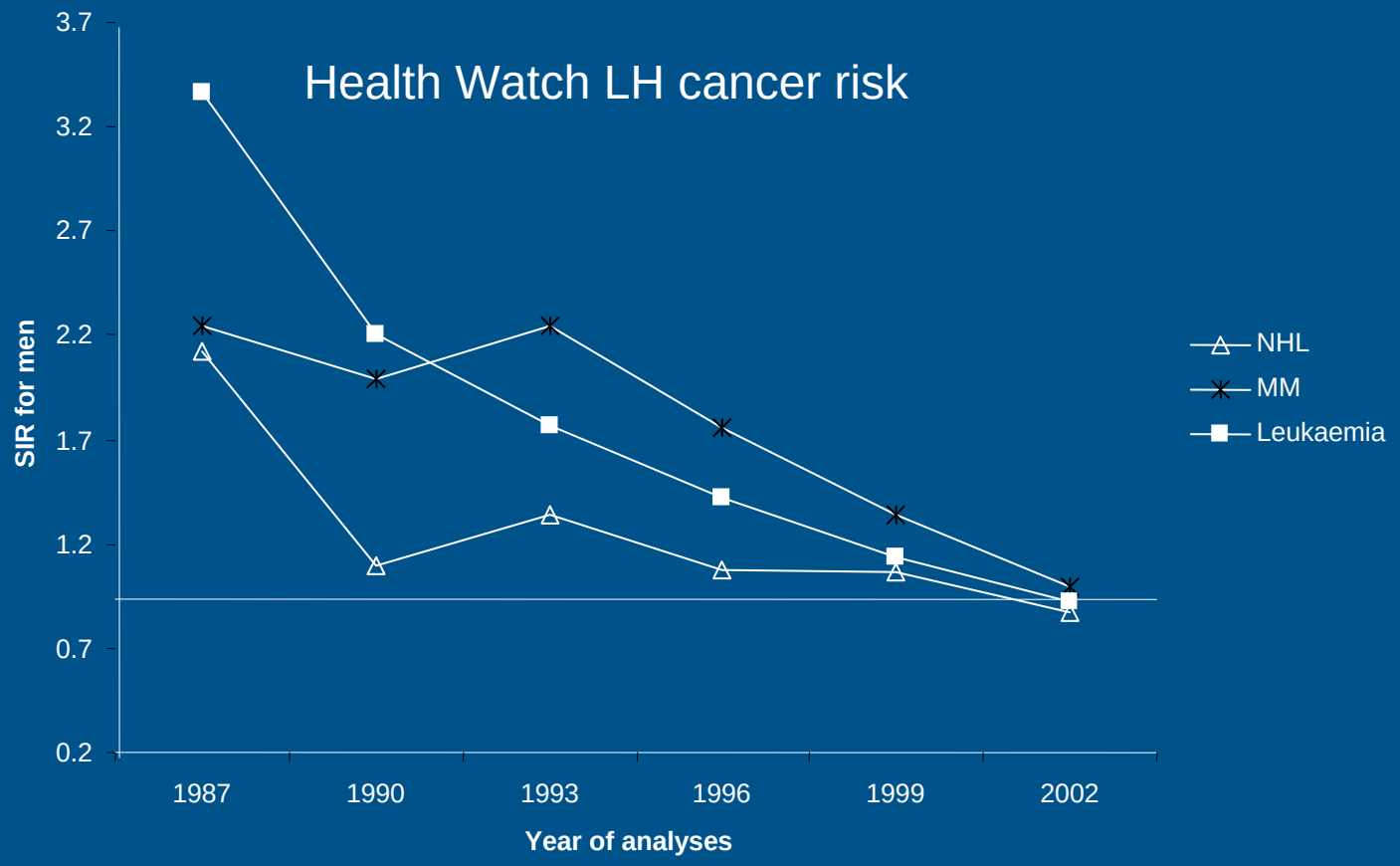
- Most exposures rated “None”
- Very tedious and time consuming to do
- Hard to be systematic and repeatable
- Hard to be an expert in everything
- Exposure to toxic metals
  - risk of BPH (OR= 1.39, 1.10 - 1.84)
  - risk of prostate cancer (OR=1.25, 0.96 - 1.61).
- Non-significant excess risks were observed for a oils and OPs

Health Watch Cohort

Prospective cohort study of mortality and cancer incidence in Australian petroleum industry employees

- Set up 1981
- Funded by Australian Institute of Petroleum
- Large companies not small independents
- 95% of blue collar employees except small sites
- >5 years in industry
- 4 health surveys including smoking and job histories
- 16,252 men and 1,273 women
- Excess of Lympho-haematopoetic (LH) cancer

Timing of the risk estimate

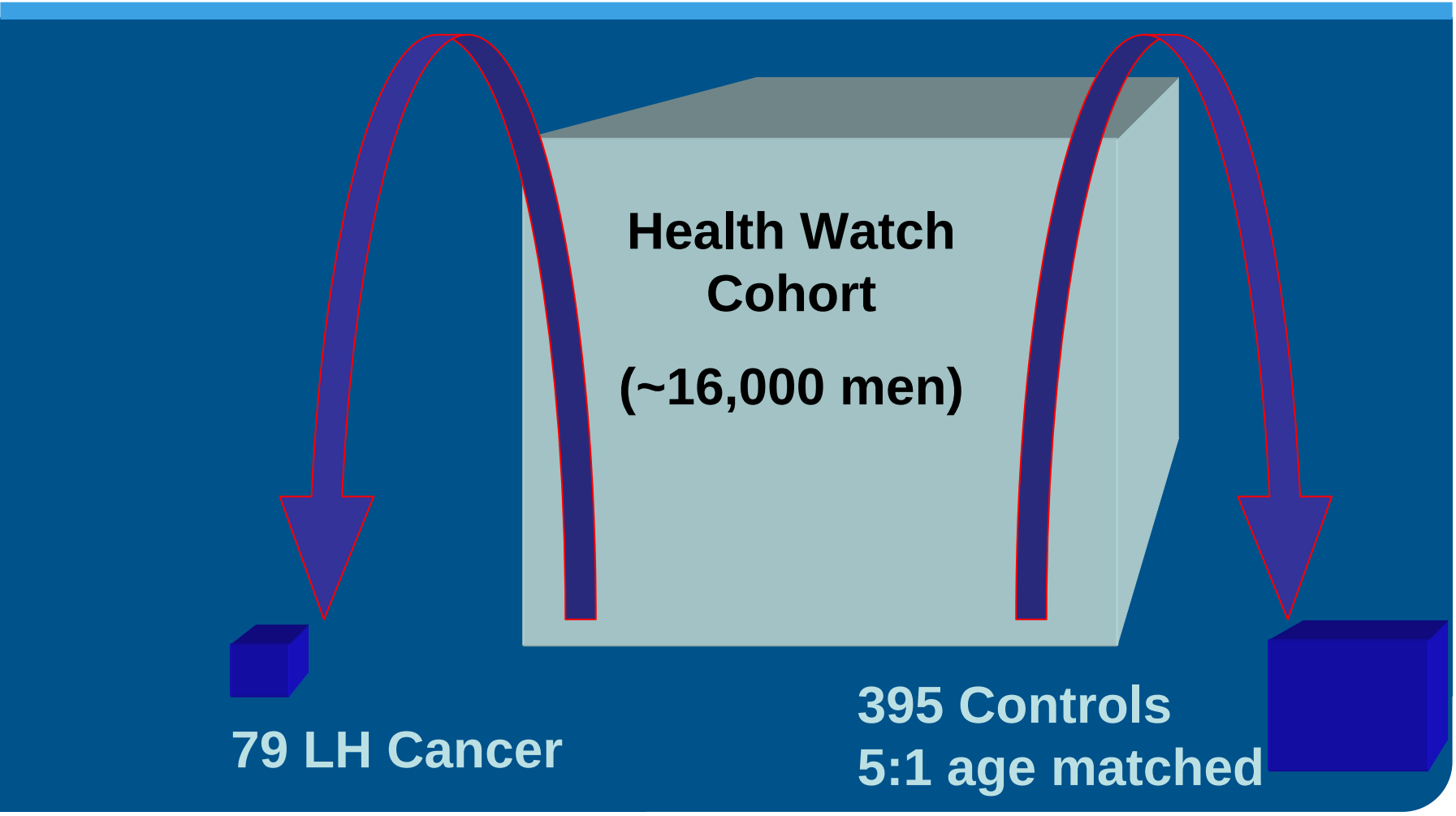


Case Control Hypothesis & Questions

LH cancers are not associated with benzene exposure

- Is benzene exposure associated with increases in:
  - Leukaemia & sub-types?
  - Non Hodgkin Lymphoma (NHL)?
  - Multiple Myeloma (MM)?
- Is there a latent period?
- Does exposure rate (peaks) matter?

Nested Case-Control Study



Quantitative Benzene Exposure Assessment

- **Detailed job histories from cohort records**
  - Interview
  - Company records
- **Contemporary colleague**
  - Structured case-blind interview
    - > tasks
    - > products
    - > technology
- **Site history**

Benzene Exposure Model

- **Exposure Measurements**
  - Company & supplementary data

    → Base Estimates for tasks (ppm)
- **Exposure Modifiers**
  - eg technology factors
- **Exposure Estimates**
  - work history + algorithm

    → individual exposure estimates (ppm-years & ppm)

Exposure Estimation 1

Task Estimate

$$TE_i = K_i \times BE_i$$

TE_i = Exposure for the ith task (ppm)

BE_i = Base Estimate (measured data) of ith task

K_i = Ratio of the variables for ith task exposure and variables associated with the BE

Exposure Estimation 2

Activity Estimate

$$AE_j = \text{Sum} (TE_i \times H_i / A_j)$$

AE_j = Exposure for Activity j (ppm)

TE_i = Task Estimate for task i

H_i = Hours per week on task i

A_j = Hours per week of activity j

Time weighted average (TWA)

Exposure Estimation 3- Intensity

Job Exposure

$$JE_k = SUM (AE_j \times H_j/35)$$

JE_k = Exposure to benzene during each job

AE_j = Exposure for Activity j (ppm)

H_j = Hours per week on Activity j

Exposure Estimation 4-Cumulative

Total Exposure

$$CE = SUM (JE_k \times Y_k)$$

CE = Total cumulative exposure to benzene

JE_k = Exposure during job k

Y_k = Years spent on job k

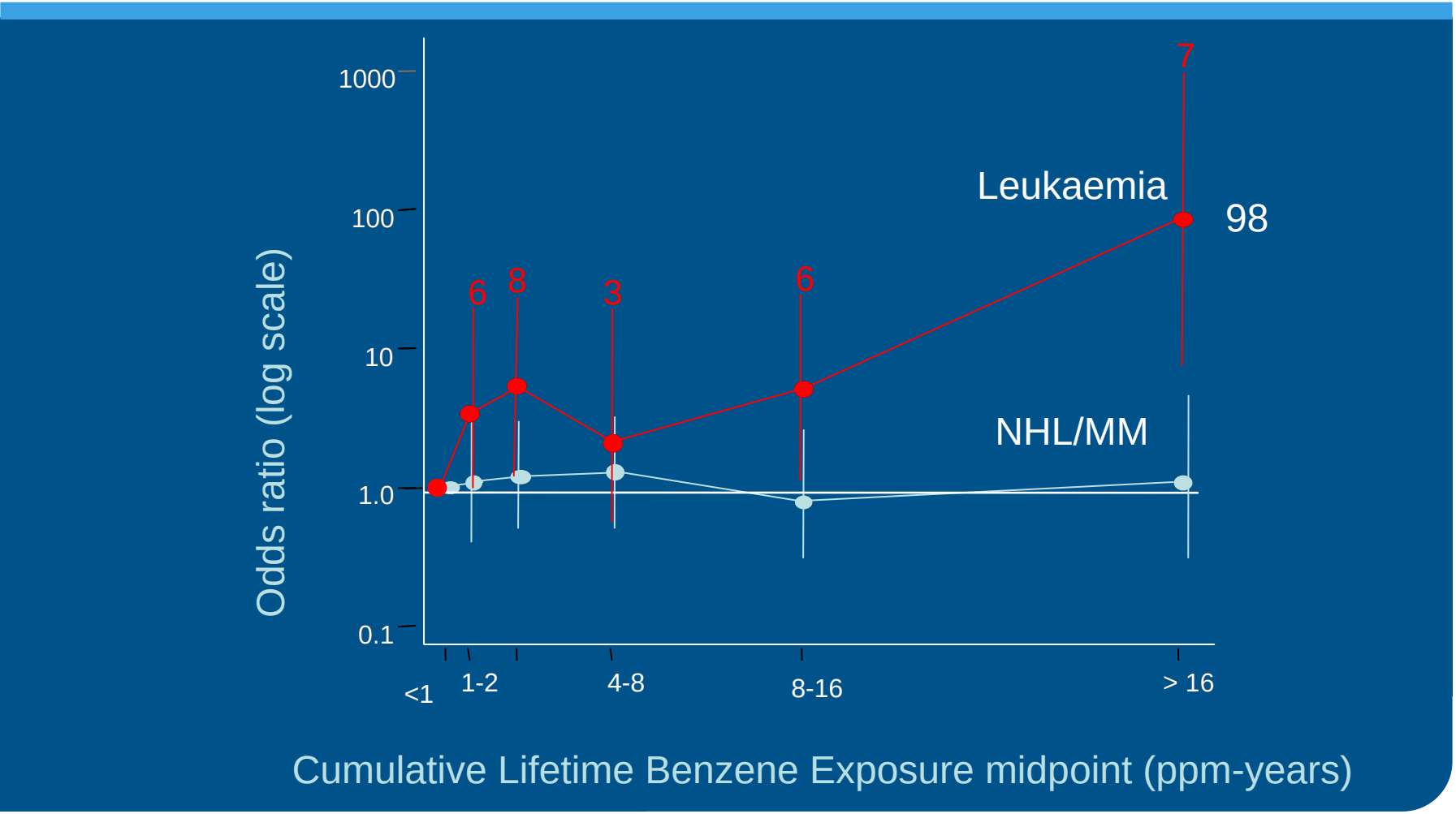
Base Estimates

- 54 BEs, 49 used in study
- 36 based on local data
  - Based on measured personal exposure to benzene
  - Data from Australian petroleum industry OHs
  - Data from Australian sites
  - More than 3870 data points
  - Identified task/job
  - Routine exposure
  - Used AM of data

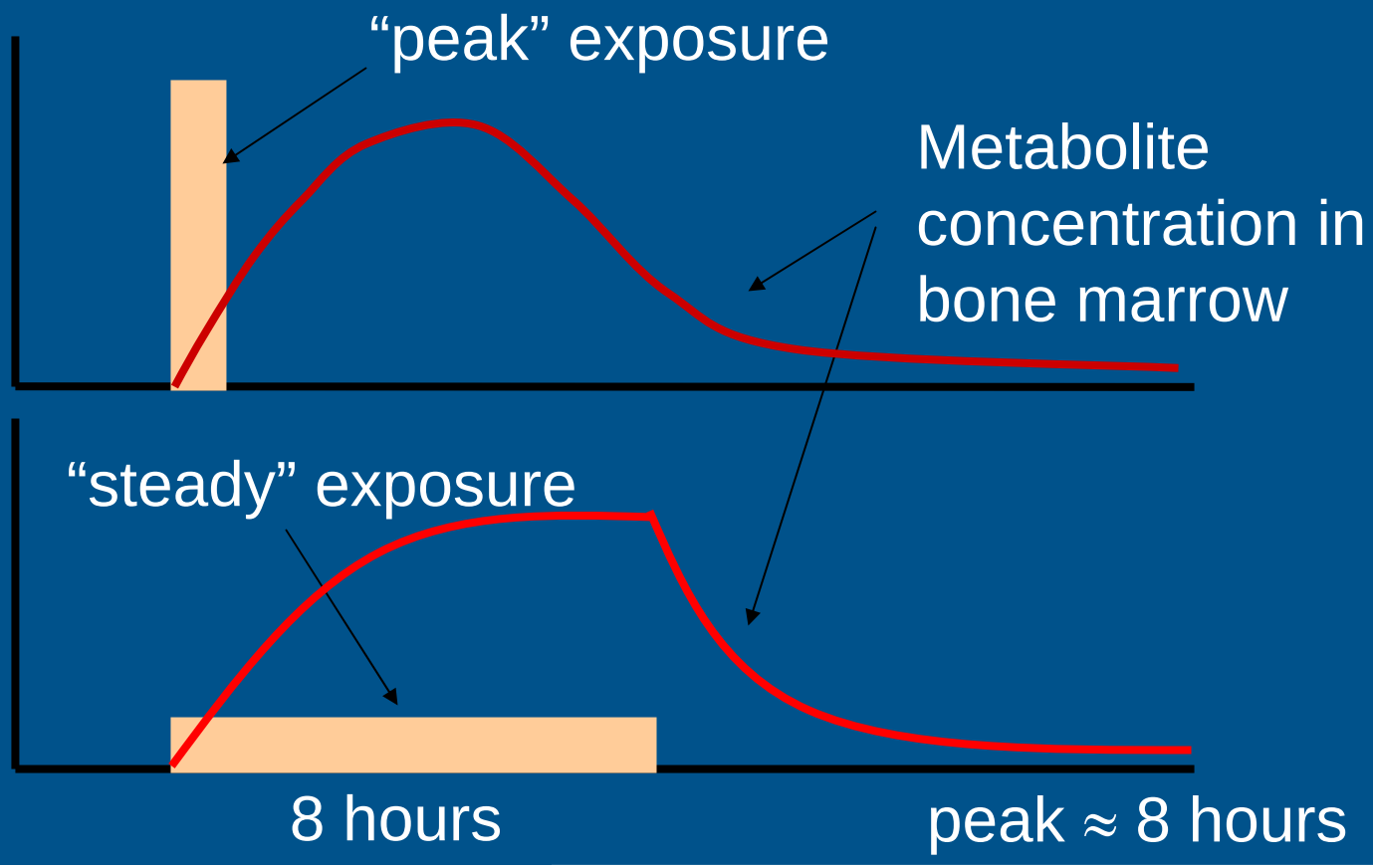
Results of Case Control Study

- 63% controls & 47% cases started employment after 1965
- Average duration 20 years (range 4-42)
- Average exposure 4.9 ppm-years (range 0.005-57.3 ppm-years)

LH cancer risk and benzene exposure



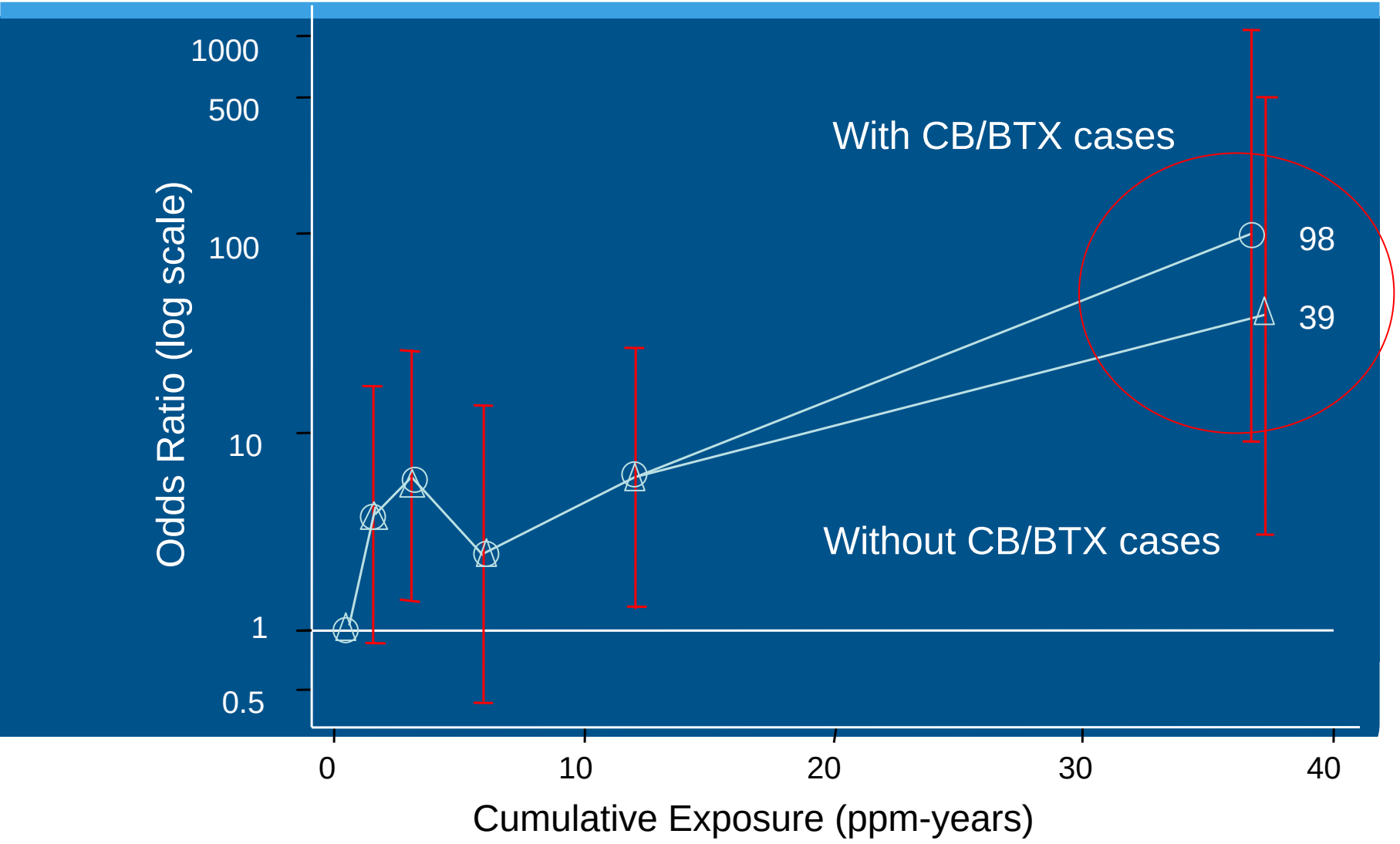
Metabolism smoothes the peaks



Benzene or BTX Exposure

- 12 subjects exposed to concentrated benzene (CB) or benzene/toluene/xylene (BTX-70% benzene)
- No NHL or MM
- 5 developed leukaemia (2 expected)
- 5 of 12 were exposed >32 ppm-years
- 4 of these developed leukaemia

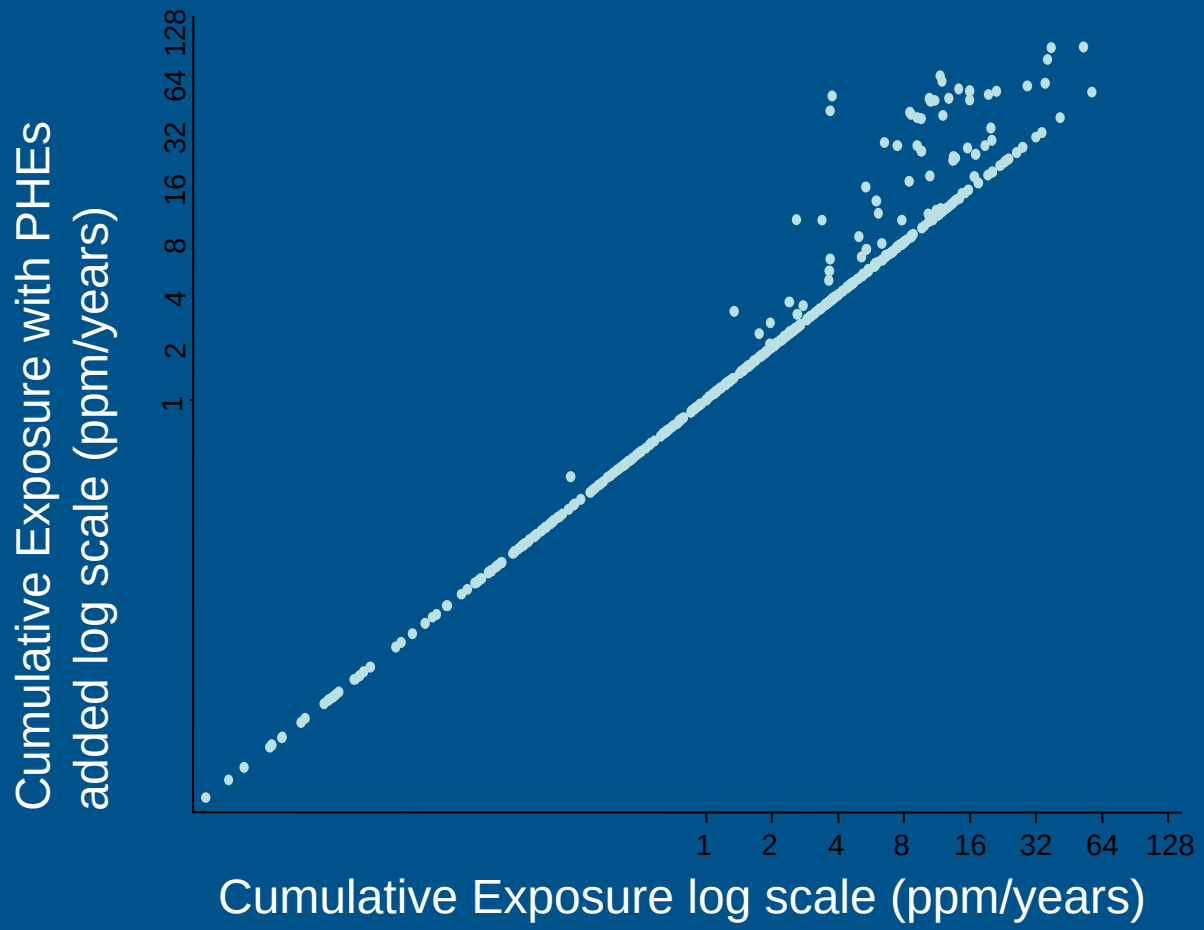
Evidence for peaks



Uncaptured exposure?

- Infrequent potentially high exposures
- Too rare to be included in Base Estimates
  - tanker spillages
  - drum double fills
  - drum fillers splashing overalls
- Possible historic exposures
  - floor mopping
  - washing overalls
  - hand washing

Adding possible high exposures



Odds ratios reduced

Benzene exposure (ppm-years)	Number of cases	Cumulative exposure and PHEs OR (95% CI)
≤2	9	1.0
>2-4	8	3.1 (1.0 - 9.3)
>4-8	3	1.2 (0.3 - 5.2)
>8-16	6	2.7 (0.7 - 10.1)
>16	7	7.8 (2.3 - 25.9)

Do workers differ?

Between and Within Worker Variance (ANOVA)

- In half of data sets individuals' means were significantly different
- Little variability between workers for some tasks

BUT

For most BWV < WWV

Future directions

- Greater use of exposure data in epidemiology:
  - Hazard identification
  - Dose-response
- Need to develop better biomarkers and other objective measures of exposure
- Better understanding of kinetics
- Greater ability to measure at lower levels of exposure
  - Fewer non-detects
  - Undertake studies at exposure levels proposed for standards

Future directions 2

- Identification of susceptible subgroups will reduce size of required populations - genetic developments
- Interaction between environmental exposures and lifestyle factors, medications etc
- Specimen banks in large cohort studies are potentially useful sources of samples which can be used to measure exposure

Acknowledgements

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- Epidemiology Supercourse: http://www.pitt.edu/~super1/