



# Benzene:

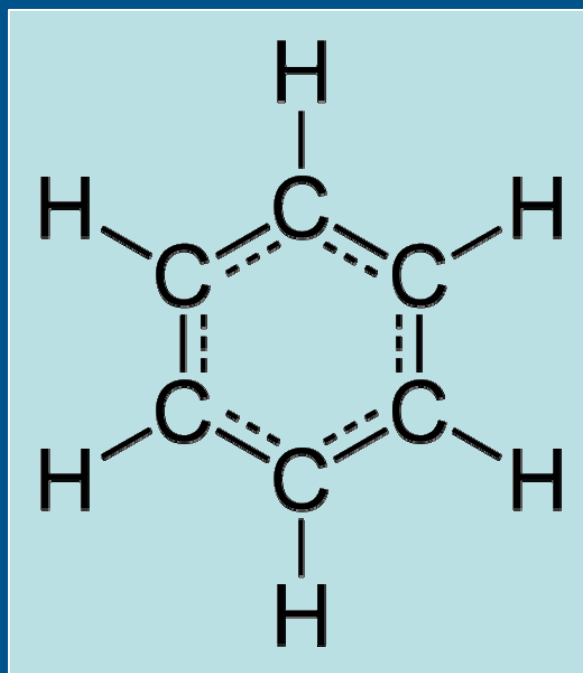
## Exploring Exposures, Epidemiology and Health Outcomes

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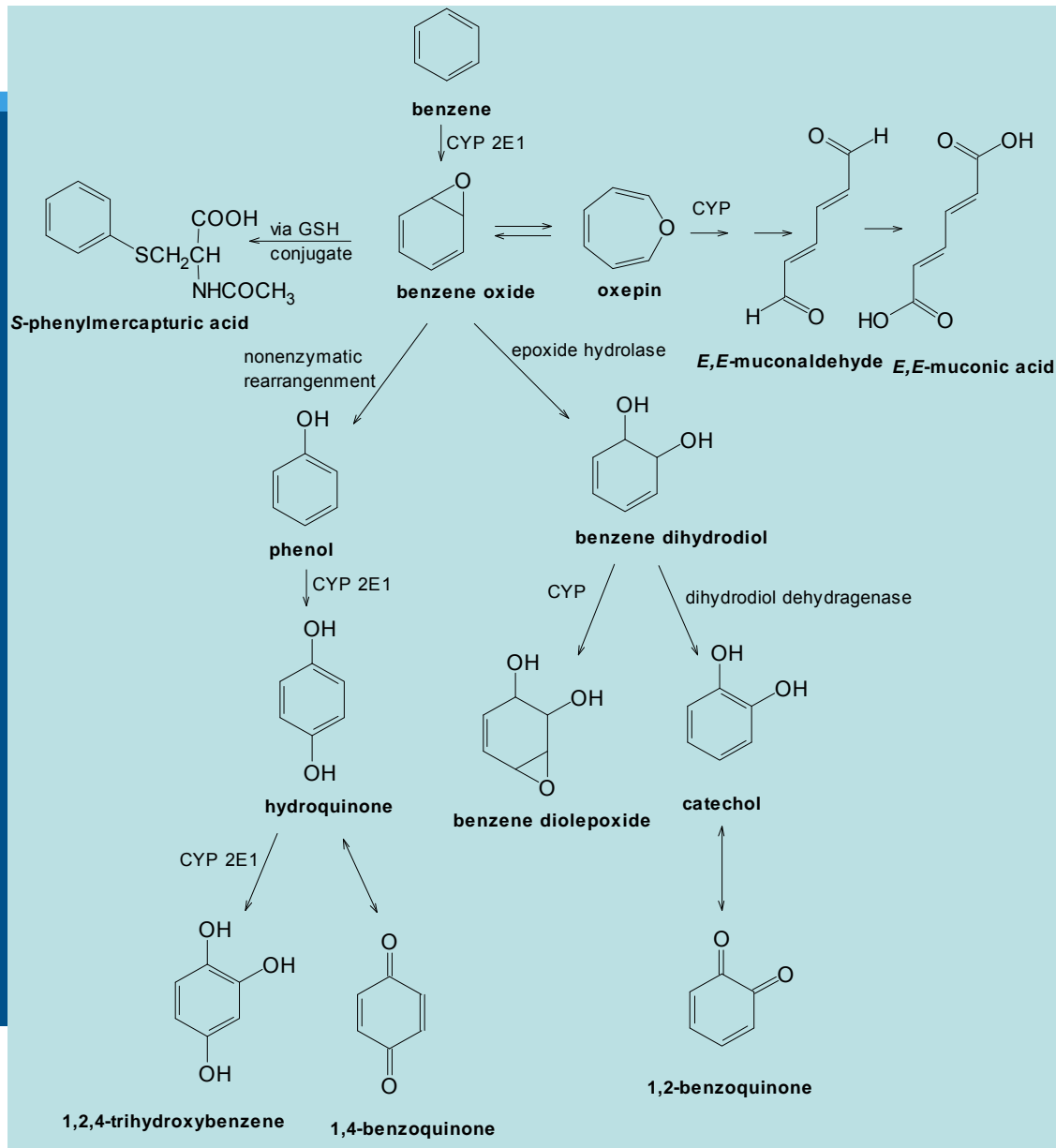


Exposure to benzene  
increases risk of  
leukemia

# Benzene



# Benzene metabolites increase risk of leukemia

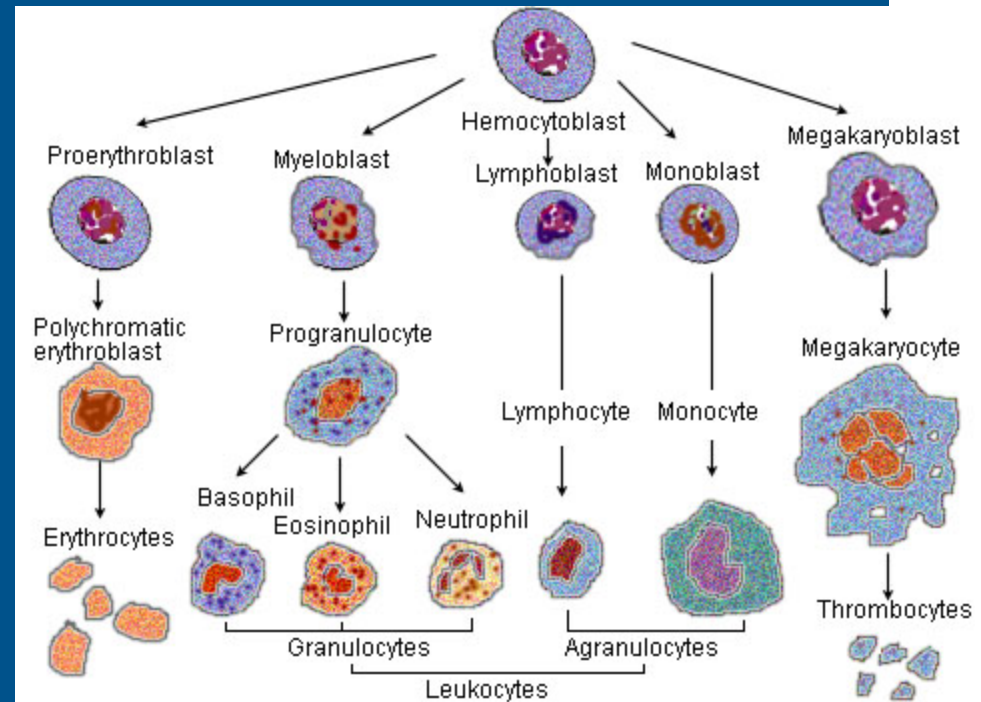


## Simplified Benzene Metabolism

Slide courtesy  
Stephen Rappaport

# Leukemia - not a single disease

- Group of diseases
  - Acute vs Chronic
  - Myeloid vs Lymphoid
  - AML, ALL, CML, CLL
- Categories change
  - 8<sup>th</sup> Rev, ICD coded CLL
  - FAB/REAL
  - WHO



# Which cancers are associated with benzene?

- AML (or acute non-lymphocytic) good evidence
  - preleukemia or myelodysplasias (MDS)
- CLL growing evidence
- Other leukemias? (CML, ALL, HCL)
  
- Multiple Myeloma & Non-Hodgkin Lymphoma



# Measuring exposure to benzene

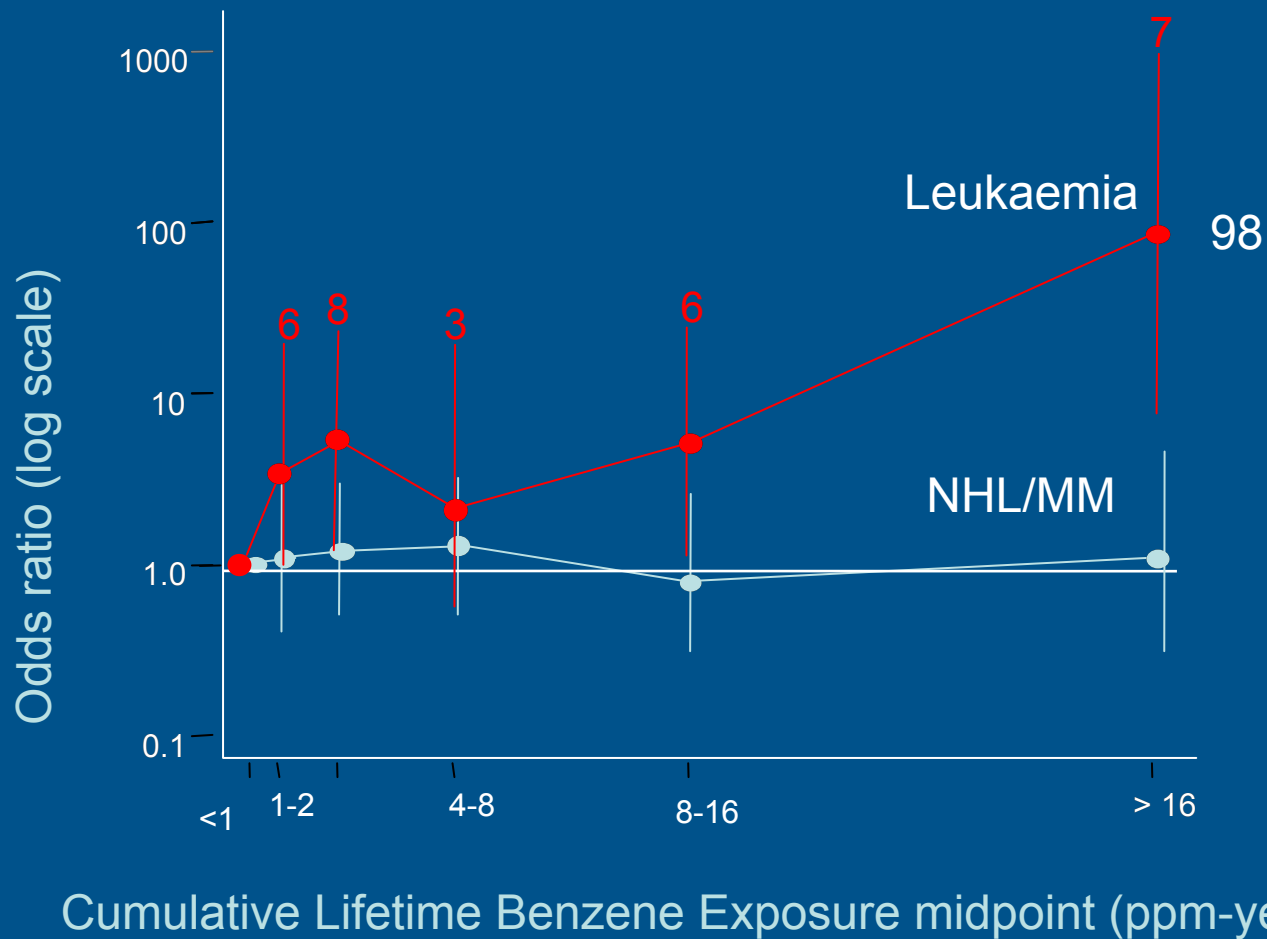
- Now: 8 hour TWA personal monitoring
  - Precise analysis
  - Repeated samples
- Then: Colorimetric tubes
  - Imprecise
  - Spot measurements
  - Often mixed exposures



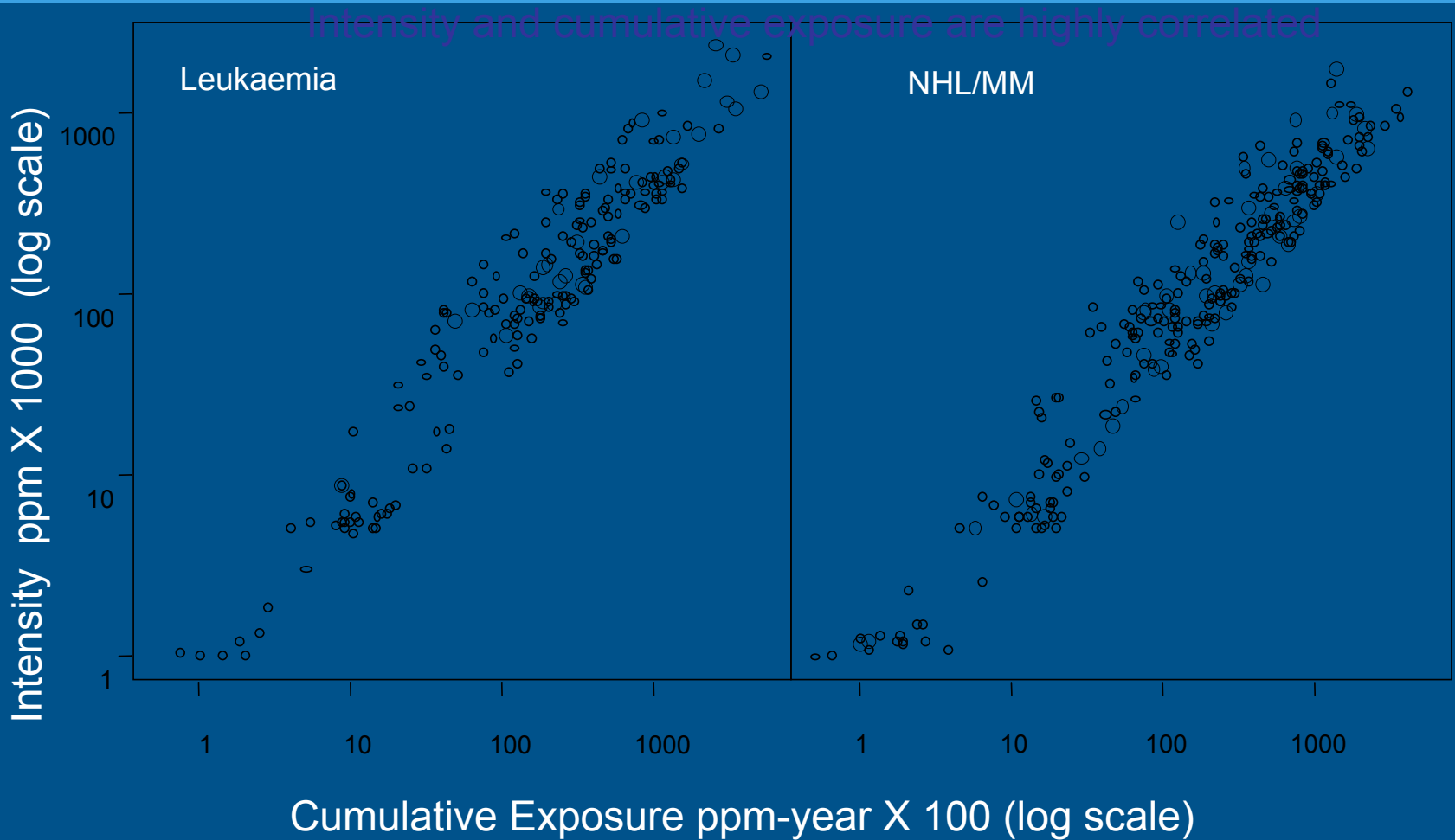
# Expressing exposure for epidemiology

- Usual metrics
  - Exposure yes/no
  - Duration (years)
  - Intensity (average daily ppm)
    - > Highest or longest job
  - Cumulative exposure (ppm-years)

# LH cancer risk and benzene exposure



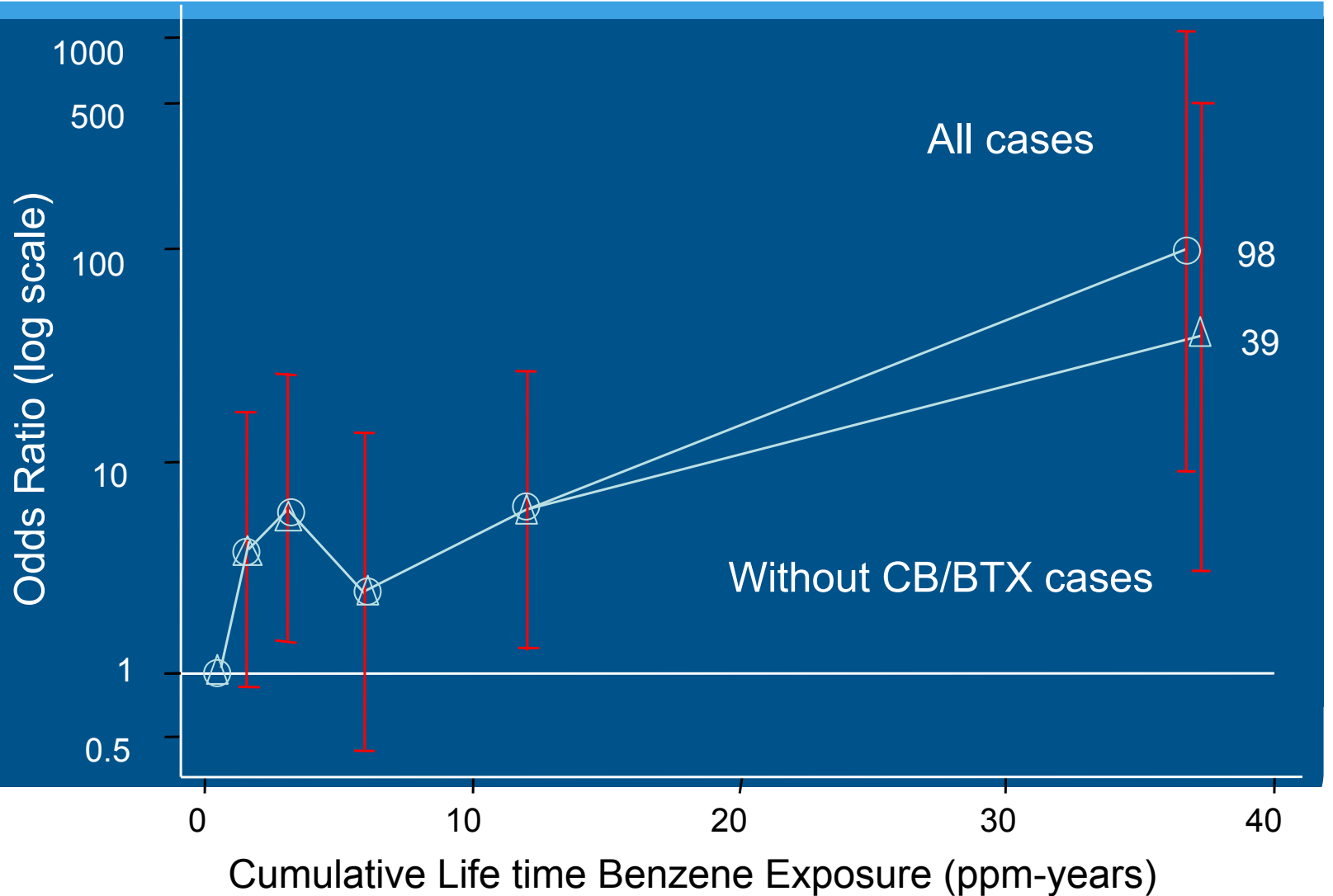
# Cumulative Exposure vs Intensity



# Other metrics

- Peak Exposure
  - Frequency
  - Height
  - Height above “normal”
- Intermittency
- Latency

# Health Watch case-control study



# Risk estimation and the Pliofilm study

1,165 men exposed to benzene 1940s USA

**Cumulative Benzene  
Exposure**

<b>ppm-years</b>	<b>SMR</b>
<30.99	1.1
40-199.9	3.2
200-399.99	11.9
>400	66.4

Rinsky et al 1987

# Accuracy of exposure estimates and models

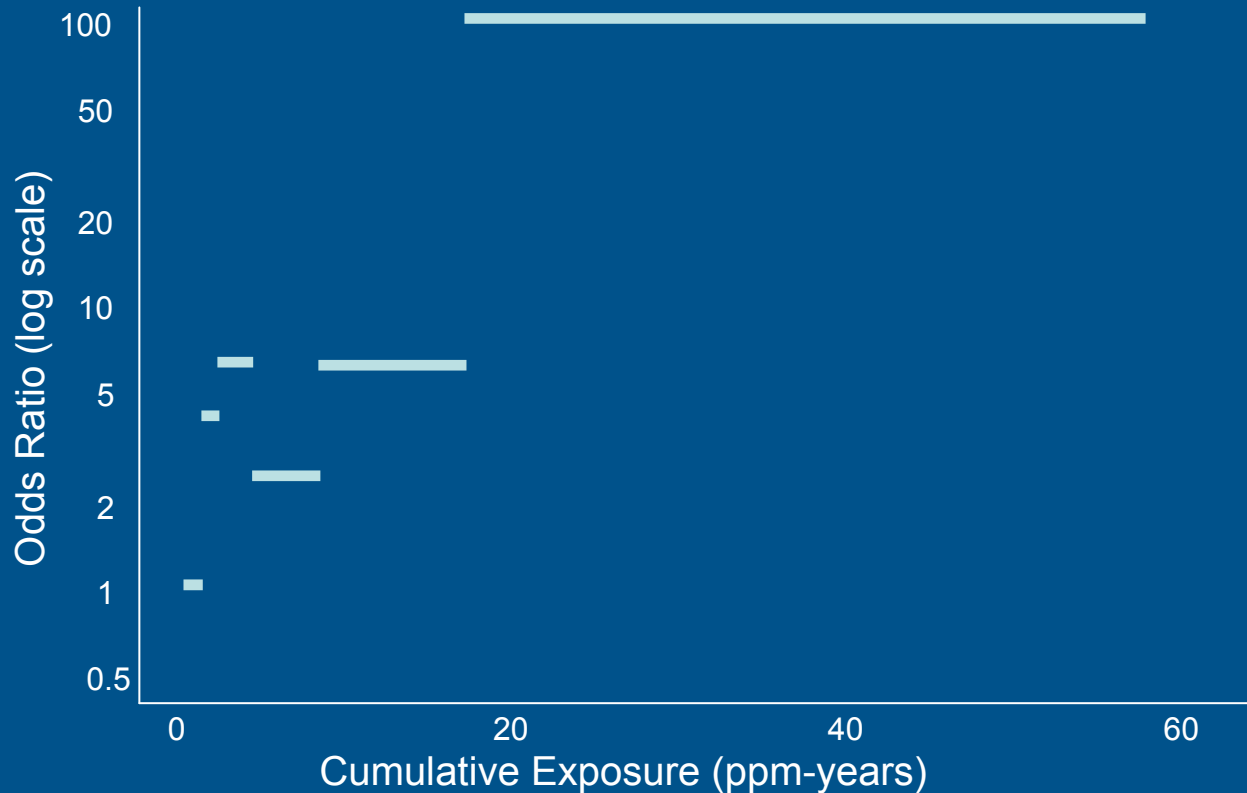
<b>Exposure assumptions</b>	<b>Additional lifetime leukemia deaths per 1000 workers at 45 ppm-years (95% CI)</b>
Rinsky	5.1 (0.8 - 11.7)
Crump and Allen 1	0.5 (0.1 – 1.0)
Crump and Allen 2	1.3 (0.3 - 2.3)

Brett et al (1989)

# Grouping people by exposure

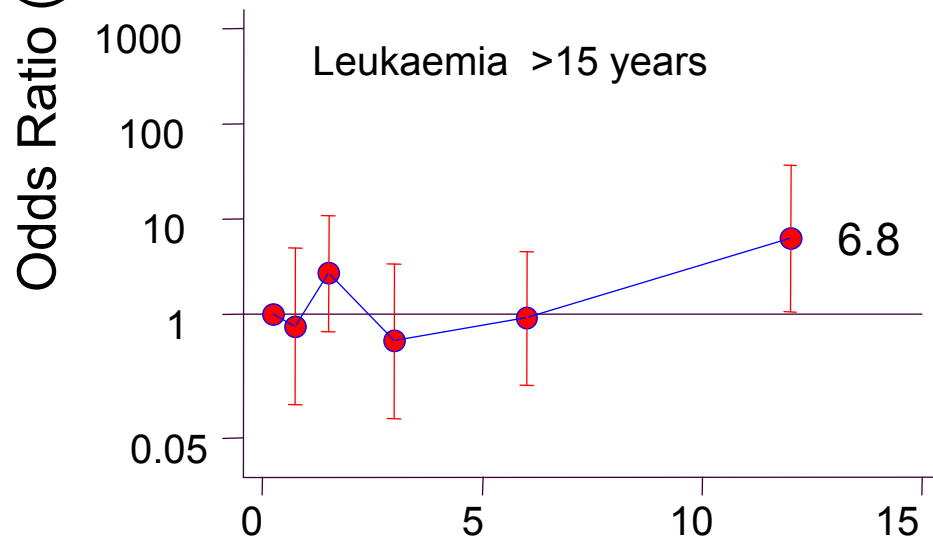
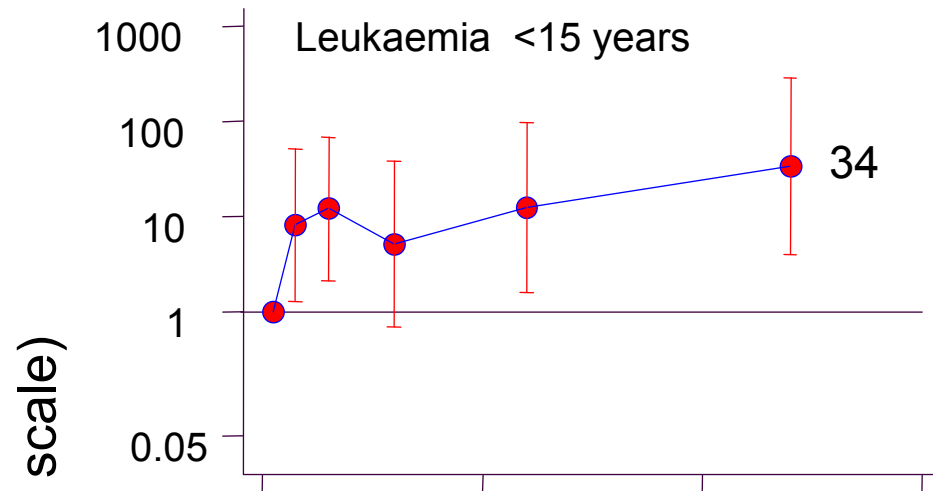
Exposure Grouping	Exposure (ppm-years)	Odds Ratio (95% CI)
As for UK	> 4.8	2.5 (1.1 - 5.7)
As for Canadian	> 8	11.3 (2.8 - 45.1)
Highest group	> 16	98.2 (8.8 - 1090)

# Benzene exposure groups



Horizontal bars indicate the range of exposure in each group

# Leukaemia Latency

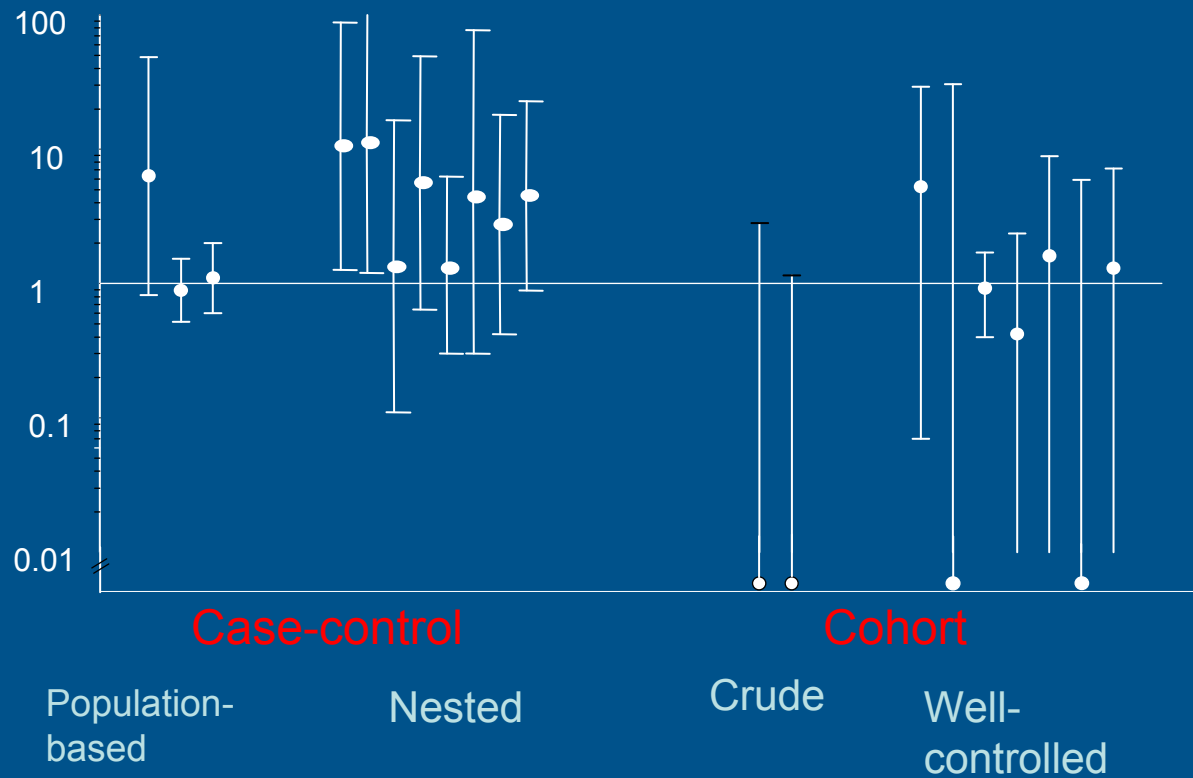


Cumulative Exposure (ppm-years)

# Putting the evidence together

- Epidemiology assesses risk for a group.  
Can it be applied to other groups?
- Risk estimates from single studies wobbly
- Pooled data or meta-analyses needed for conclusions about causation

# CLL results by study design



Schnatter et al 2005

# Population risk vs individual risk

- Attribution at a population level
  - Benzene exposure increases the incidence of leukemia
- Attribution for an individual
  - Benzene exposure caused leukemia in this person

# Are benzene-induced leukemias different?

- Biomarkers of exposure
  - benzene metabolites in urine
  - protein adducts
- Chromosomal damage
  - reported in chromosomes 1-22 and X
  - loss part or all of 5, 6, 7, 10
  - trisomy 8, 9, 17, 18, 22
  - translocation 21;22
- Disease progression different?

# Is there a threshold?

- For an individual or a population?
- Effects seen after <1ppm for short period
  - Reduced blood cell production
  - Genetic damage
  - Neurophysiological effects?
- Control banding vs measured exposure limit

# What we still need to know:

- Which diseases?
- Which exposure metric?
- Exposure-risk relationship at low exposures?
- Effect of genotype?
- Can benzene-induced leukemias identified?

Careful exposure assessment MATTERS

# The evolution of understanding

Crude exposure data →

Benzene exposure and AML risk associated

Better exposure measurement →

Quantitative risk estimates for leuk sub-types

Paired exposure/outcome data →

Better understanding of mechanisms

Pharmacokinetic data →

Better choice of metric for epidemiology

Better metric and precise exposure estimates →

Better risk estimates, less misclassification



# Summary

Exposure to benzene increases risk of leukemia

Yes

(but we still know so little)

Please send more money for research!