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# Recent Benzene Science: Potential Implications

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# Benzene

- Ubiquitous substance. Human carcinogen. Risk Assessment bellwether

- Often assumed to have no safe level by regulatory authorities
  - Lacks a reliable animal model for cancer effects...human studies important
  - Cancer mechanism not known...complex metabolism
  - Genotoxic, but does not bind DNA well
  - Practical, rather than science-based thresholds

- Often a driver for
  - Product formulations (e.g. Mogas benzene concentration)
  - Clean up targets
  - Workplace exposure (OELs)
  - Environmental emissions (AQLVs and EQSs)
  - MSDS labels, carcinogen classification
  - Exposure scenarios for products under REACH

# Science on Benzene Toxicity

- Science on health effects has evolved over time and is still evolving

*blood effects* → *cancer* → *cancer subtypes* → *clinical markers*

1950 1970 1990 2010

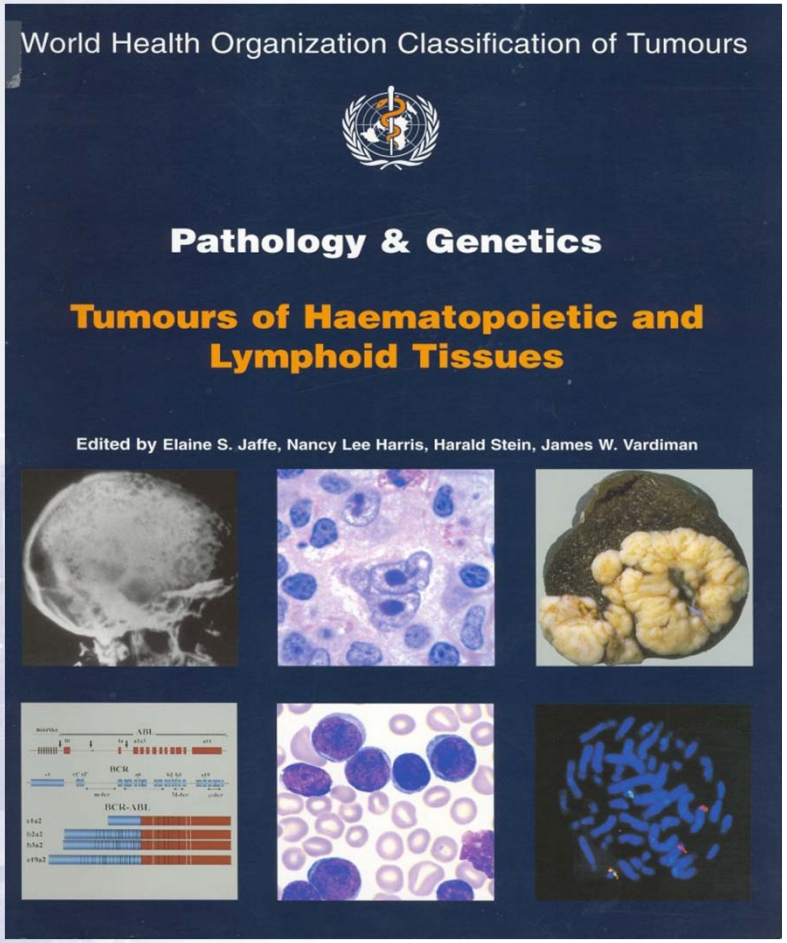
*case reports* → *standard tox/epi* → *mechanistic tox/molecular epid* → *multi-disciplinary*

- Industry has actively funded benzene research since the mid 1980s
  - Satisfies industry's product stewardship obligations
  - Helps ensure regulatory actions are science-based
  - Enhances likelihood of a "seat at the table"

# Recent Past Decisions

| Topic | Activity | Funding | Consequences | Impact |
|---|---|---|---|---|
| OEL | Criteria Document and impact assessment<br>Case-control epidemiology studies<br>Pliofilm Study Reassessment | CONCAWE / CEFIC<br>IP / EI<br>API | EU OEL agreed at 1ppm (0.1 ppm proposal)<br>ACGIH 0.5 ppm (0.1 ppm proposal) | **Moderate** |
| AQLV | AQ Criteria Document → catalysed EU expert review of WHO recommendations<br>Industry observer | CONCAWE / CEFIC / EUROPIA | AQLV of 5ug/m3 (1ug/m3 proposal)<br>Current mogas Bz limits re-affirmed. | **High** |
| EU Risk Assessment Report (RAR) | Risk characterisation under existing substances → inform basis for EU document and dialogue with rapporteur | CONCAWE / CEFIC / EUROPIA | AML is the leukemia subtype linked to exposure.<br>Children at no greater risk of cancer than adults | **High** |
| IARC Volume 100 Review | Review of recent benzene science (EU RAR)<br>NHL meta-analysis<br>Industry observer | ECETOC / CONCAWE / ACC | AML causally linked to exposure.<br>Other LH cancers will be re-reviewed | **High** |

# Lymphohematopoietic (LH) Cancer: Paradigm Shift Recently Occurred




**Traditional Paradigm: Anatomy**

LEUKAEMIAS (CA in peripheral blood)

LYMPHOMAS (CA in lymph system)

**New Paradigm: Cell of Origin**

MYELOID tumours

*Myeloproliferative Disease (MPD)*

*Myelodysplastic Syndrome (MDS)*

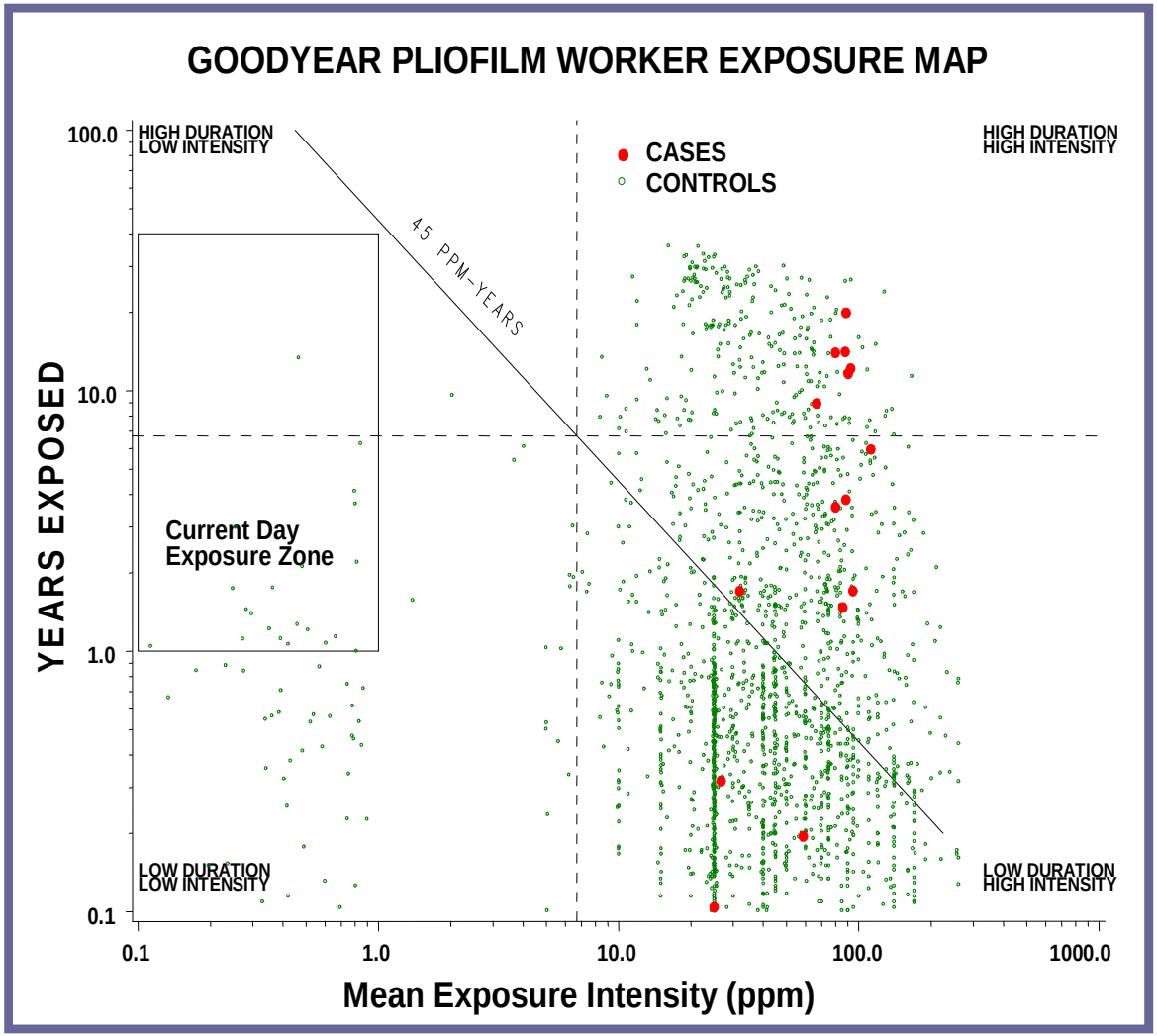
*Acute Myeloid Leukaemias (AML)*

LYMPHOID tumours

B-cells
T-cells
> (leukemias and lymphomas)

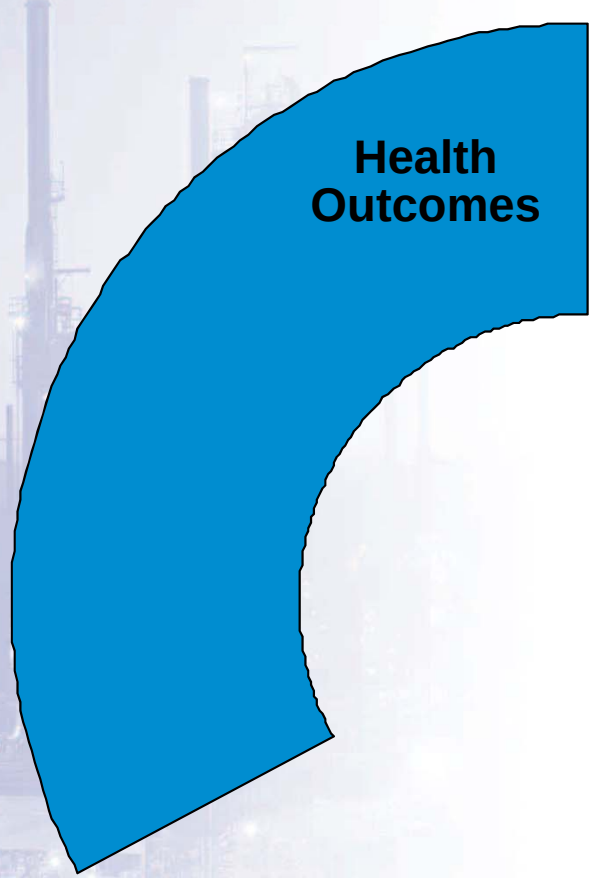
New paradigm: biologically justified → affects new benzene science → will affect future benzene regulations

# Basis for Benzene Health Standards




- Most BZ risk assessments based on Pliofilm study
  - Relatively small study
  - **All** leukemia subtypes
  - Little empirical data on lower (<10 ppm) exposures)
  - Industry funded exposure assessment, analysis
- Predicted risk of leukemia from linear model default:
  - 1 x $10^{-6}$ risk ~ .04 ppb over a lifetime . . . below ambient concentrations

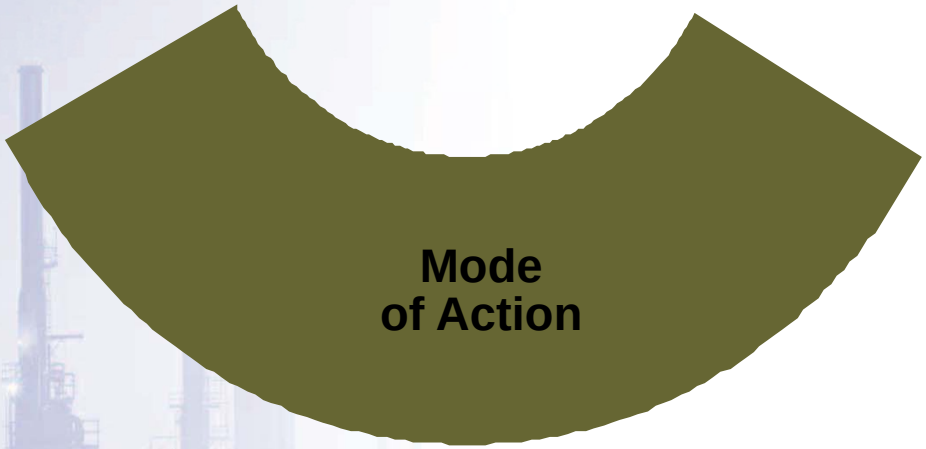
# Risk Assessment Leaves Questions




## Which LH cancer subtypes are related to benzene (hazard)

- Pliofilm study suggests AML, but,
  - Cancer classification from death certificates
  - New WHO paradigm not in effect
  - No information on MDS (myeloid)
- NCI study → non-Hodgkin lymphoma (NHL)
  - A prevalent lymphoid tumour
- Plethora of less well-designed studies raise issues on other tumour types
  - Some meta-analyses of literature

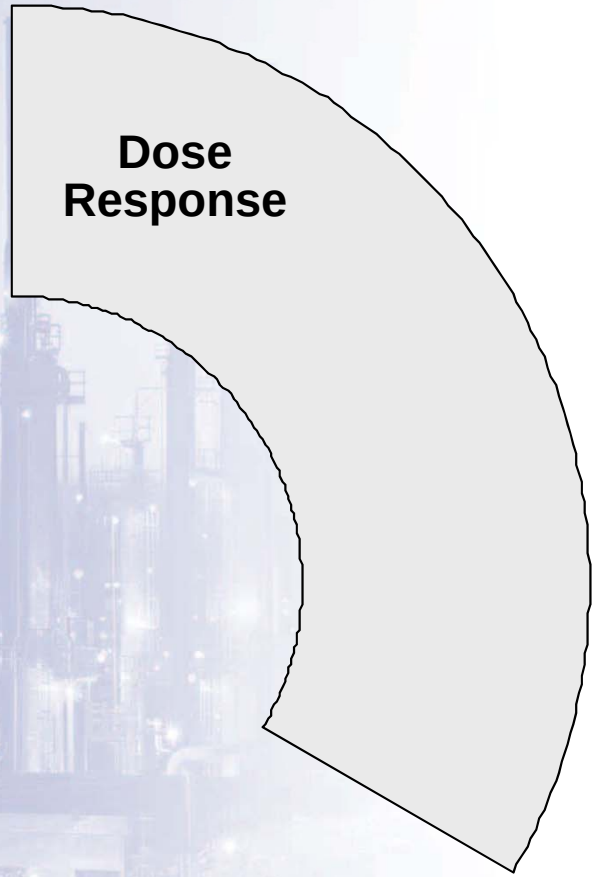
# Risk Assessment Leaves Questions




Mode of action: How does benzene produce effects? (threshold-based?)

- Pliofilm study → no information on MOA
- How BZ might produce AML has been a topic for decades, with no consensus
  - Must be metabolized, but not a classic (point-mutation) carcinogen
  - Several hypotheses:
    - + Parallels to chemotherapeutic drugs (chromosomes 5 and 7)
    - + Role of blood cell count reductions, bone marrow changes?
    - + Enzyme that winds, unwinds DNA
- No consensus → no threshold → stringent standards

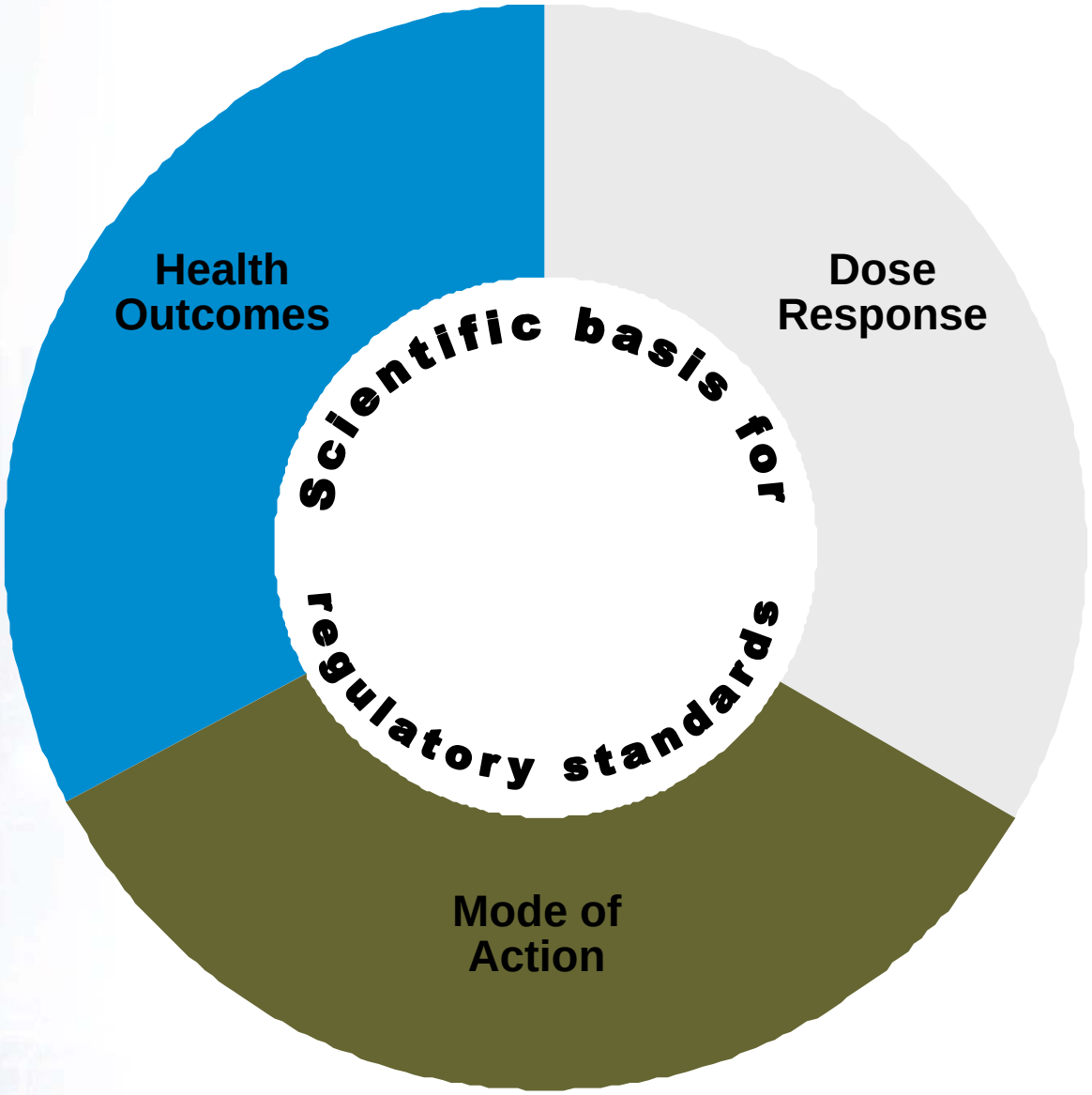
# Risk Assessment Leaves Questions




## What is the dose response at lower concentrations?

- Pliofilm study suggests sub-linear dose response for AML, but “no threshold” policies temper regulatory interpretations
- Many less well-designed studies suggest higher (and lower!) risk for low-level exposure
- Studies on lower benzene exposure levels could provide less extrapolation, stronger basis for standards

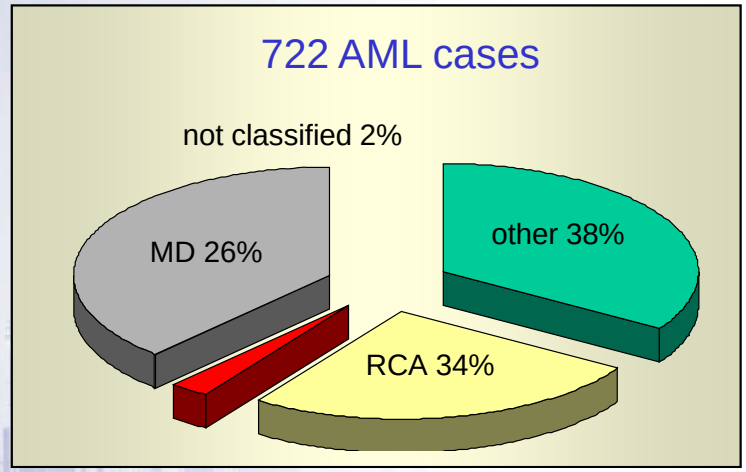
# Benzene Science and Regulatory Standards



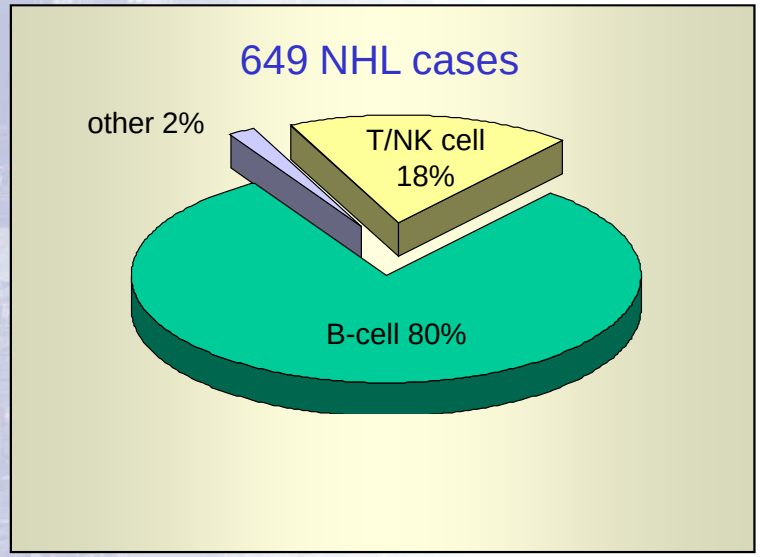
# Open Questions for Benzene Risk Assessment

| | Shanghai Study | Pooled Analysis | NHL Meta Analysis | Pliofilm URE |
|---|---|---|---|---|
| Which leukemia/LH cancer subtypes are associated with benzene? | ✓ | ✓ | ✓ | |
| How does benzene act to produce leukemia, other diseases? | ✓ | | | |
| What is dose response at lower concentrations? | | ✓ | | ✓ |

# SHS Case Control Results



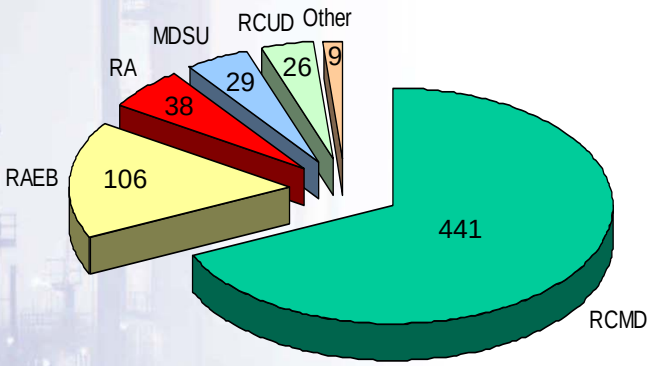

- Benzene resulted in significant 1.43-fold risk for all AMLs
- No association seen for chromosomes 5 and/or 7 AML subtypes
  - Argues against parallels to cancer chemotherepeutic agents
- Significant AML risk validates study design, but risk was smaller than expected




- Total NHL not related to benzene
  - Most subtypes also showed no link to benzene
  - Insecticide/herbicides, sewing/cutting workers showed excess risk

# SHS Case Control Results (cont'd)

MDS cases: 649




Selected 29 cases more highly exposed to benzene (>21 ppm)

Compared to other MDS cases, the benzene-exposed cases showed fewer chromosome changes and more bone marrow inflammation. Cell changes suggest an autoimmune MOA

## What do SHS results mean?

Which health effects: MDS, AML….not NHL

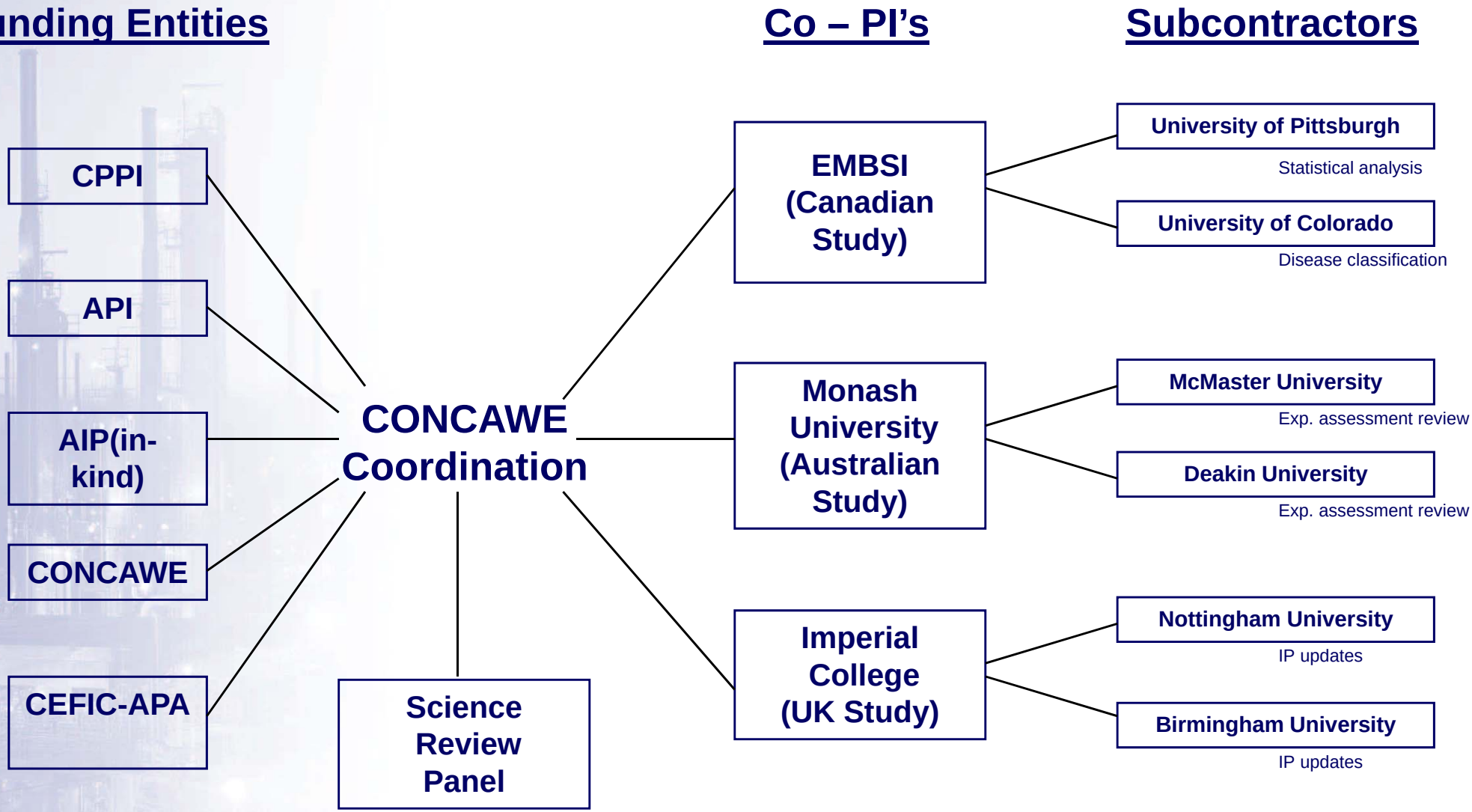
Mode of action: little support for chromosomal effects, especially in MDS. Threshold-based MOA supported for MDS

## How have SHS results been used?

Confirms adequacy of existing controls on benzene exposure

Subset of the study (blood effects) used as key study in REACH dossier for non-cancer health effects

# Pooled Analysis – Study Structure

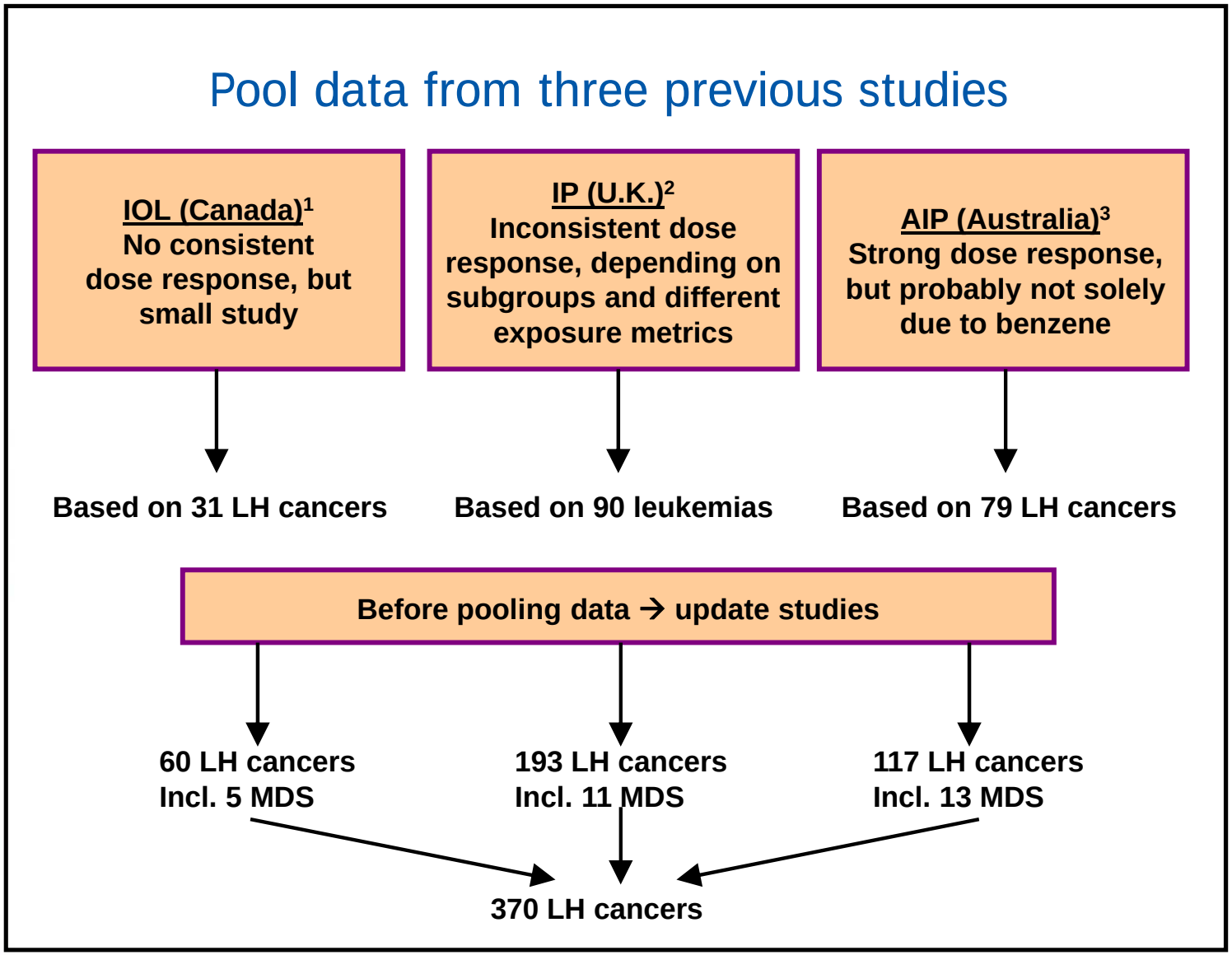



Designed to:

Provide greater precision on benzene and LH cancer subtypes

Incorporate new (WHO) classification scheme for LH cancer

# Pooled Analysis: Background



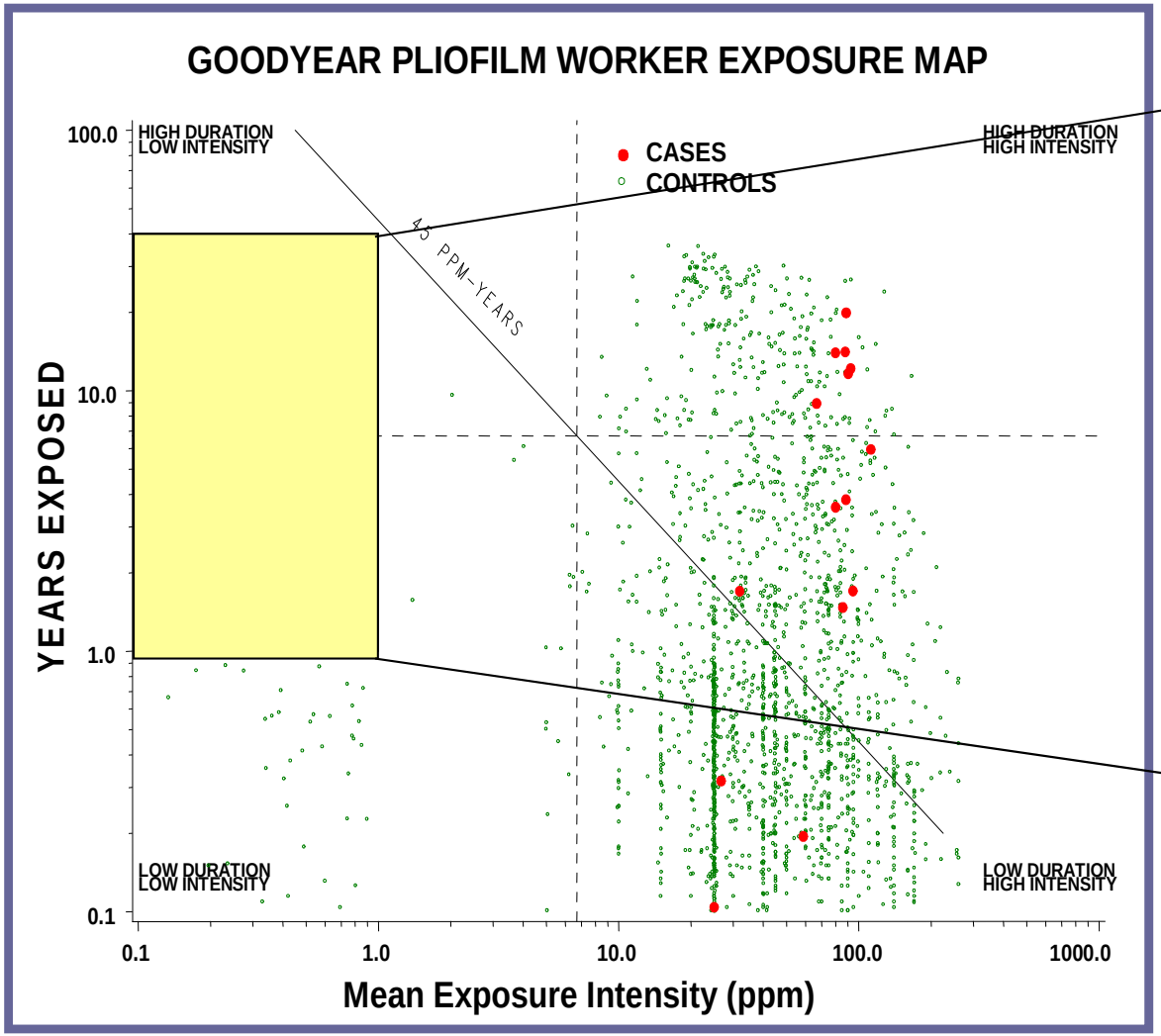

References:

1) Occ. Env. Med. 1996; 53:773-781

2) Occ. Env. Med. 1997; 54:152-166

3) Epidemiol. 2003; 14:569-577

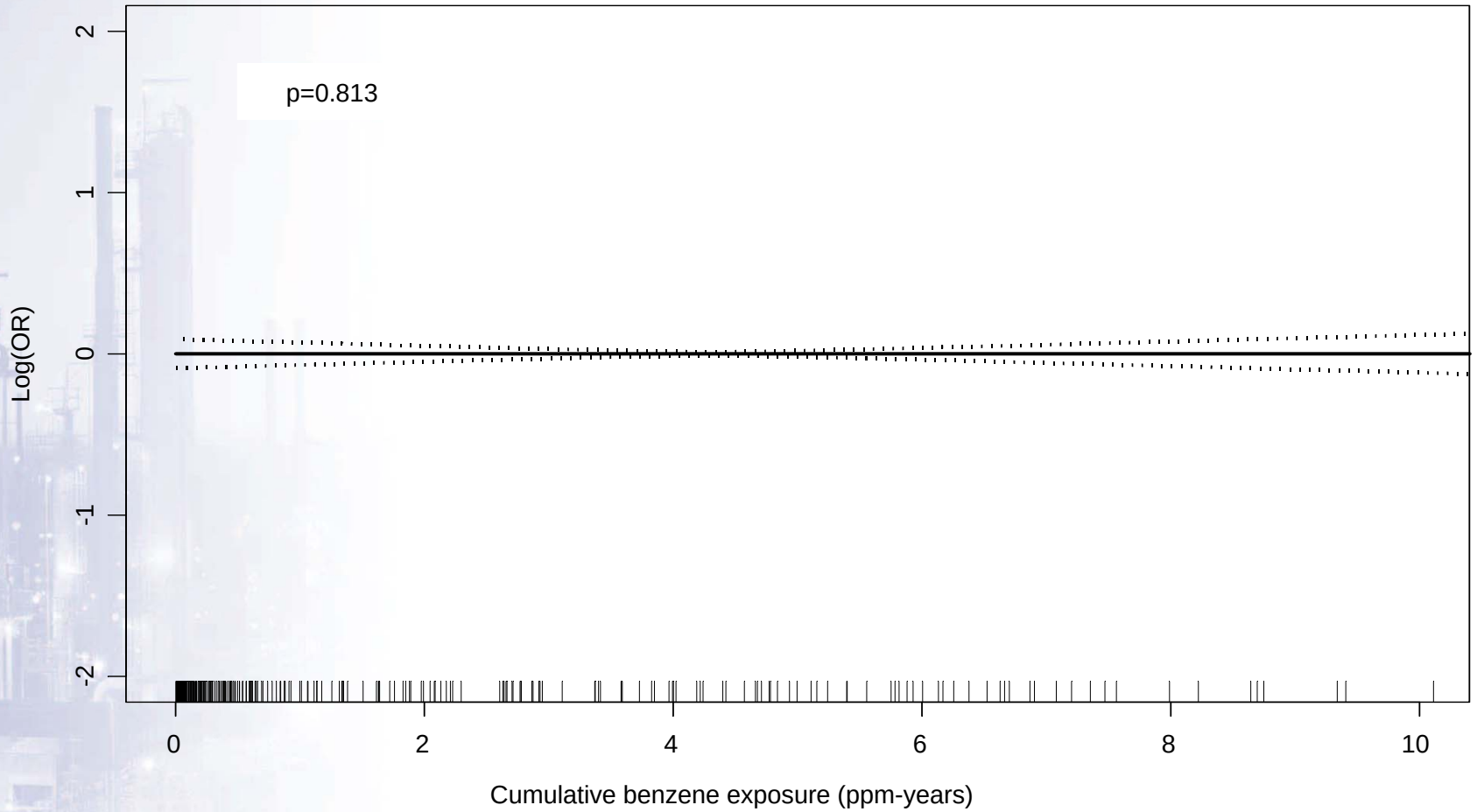
# Basis for Benzene Health Standards




Current day exposure zone:

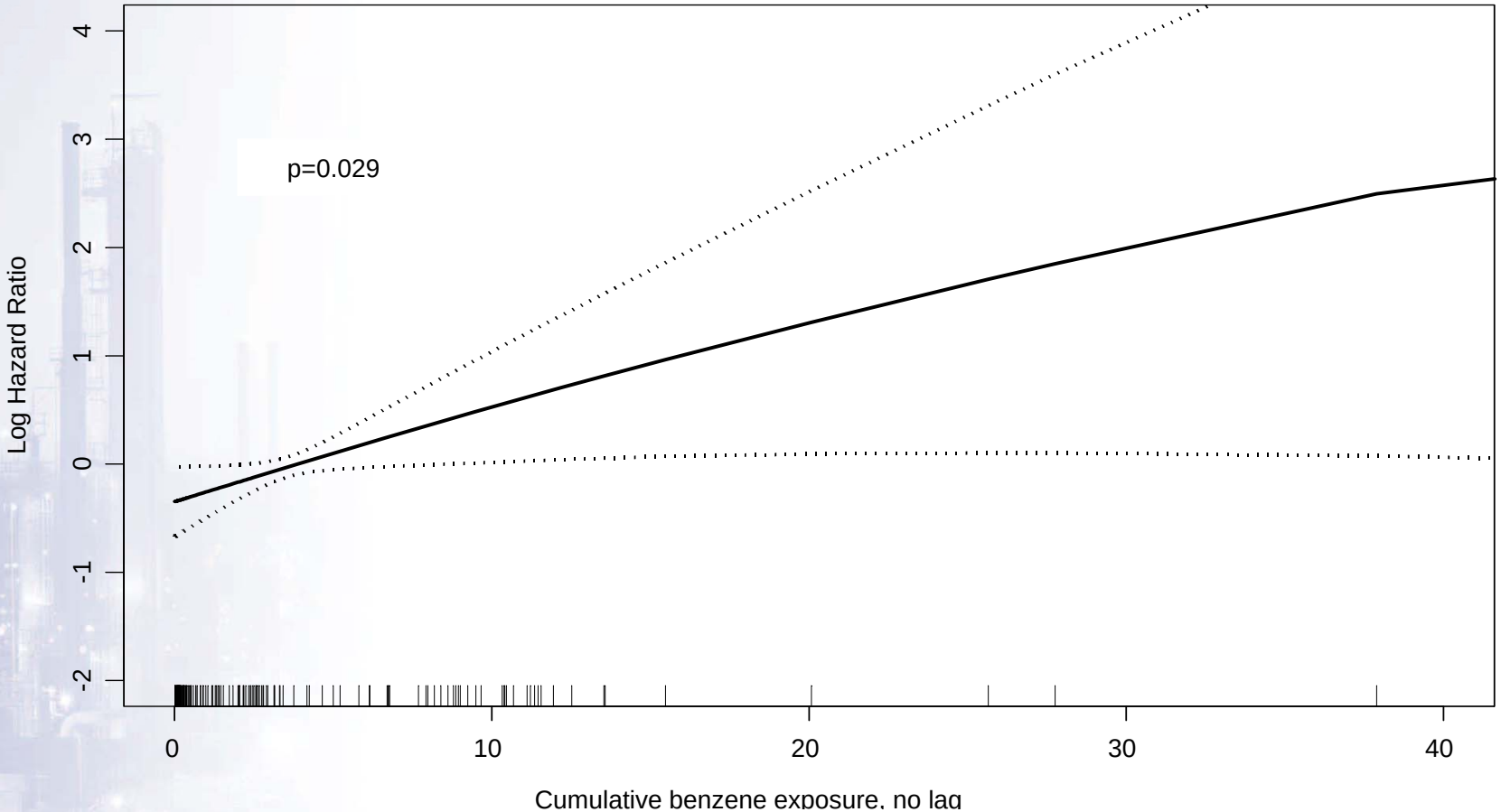
Focus of pooled analysis

# AML and Cumulative Benzene Exposure




- Little evidence for dose-response in overall population…pliofilm study predicts an excess risk for these exposures
- Future Pliofilm URE project will aim to “harmonize” these studies using confidence intervals

# MDS and Cumulative Benzene Exposure




- Overall, MDS shows a stronger dose-response than AML
  - However, peak exposure and maximum exposure show stronger relationships to MDS
  - Threshold analyses are ongoing

# Benzene and Myelodysplastic Syndrome (MDS)

- MDS is a 'relatively' new disease…defined in 1982 "pre-leukaemia"....now a cancer
- US incidence increasing... 1995: 1500 cases; 2003: 15,000 cases
- Benzene is a known cause of MDS...a myeloid tumour
- Some emerging data on levels of BZ associated with MDS
  - NCI, 1997 China → ~10+ ppm
  - Kang, 2005 S. Korea → ~1 ppm (case reports)
  - Recent independent analysis of SHS subset: ~gasoline exposure
  - SHS data could provide further insights on exposure levels linked to MDS
  - Pooled analysis (preliminary): higher occupational exposures, especially if also exposed to peaks
- Several lines of evidence report to a threshold-mediated process for benzene-induced MDS
  - No dogma that MDS starts with point mutation
  - Immune mechanism suggested
  - Successful treatment with immunosuppressants supports this mechanism
  - MDS likely to be more closely related to non-cancer (e.g. blood) effects via bone marrow
- Initial indications on this body of data would suggest:
  - OEL of 1 ppm consistent with data
  - Extrapolation to ambient concentrations would yield higher "safe" levels than no threshold default process

# Current Strategy

| Topic | Activity | Leverage | Anticipated Time Frame | Potential Impact |
|---|---|---|---|---|
| AQLV | Finalize pooled analysis to determine hazards and risks at present day exposure levels | CONCAWE / CEFIC / API | 2011 / 2012 | High |
| OEL and biomonitoring | Develop revised URE based on API Pliofilm re-assessment and increased power of pooled analysis | API / CONCAWE / CEFIC | 2012 - 2014 | Moderate |
| REACH Authorisation | Under discussion: SEA activity will be confined to companies selling Bz for non-intermediate uses | CEFIC / CONCAWE | 2012 onwards | Limited |
| IARC re-review of benzene | Incorporate new knowledge on myeloid and lymphoid tumors | API / CONCAWE / Companies | 2013 -2014? | High |

# Where Does This Leave Us?

- Many groups continue research on benzene
  - Prevalent over-interpretation of metabolism/biomonitoring effect studies
- MDS and Benzene deserves further research
  - Levels associated with disease....further analyses ongoing
  - SHS studies could provide more insight on dose-response, mode of action
  - Blood effects → pancytopenia → myelodysplasia → MDS

*Bone marrow inflamation/autoimmunity*

- Pooled analysis results for AML
  - Can serve as an upper bound on pliofilm-based unit risk estimate
- Several lines of research suggests benzene's effect is limited to myeloid tumours
  - NHL meta-analysis
  - SHS study
  - Pooled analysis
- Industry-funded research will continue to have a major influential role in regulatory decisions on benzene