

Report of the HEI Diesel Epidemiology Panel (Part II): Diesel Epidemiology and Lung Cancer

Introduction and Framing

Katherine Walker, Health Effects Institute

Outline

- A short history of diesel exhaust, epidemiology and risk assessment
- A tale of 2 studies
- A project design
- A panel
- A charge
- HEI's evaluation approach

A short history : Diesel exhaust, epidemiology and risk assessment

- Two decades of systematic reviews (IARC, WHO, EPA, etc) associate exposures to older technology diesel engine exhaust with increased rates of lung cancer
- However, setting risk-based quantitative standards or guidelines limited by exposure assessments
- 1999 HEI Report recommended against use of the then available epidemiologic studies in railroad workers and in teamsters for quantitative risk assessment

**Diesel Emissions
and Lung Cancer:**

**Epidemiology and Quantitative
Risk Assessment**

A Special Report of the Institute's
Diesel Epidemiology Expert Panel

Health Effects Institute
June 1999

HEI

A short history:

Research Needs for Quantitative Risk Assessment (HEI 1999, 2002)

Better measures of exposure

- Measures of diesel constituents
- Valid chemical markers of the complex mix of diesel exhaust emissions.
- Specific biomarkers of diesel exposures, health outcomes, and susceptibility

Better models of exposure

- More use of personal monitors, area monitors placed where diesel exposure is likely to occur, and current and historical data regarding emission sources.
- reliable estimates of past emissions and of factors affecting historical exposures

Better study designs for exposure-response

- Exposures should be adequately and accurately characterized with respect to magnitude, frequency, and duration, rather than solely by duration of employment.
- Exposures should be close to levels of regulatory concern, including a range of exposures to provide a base for understanding the relation between exposure and health effects.
- Errors and uncertainties in exposure measurements should be quantified where possible;
- These should be fully reported to users, and taken into account in both power calculations and exposure–response analyses.
- Cigarette smoking must be controlled for in any study of risk factors for this disease.
- A cohort study subset that uses a case-control or case-cohort design with smoking histories will strengthen the interpretation of results.

A short history :

IARC re-classifies diesel exhaust as Group 1



Lyon, France, June 12, 2012 -- After a week-long meeting of international experts, the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO), today classified diesel engine exhaust as **carcinogenic to humans (Group 1)**, based on sufficient evidence that exposure is associated with an increased risk for lung cancer.

KEY COMPONENTS:

- **The US Truckers Study and Diesel Exhaust in Miners Study (DEMS)**

CAVEATS:

- **Based on animal and human studies with old technology diesel exhaust**
- **IARC noted substantial (>98%) improvements in new technology diesel, but**
 - **Only new technology diesel study: HEI's Advanced Collaborative Emissions Study (ACES)**
 - **Suggest relevance of their review where fleet turnover incomplete or slow (as in less developed countries)**

A tale of 2 studies:



Lung Cancer and Elemental Carbon Exposure in Trucking Industry Workers

Eric Garshick,^{1,2} Francine Laden,^{2,3,4} Jaime E. Hart,² Mary E. Davis,^{3,5} Ellen A. Eisen,^{6,7} and Thomas J. Smith³

¹Pulmonary and Critical Care Medicine Section, VA Boston Healthcare System, Boston, Massachusetts, USA; ²Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; ³Exposure, Epidemiology and Risk Program, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, USA; ⁴Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA; ⁵ Department of Urban and Environmental Policy and Planning, Tufts University, Medford, Massachusetts, USA; ⁶Environmental and Occupational Medicine and Epidemiology Program, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, USA; ⁷Environmental Health Sciences Division, School of Public Health, University of California, Berkeley, California, USA



National Cancer Institute/ National Institute of Occupational Safety and Health (NCI/NIOSH)

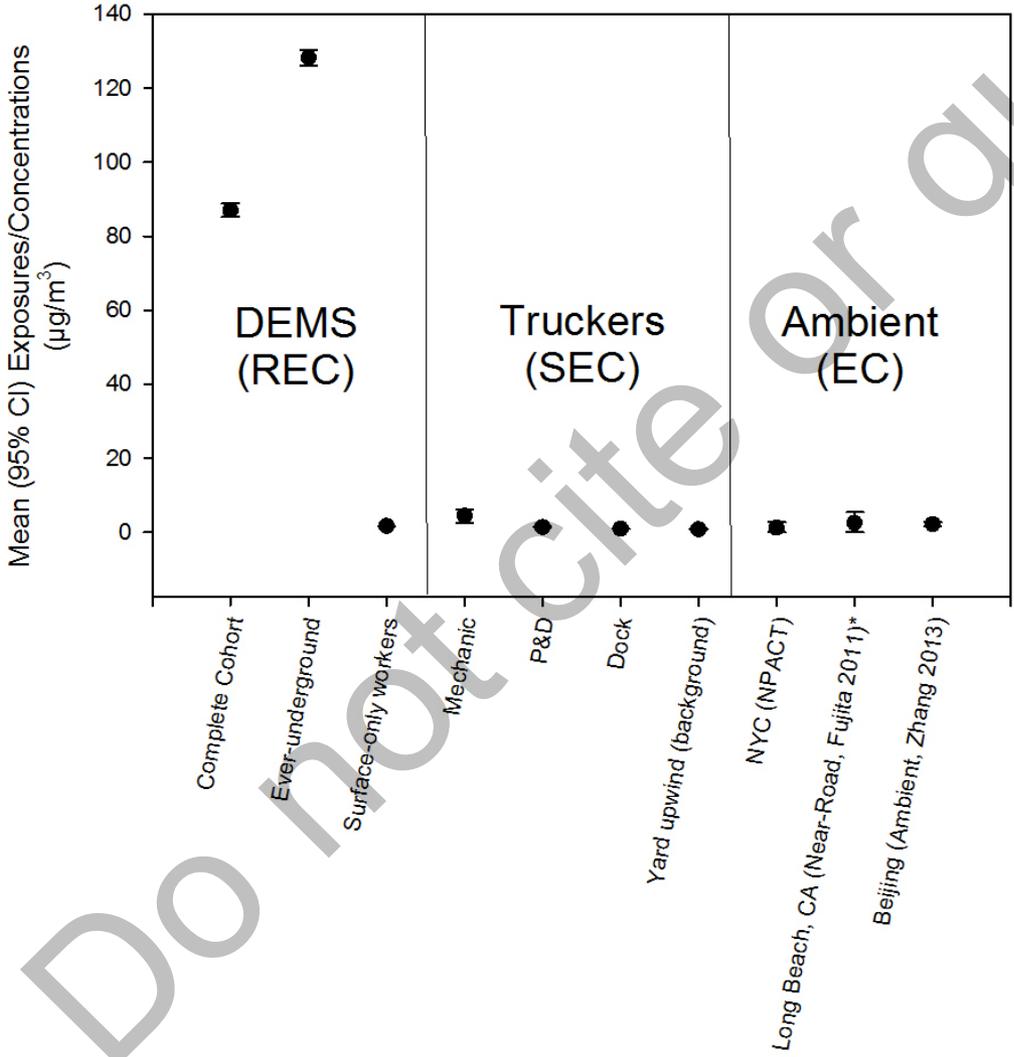
The Diesel Exhaust in Miners Study: A Nested Case-Control Study of Lung Cancer and Diesel Exhaust

Debra T. Silverman, Claudine M. Samanic, Jay H. Lubin, Aaron E. Blair, Patricia A. Stewart, Roel Vermeulen, Joseph B. Coble, Nathaniel Rothman, Patricia L. Schleiff, William D. Travis, Regina G. Ziegler, Sholom Wacholder, Michael D. Attfield

DEMS and Truckers: Overview

	DEMS	Truckers
Design	Cohort and Nested Case-Control	Cohort
Questionnaire	Yes, individual level risk factors	No
Population	8 U.S. non-metal mines (limestone, trona, salt, potash) 12,315 miners: 96% male, 88% white	139 U.S. Trucking terminals 31,135 worker: 100% male, 85% white
Lung cancer	198 lung cancer cases, 563 controls matched on mine, sex, race, and birth year	779 lung cancer cases
End of follow-up	1997	2000
Metric of personal exposure	Respirable elemental carbon (REC) $\leq 3.5 \mu\text{g}/\text{m}^3$	Submicron Elemental Carbon (SEC) $\leq 1 \mu\text{g}/\text{m}^3$

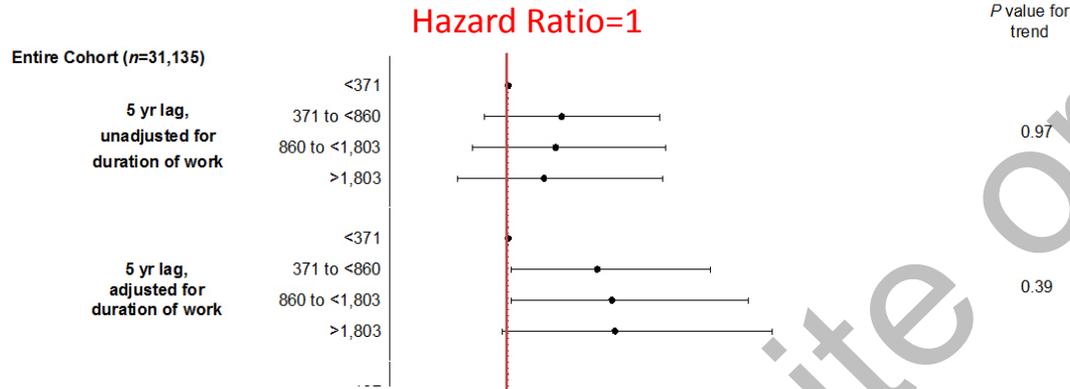
DEMS and Truckers: Range of Exposures



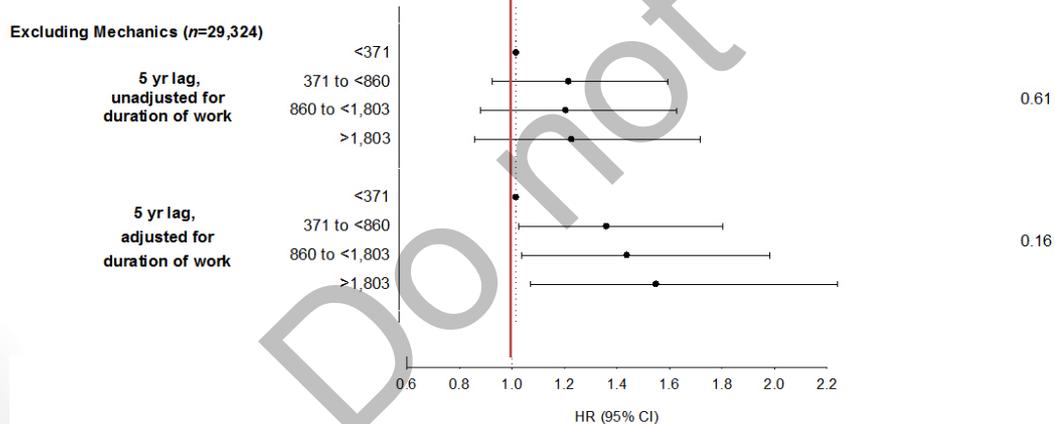
*Fujita (2011) reported as Median (Max, Min)

Truckers Main results

Entire Cohort



Excluding Mechanics

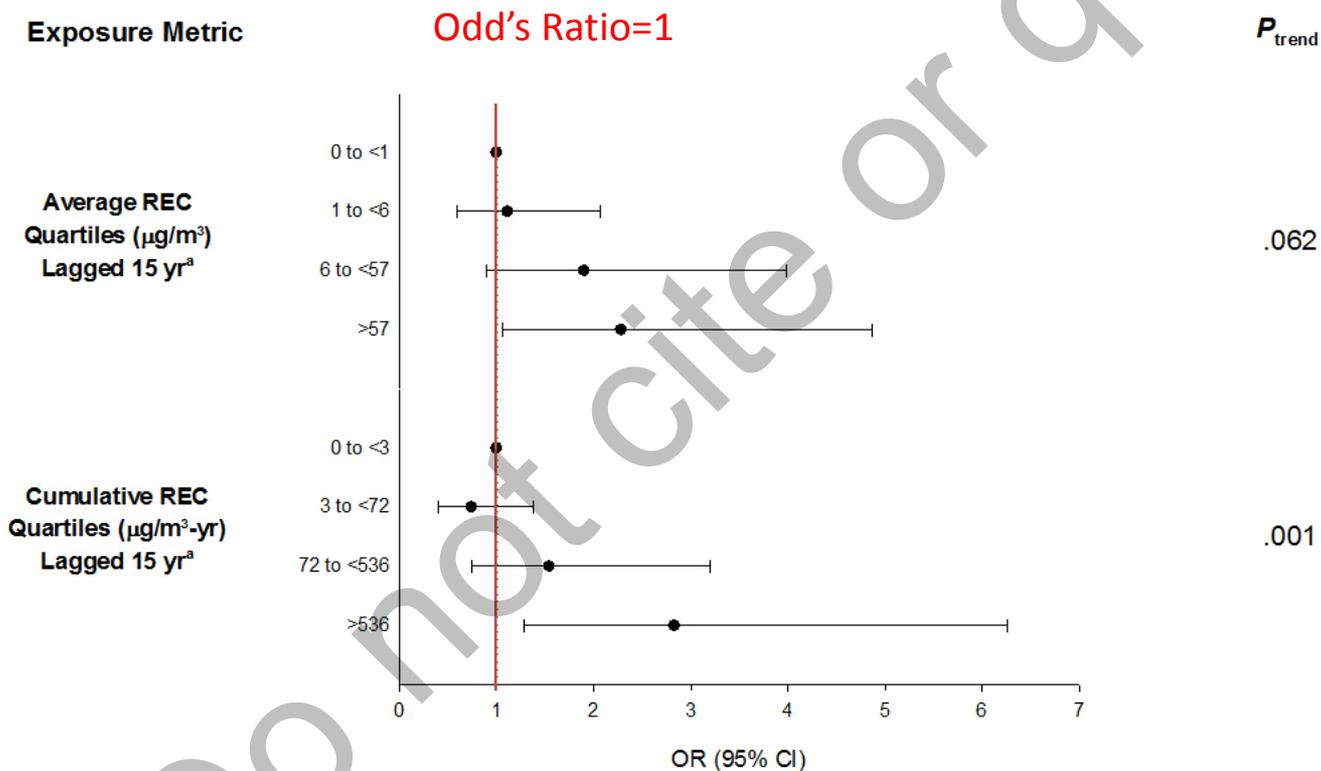


Main Models

- Cumulative exposure
- 5-year lagged
- Adjustment for duration of work – healthy worker effect

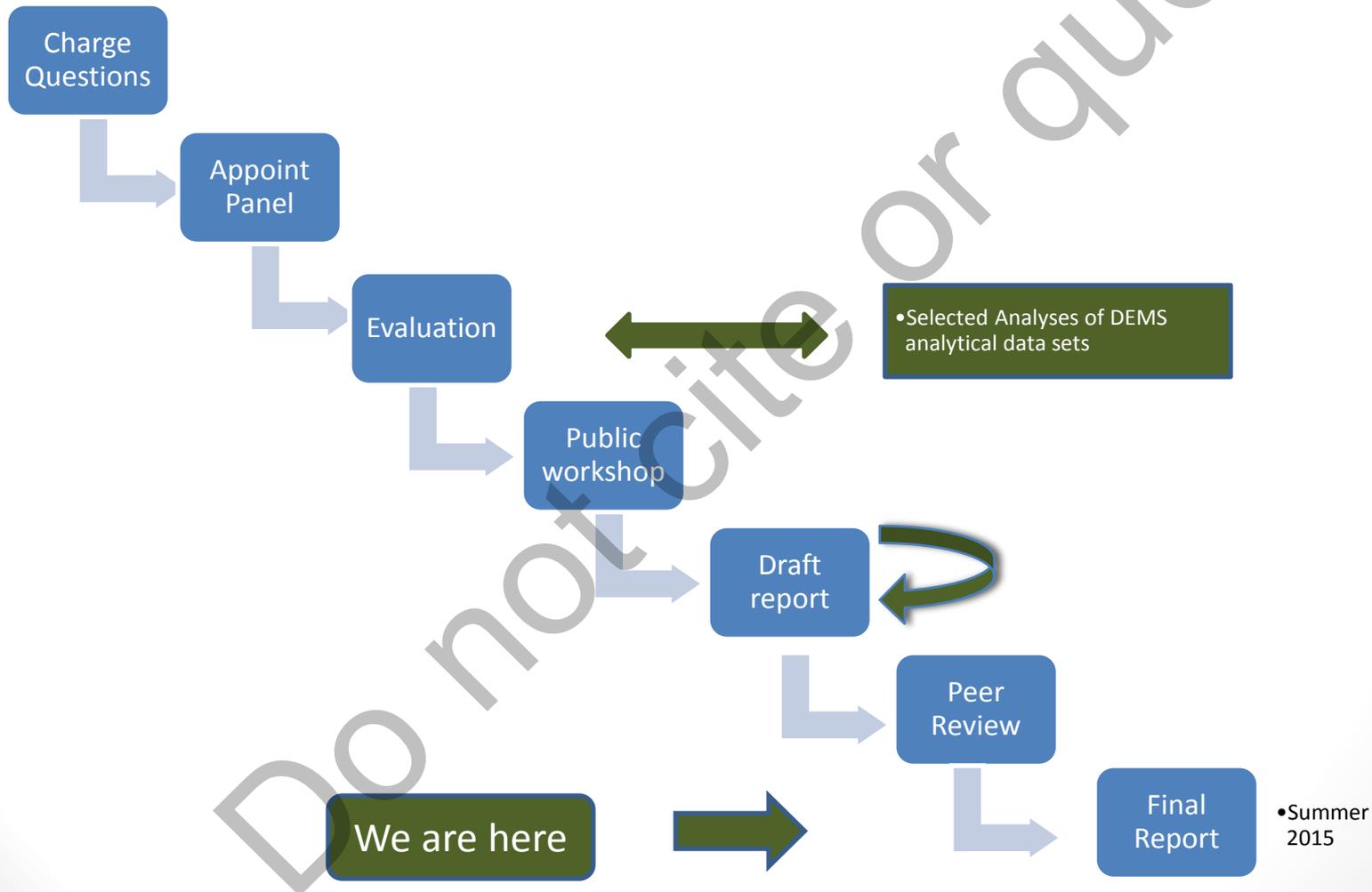
DEMS Main Results: Case-Control

All Subjects



Silverman et al. 2012

An Overall Project Design: Diesel Epidemiology Project II



A Charge

1. Reviewing the findings of the 1999 HEI Special Report on epidemiology and risk assessment
2. For recent epidemiologic studies, reviewing their design, data, and exposure estimates, ... analyzing such data as needed.
3. Exploring whether the data from these new studies enables analyses to extend concentration–response relationships to lower ambient concentrations
4. Identifying data gaps and sources of uncertainty.
5. Making recommendations about extension or further analyses of existing data sets.
6. Making recommendations, if necessary, about the design of new studies that would provide a stronger basis for risk assessment.

A Panel: Diesel Epidemiology Project

Daniel Krewski, PhD, Chair	Professor and Director of the R. Samuel McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa
Paul Demers, PhD	Director, Occupational Cancer Research Centre, Cancer Care Ontario and Professor, Dalla Lana School of Public Health, University of Toronto
David Foster, PhD	Professor Emeritus, Department of Mechanical Engineering, University of Wisconsin Madison
Joel Kaufman, MD, MPH	Professor, Environmental and Occupational Health Sciences, Medicine and Epidemiology; School of Public Health and School of Medicine, University of Washington
Jonathan Levy, ScD	Professor and Associate Chair, Department of Environmental Health, Boston University School of Public Health
Charles Poole, ScD, MPH	Associate Professor, Department of Epidemiology, University of North Carolina School of Public Health
Nancy Reid, PhD	University Professor of Statistics, Canada Research Chair in Statistical Theory and Applications, University of Toronto
Martie van Tongeren, PhD	Director, Centre for Human Exposure Science, Institute of Occupational Medicine, Edinburgh, Scotland, UK
Susan R. Woskie, PhD, CIH	Professor, Department of Work Environment, University of Massachusetts-Lowell.

Panel evaluation approach

- Internal Panel Deliberations April 2013 to September 2014
 - Review of each study
 - Review of published commentaries on both studies and investigator responses
- Public Workshop and Presentations – March 6, 2014
 - DEMS: Silverman, Stewart, Vermeulen, Attfield
 - Truckers: Garshick
 - EMA-led Consortium: Crump and Moolgavkar
 - Risk Assessors/Managers: Cogliano/EPA; Park/NIOSH; Rodricks/Environ Corp.
- Analyses in DEMS analytical data sets:
 - Replication of main results
 - Evaluation of smoking, radon and other analyses

Panel Evaluation Process: Analyses of DEMS data

Analytical data sets

- Case-control variables
- Cohort variables
- Obtained by application to NCI and NIOSH, with IRB approval
 - In secure facility at U of Ottawa
 - By data use agreement, cannot be linked
- Exposure data sets: downloadable on-line from NIOSH website

Additional opportunities

- Linkage available through further application National Center for Health Statistics Research Data Center
- Extensive underlying mine and job data collected by authors
 - Obtained by EMA by FOIA
 - Now available to public

Evaluation Approach (Cont'd)

“Reanalysis of the DEMS Nested-case control study of lung cancer and diesel exhaust: suitability for quantitative risk analysis”

Crump et al. (2015) *

- Case-control (linked to cohort)
- 6 Alternative REC estimates and exposure assignments
- Alternative variable selection for main CPH models
- Control for cumulative radon (WLMs)
- Alternative tests for trend
- Subset analysis with only-underground workers
- “leave one out” analysis of individual mines

“Diesel engine exhaust and lung cancer mortality ---time-related factors in exposure and risk”

Moolgavkar et al. (2015)*

- Cohort analytical dataset
- Time-dependent exposure modeling with TSCE model
- Subset analysis with only-underground workers
- Individual mine-by-mine analysis of risk using TSCE and CPH models

* Funded by consortium of companies led by the Engine Manufacturers Association

NRC Paradigm: Quantitative risk assessment

Research-Based Data Streams

Human

- Experimental
- Epidemiology

Animal Mechanistic

Pharmacokinetic

- Absorption, distribution, metabolism, excretion
- Dosimetry modeling

Exposure measurements, predictions, biomonitoring

Risk Assessment

IARC, others

Hazard Identification

Exposure-Response
Assessment

Exposure Assessment

Risk Management

Regulatory options

Evaluate consequences of options

- Public health
- Economic
- Social
- Political
- Other

Agency decisions and actions

Characterization of Risk
and Uncertainty

Stakeholder input

Translation from study to target population via quantitative risk analysis

What is the observed risk of lung cancer?



Risk characterization: modeling, assumptions, adjustments uncertainties:

- Population demographics
- Differences in smoking, other risk factors
- Levels and timing of personal exposures over a lifetime
- Changes in emission levels and composition

What is the predicted risk of lung cancer?



Other relevant data methods, and analyses

What does it mean to evaluate epidemiologic studies for use in QRA?

Epidemiologic evaluation

- What are the strengths/limitations of the study in relation to the hypotheses which it was designed to test?

Risk assessment

- How can a study be used in the prediction of risks associated with different levels of exposures, in different populations?
- What are the uncertainties?



Panel Evaluation Criteria

- **a study design** that is clearly documented and scientifically justified to test the study hypotheses, including adequate power and precision, the appropriate study population, and plans for evaluation of effect modification and control for confounding variables;
- **an analytical approach** that is appropriate to the data and hypotheses, including complete reporting of results;
- **health outcome assessment** that is complete, reliable, and verifiable; is blind to assignment of exposure;
- **an exposure assessment** that includes an appropriate measure of exposure, a range of exposures relevant to exposure–response assessment in the populations of interest, provides some insight to the magnitude and potential influence of key uncertainties in exposure assignment, and that is blind to identification of health outcomes;
- **an exposure–response assessment** based on models that fit the data well, reflect a range of plausible alternatives, including biological relevance; and
- **sensitivity and uncertainty analyses** that test the robustness of findings to major assumptions in the design and analysis of the study.

More detailed evaluations

- **Understanding the Potential Influence of Smoking, Radon, and Other Factors** (*Jonathan Levy*, Boston University School of Public Health)
- **Evaluation of the Historical Estimates of Exposure to Diesel Exhaust** (*Paul Demers*, Occupational Cancer Research Center, Canada)
- **Conclusions and Recommendations** (*Dan Krewski*, Chair, University of Ottawa)

Report of the HEI Diesel Epidemiology Panel (Part II): Diesel Epidemiology and Lung Cancer

**Understanding the Potential Influence of Smoking, Radon,
and Other Factors**

Jonathan Levy

Boston University School of Public Health

Panel Evaluation Criteria

- **a study design** that is clearly documented and scientifically justified to test the study hypotheses, including:
 - adequate power and precision,
 - the appropriate study population, and
 - **plans for evaluation of effect-measure modification and control for confounding variables.**
- **sensitivity and uncertainty analyses** that test the robustness of findings to major assumptions in the design and analysis of the study.

Some definitions

- Confounding: An unobserved (or mischaracterized) factor distorts the observed association between an exposure and disease
 - Confounder must be associated with both the exposure and the disease
 - Confounders can be positive or negative depending on correlations among exposures or distributions in comparison groups
- Effect-measure modification: The association between an exposure and a disease varies by levels of a third factor
 - Confounding will distort the true relationship and should be controlled (by design or analysis); effect-measure modification cannot be controlled but should be understood

Risk assessment perspective

- Substantial confounding could lead to biased concentration-response functions by misstating the true association
- Appreciable effect-measure modification could also lead to biased concentration-response functions if effect modifiers are not explored and are distributed differently in the target population than in the study population
- Uncertainties in epidemiological studies should be characterized but do not preclude use of the studies in quantitative risk assessment

Diesel/lung cancer context

- Important risk factors for lung cancer
 - Smoking
 - Secondhand smoke
 - Occupational exposures (e.g., asbestos, silica, PAHs)
 - Radon

Do not cite or quote

Panel evaluation of Truckers

- Smoking
 - Retrospective occupational cohort → lack of information on individual smoking status
 - Indirect adjustment done in earlier analysis based on smoking survey to stratified random sample of 11,986 current or recently retired employees of three companies
 - Assuming standard lung cancer relative risks from the literature for current/former/never smokers, the authors constructed adjustment factors by job title, which ranged from 0.92 to 1.17
 - Authors argued that smoking would not have appreciable influence on findings given small adjustment factors and socioeconomic similarity of cohort
 - Panel concurred and concluded that lack of control for smoking in Truckers is a limitation but not one that should preclude use of the study in quantitative risk assessments

Panel evaluation of Truckers

- Healthy worker bias
 - Core models adjusted for total years of employment, given previous findings that duration of employment was associated with reduced lung cancer mortality, posited to be a sign of survivor bias (control for a negative confounder)
 - Panel concluded that this addressed an important issue but created potential interpretability challenges given role of duration of employment in cumulative EC metrics
- Other occupational exposures
 - No obvious candidates that would be correlated with both exposure and outcome
 - Personal exposures predicted by terminal-specific characteristics, ventilation, job location in the terminal, and background exposures (predicted by local weather, proximity to major road, land use, and region)

Panel evaluation of DEMS

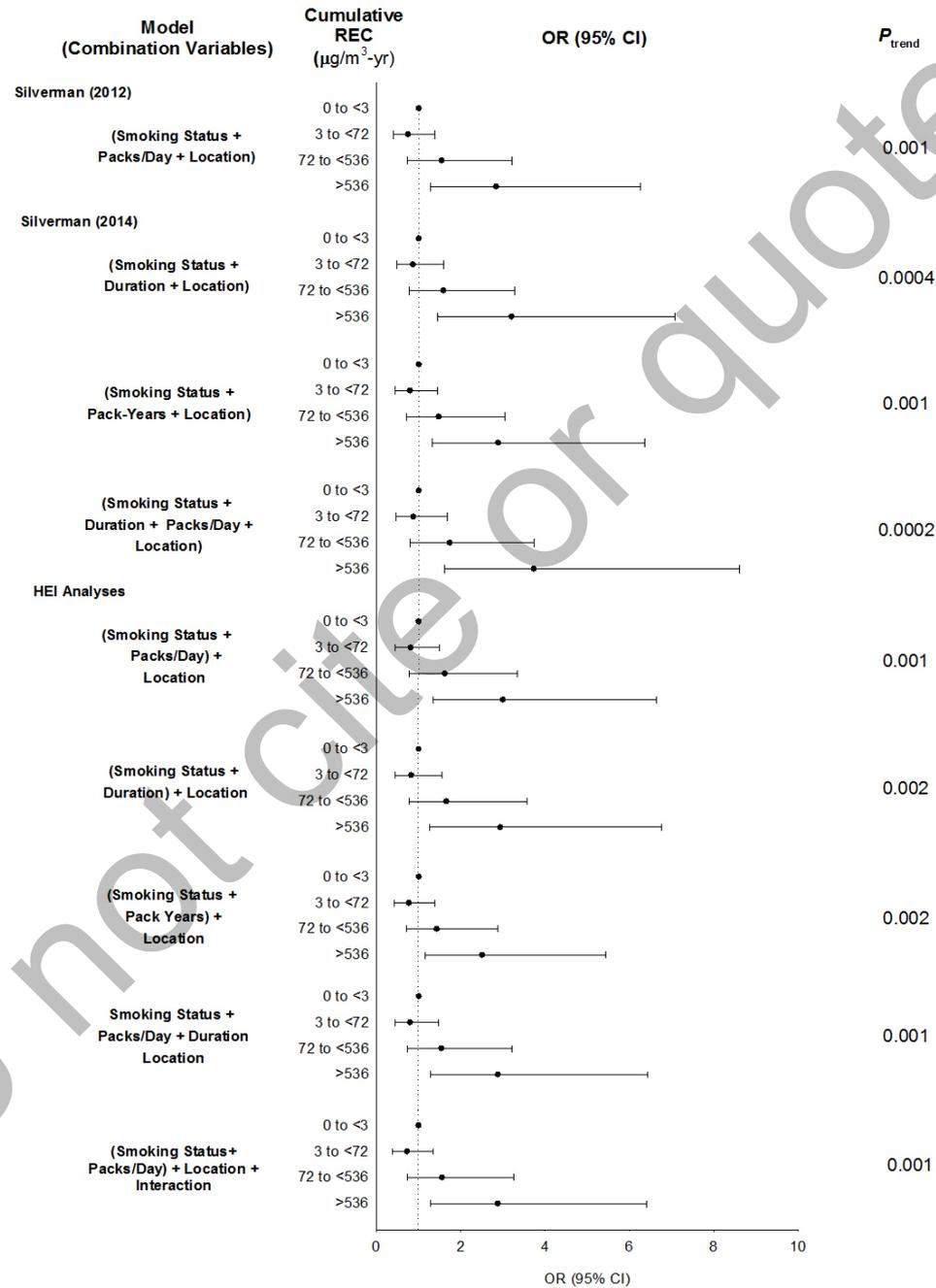
- General attributes of the study design:
 - Nested case-control study allowed for more detailed evaluation of potential confounders
 - Smoking
 - Secondhand smoke
 - Employment in other high risk occupations
 - History of respiratory disease
 - Family history of lung cancer
 - Physical activity
 - Education
 - Diet
 - Mines selected by design to have low levels of exposure to other pollutants that also have associations with lung cancer (e.g. silica, asbestos, radon, respirable dust, non-diesel PAHs)
 - Could radon still serve as a confounder?

Panel evaluation of DEMS

- Smoking (original studies):
 - Telephone interviews for individuals or next of kin
 - Lung cancer odds ratios estimated by smoking category for all subjects and by work location, by quartile of REC exposure, and by tertile of cumulative REC
 - Dose-response between smoking and lung cancer strong and monotonic, with diminished effect in ever-underground workers
 - Addressed in part with indicator variable reflecting combination of smoking status, intensity, and location
- Smoking (Panel analyses):
 - Confirmation of negative confounding
 - Sensitivity of findings to the measure of smoking used and how it was incorporated in the models
 - Development of a more direct estimate of interaction between location and smoking that might be more informative for risk assessment

	Silverman et al. 2012	Silverman et al. 2014	HEI Panel
Exposure metric:	Average REC, lag 0, 15 yr Cumulative REC, lag 0, 15 yr Duration of REC exposure (yrs)	Average REC, lag 15 yr Cumulative REC, lag 15 yr	Average REC, lag 0, 15 yr Cumulative REC, lag 0, 15 yr
Smoking status:	Never, former, current, unknown; Intensity	Status–Duration; Status–Pack-years; Status–Packs/day and duration	Status–Duration; Status–Packs; Status–Pack-years; Status (Never, former, current, unknown) and Duration (continuous); Status and Packs/day (continuous); Status and Pack-years (continuous)
Interactions:	None (Smoking status and work location were combined in the analysis)	None (Smoking status and work location were combined in the analysis)	Location of employment (ever underground/surface only) and duration, packs/day, and pack-years as continuous variables

Comparison of HEI analyses to those of Silverman et al. (2012, 2014)



Panel evaluation of DEMS

- Radon (Original analyses)
 - Attfield et al. (2012) found association with cancer risk but in a subset of older workers hired before 1947. Considered anomalous and did not include.
 - Silverman et al. (2012) evaluated cumulative radon in the model but concluded they changed point estimates of ORs by $\leq 10\%$ so did not include in final models.
 - At HEI Workshop, noted that cumulative radon did have expected association on lung cancer risk in workers with long tenures; challenging interpretation given work duration in the model.
- Radon (Panel analyses):
 - Although radon levels low by occupational standards, residential exposures at these levels have estimated effects substantial enough to create potential for appreciable confounding, and exposures correlate with underground status (no radon exposure at surface)
 - Conducted additional analyses
 - Radon added to main study models
 - Implemented additional models with term for duration of exposure, then radon given significant correlation between cumulative REC and cumulative radon

Incorporating radon into analysis:

- Extent and quality of data were limited.

Facility	Mine Type	% values <LOD	Mean Area Concentration (pCi/L)	Mean Area Ever-UG workers (Working Level)*
A	Limestone	15%	3.5	0.009
B	Potash	56%	3.0	0.017
D	Potash	61%	3.3	0.016
E	Salt	30%	4.5	0.016
G	Trona	76%	4.2	0.017
H	Trona	85%	2.1	0.008
I	Trona	80%	2.8	0.008
J	Potash	62%	2.2	0.009

USEPA
Residential
action level =
4 pCi/L

- Personal radon exposure (working level months) is a function of WL and duration of exposure.
- Control for radon does have small effect on REC associations

*Working level = a measure of exposure to radon and daughters. Source: Attfield et al. 2012.

Conclusions

- Although there are many candidate confounders for lung cancer, the Panel concluded that there was no evidence indicating substantial confounding that would invalidate the application of the Truckers or DEMS studies for quantitative risk assessment
- The most salient issue for future quantitative risk assessment would be the ability to understand the implications of any information gaps or differences in risk factors (i.e., smoking status and intensity) on the degree of uncertainty in the exposure-response relationship for the target population

Report of the HEI Diesel Epidemiology
Panel (Part II):

Diesel Epidemiology and Lung Cancer

**Evaluation of the Historical Estimates of Exposure to
Diesel Exhaust**

**Paul Demers, Occupational Cancer Research Center,
Canada**

Major Challenges in Retrospective Exposure Assessment for Epidemiologic Studies

- Historical measurements are often lacking entirely or are incomplete in various ways, measurement technologies have changed, and exposures themselves are changing over time
 - For Diesel Engine Exhaust very little is known about the levels of elemental carbon exposure when diesel engines were first introduced, although they will likely have been higher than present due to improvements in diesel engines and incremental improvements in working conditions
- Investigators have over the last few decades developed approaches to reconstructing historical levels of exposures using a broad array of information

Characteristics of a Strong Exposure Assessment

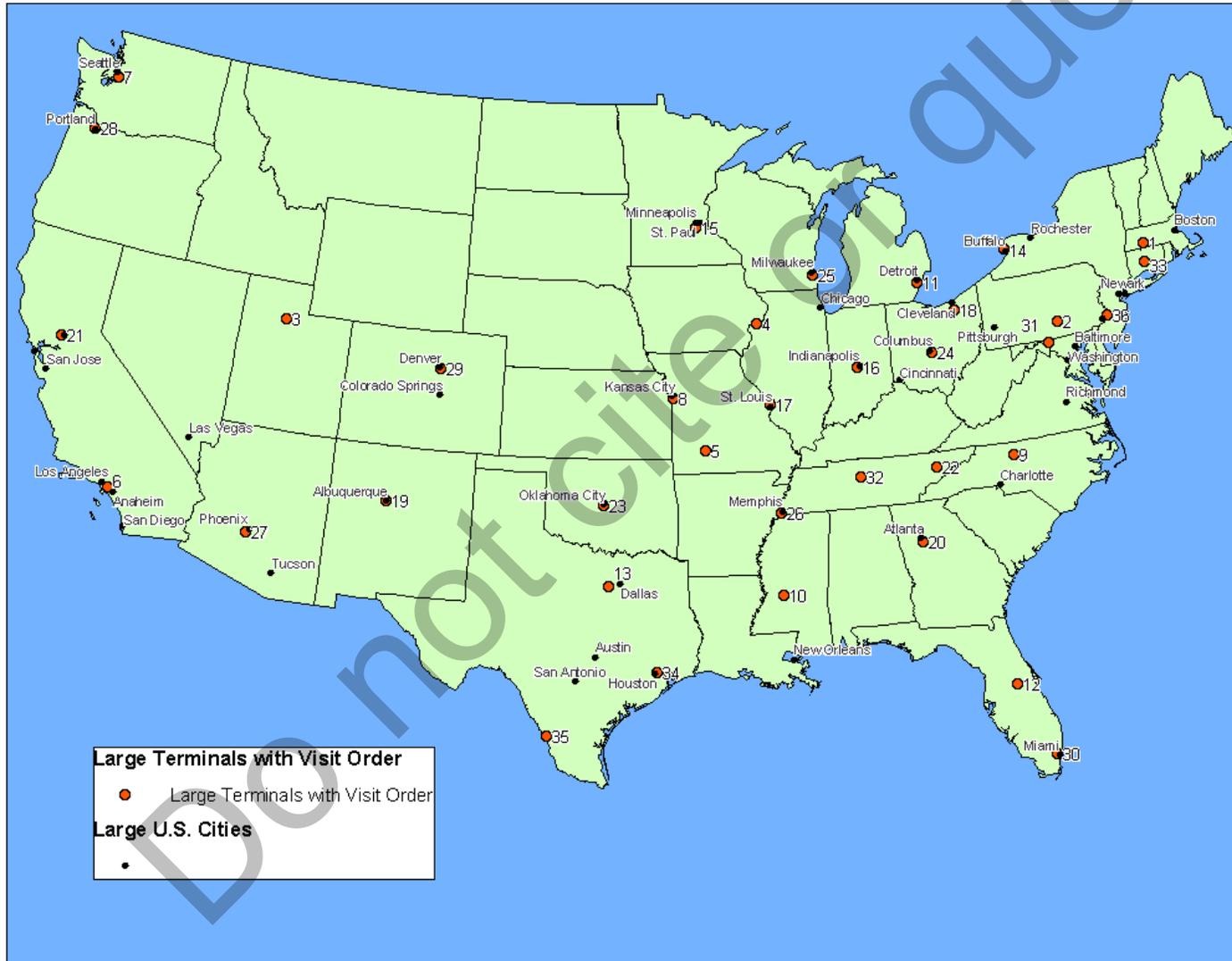
An exposure assessment that includes

- An appropriate measure of exposure
- A range of exposures relevant to concentration response assessment in the populations of interest
- Blind to health outcome in study subjects
- Characterization of error or uncertainty in exposure estimates

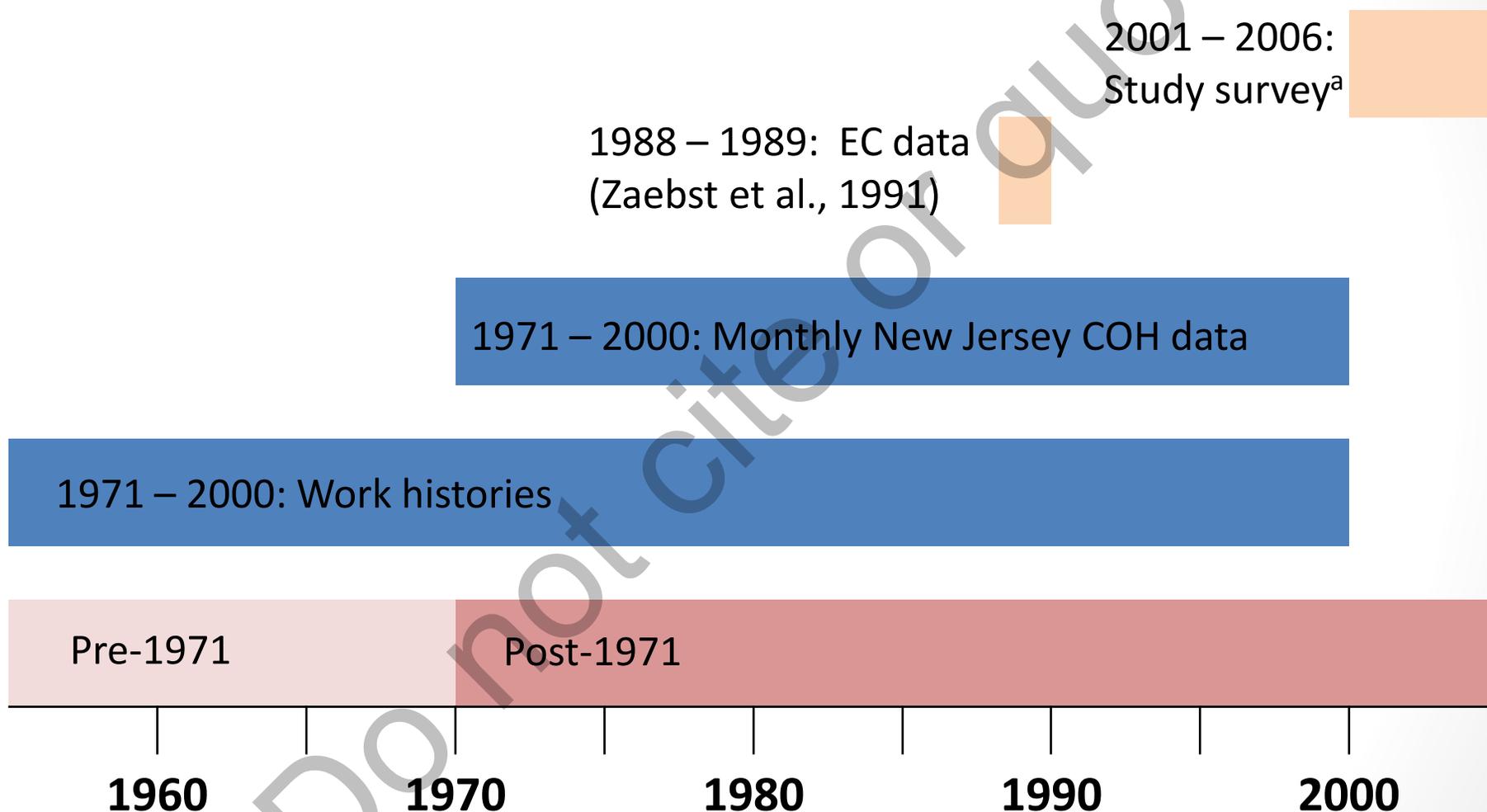
Shared Strengths of the Exposure Assessments for Truckers and DEMS

- Used elemental carbon as marker of exposure (although somewhat different measures, respirable and sub-micron elemental carbon, REC and SEC)
- Blind to outcome status
- Intensive assessment of current exposure
- Modeled historical exposure
- Performed validation studies
- Well documented with many peer-reviewed publications

The Trucking Industry Particles Study



Truckers Study: Data Available

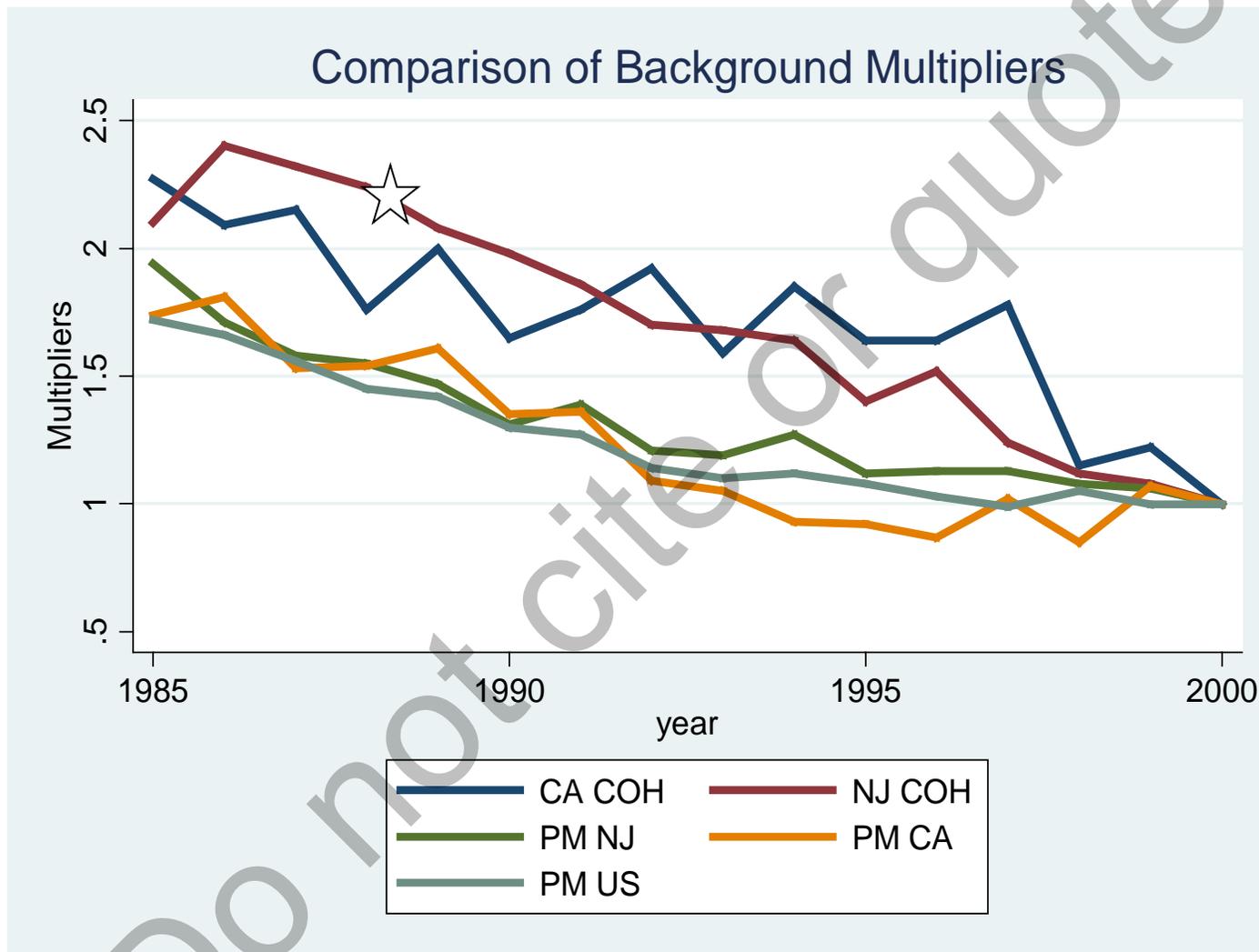


^a ~ 4000 personal/area samples (8-12 hrs) for EC in PM_{1.0}
Measurements in 36 of 139 large terminals (and 44 nearby small terminals)

Truckers Study: Modelling methods

- Terminal Based Jobs: Structural Equation Modeling
 - Terminal Background: weather, road proximity, %-industrial land, US region
 - Work Area: terminal features, ventilation, job, background
 - Personal (dock, mechanic): Work area
- Spatial extrapolation to other terminals
- Drivers - ratio of observed/background
 - Different ratios for long haul and P&D (warm vs cold environments)
- Historical extrapolation of exposure
 - Coefficient of Haze
 - Adjustment for the use diesel fork-lifts
- Zaebs et al, 1991 provided data for validation

Trends in Median Coefficient of Haze



☆ Ratio of Zaebst et al (1991) median background to current study (2.2).

Truckers Study Exposure Assessment: Panel Evaluation

Strengths

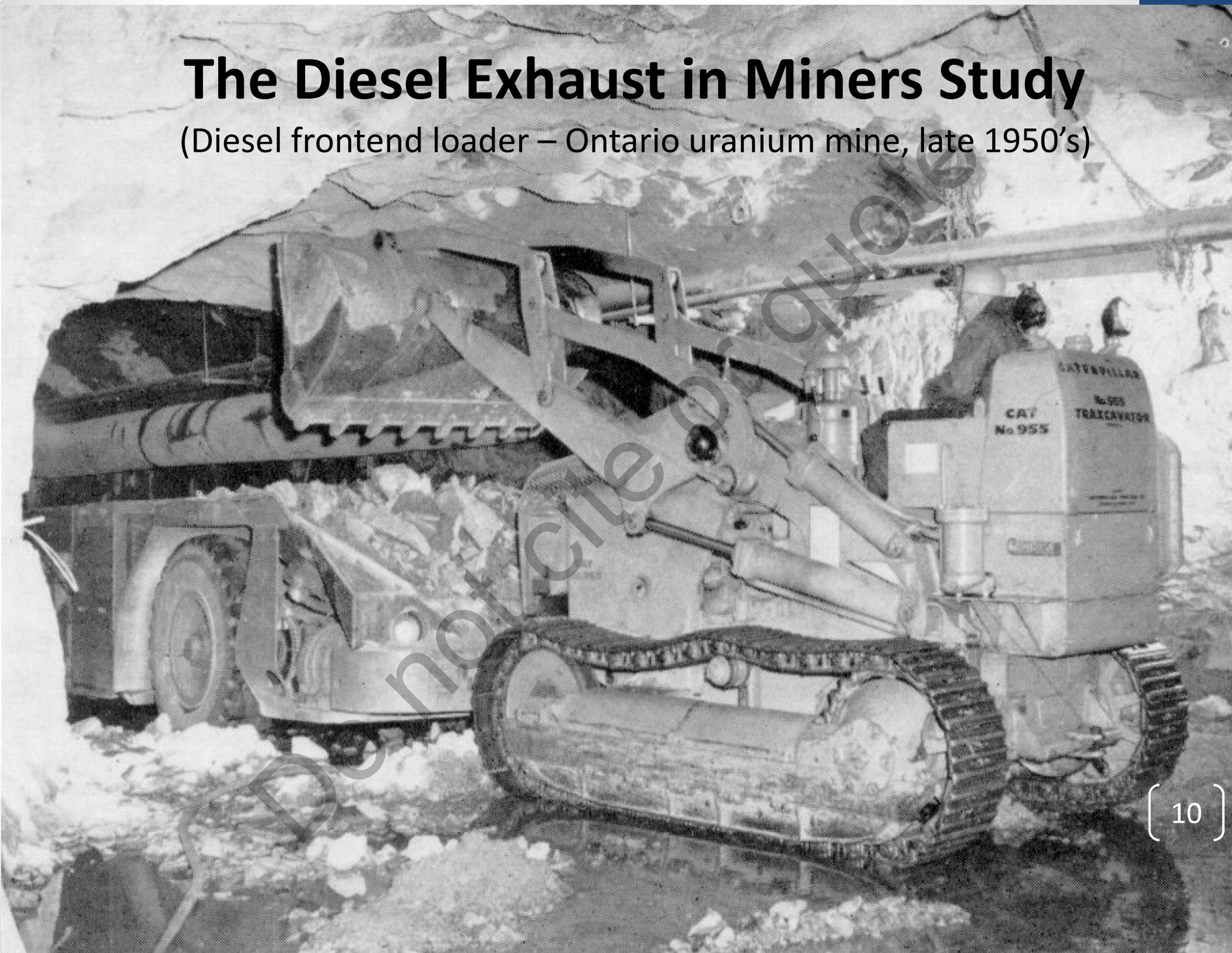
- Conceptually and statistically sound approach
- Limited external data used to refine exposure assessment
- Exposure levels low relative to miners, but in a good range for general population risk assessment

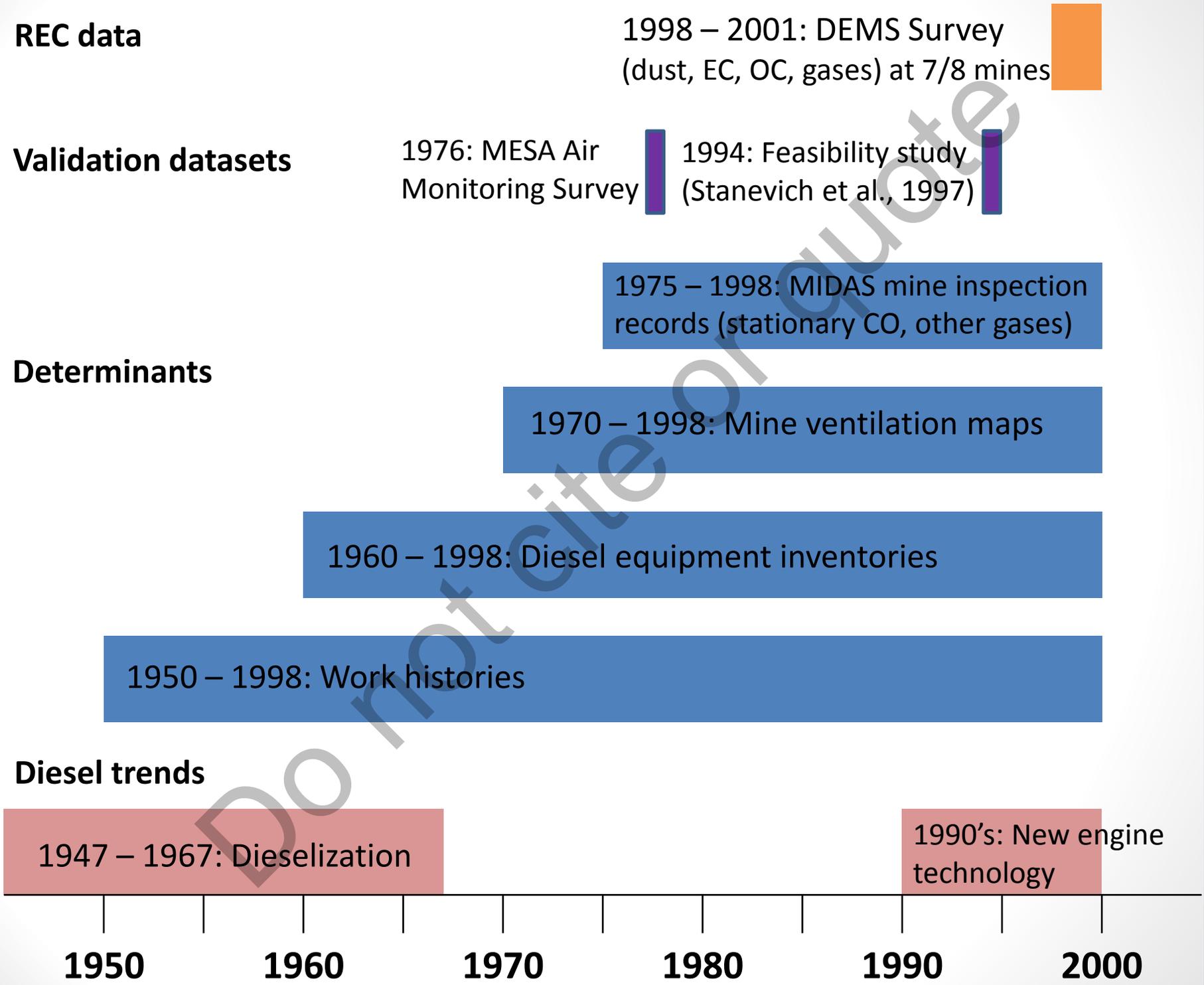
Limitations

- Specificity of SEC for diesel exposure?
- The COH approach may not capture regional differences and fuel use changes over time

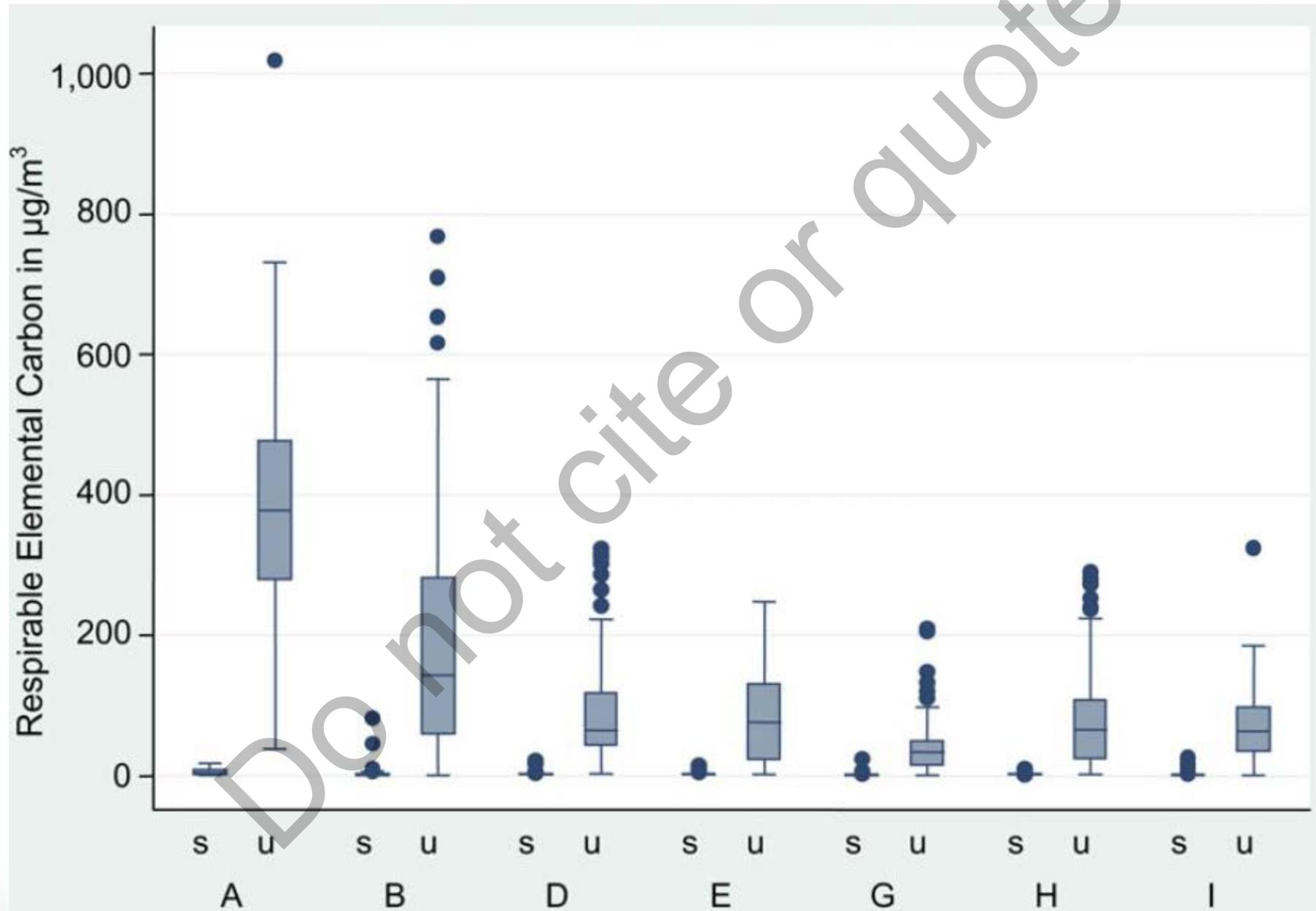
The Diesel Exhaust in Miners Study

(Diesel frontend loader – Ontario uranium mine, late 1950's)





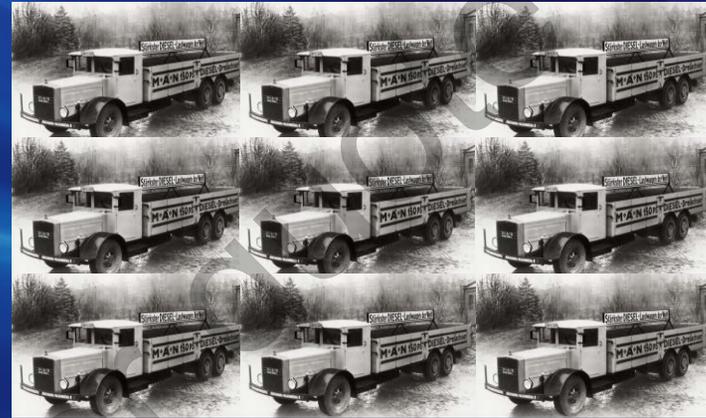
Personal REC measurements (1998-2001) for surface and underground jobs by mining facility



Miners Study: Modeling Methods (underground)

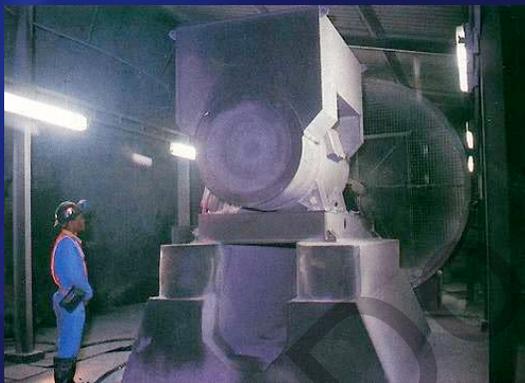
- CO chosen as a surrogate for the historical trend in REC exposure
- A model was developed to estimate CO levels back to 1947 using facility-specific determinant information (adjusted horsepower (the sum of $HP * \%use$), ventilation (in CFM), & a factor for equipment acquired after 1990)
- By combining these modeled CO levels with available REC measurements from 1998-2001, a model was developed to estimate REC exposure back to 1947
- 1994 NIOSH feasibility study and 1996 MESA Air Monitoring Survey provided data for limited validation studies

Correlations



EC ↑

CO ↑



EC ↓

CO ↓

National Cancer Institute

Evaluation and Validation Steps Taken by DEMS

- Evaluation of baseline REC data measurements
 - Comparisons with REC samples collected concurrently & feasibility study
- Processing of work histories
 - Comparisons of locations from work history records and long-term workers
- Defining exposure determinants to estimate historical REC levels
 - Correlation between CO & other gaseous components
 - Factor analysis of diesel exhaust components
 - Mixed effects modeling between REC & both CO & NO₂, allowing facility-specific intercepts & slopes
 - Non-parametric regression allowing facility-specific intercepts using GAMs
- Development of REC exposure estimates
 - The impact of using arithmetic means versus medians evaluated
 - Evaluated the impact of alternate underground & surface grouping strategies
 - Evaluated potential use of NO₂ or CO₂ rather than CO
- Evaluations
 - Compared predicted CO to measured in the MESA and Feasibility Study data
 - Comparison with CO^{0.58} & 5-year average CO with CO^{1.0}

Alternative REC estimates

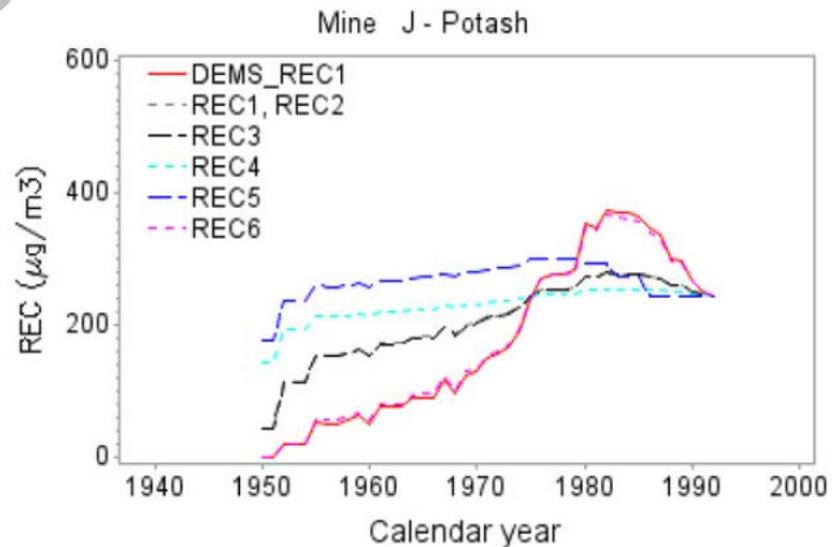
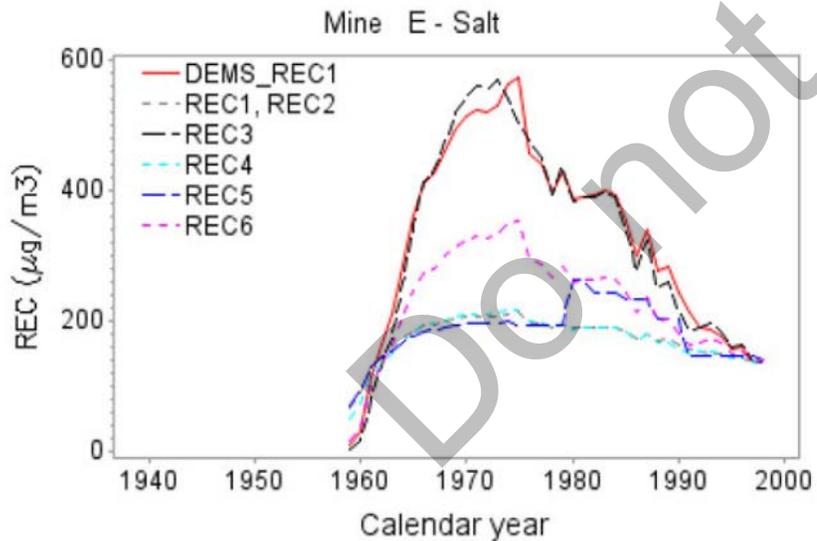
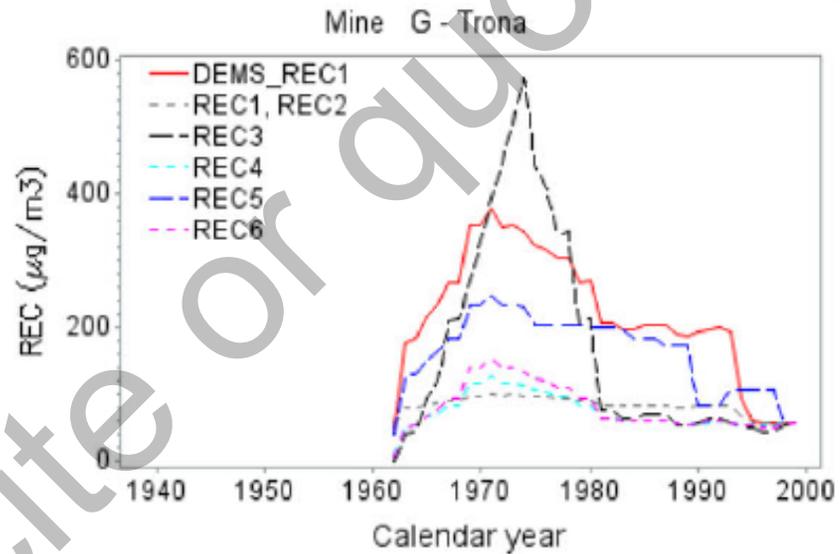
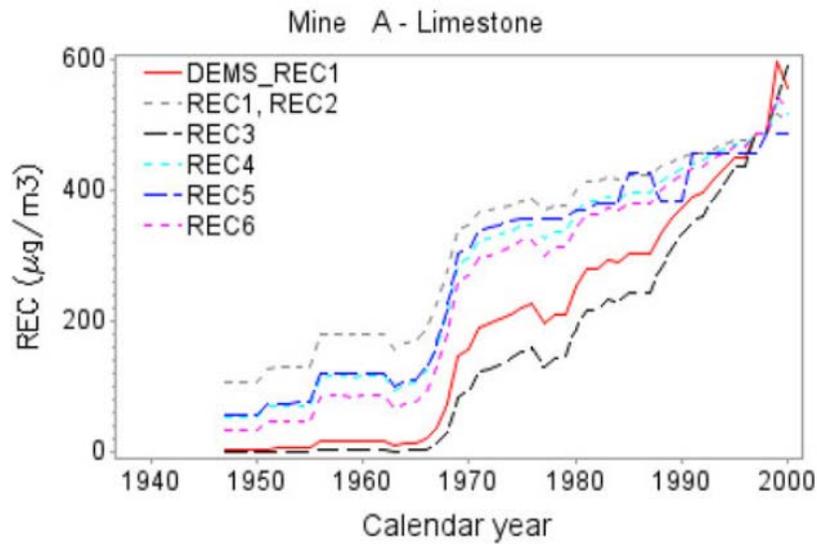
Silverman et al. (2012, 2014)

- **DEMS REC:** $\beta=1$, used in case-control study
- **DEMS ALT REC 1:** 5 yr average CO after 1976,
- **DEMS ALT REC 2:** $\beta=0.58$
- **DEMS ALT REC 3:** Median REC

Crump et al (2015)

- **ALT REC 1:** Independent imputation; assignments; $\beta=0.3$
- **ALT REC 2:** Removed “High-Period” variable; $\beta=0.3$
- **ALT REC 3:** Removed “High Period” & AdjHP1990+ term; $\beta=1$
- **ALT REC 4:** ALT REC 3 w/ $\beta=0.3$
- **ALT REC 5:** 3 yr average CO post 1975; $\beta=0.3$
- **ALT REC 6:** Independent of CO data

Impact of alternative approaches on historical underground exposure predictions: Mine Operator*



*loader operator for mine A

Crump et al. (2015), Figure 1

How sensitive are Odds Ratios to alternative exposure estimates?

Silverman et al. (2014) Table 1.

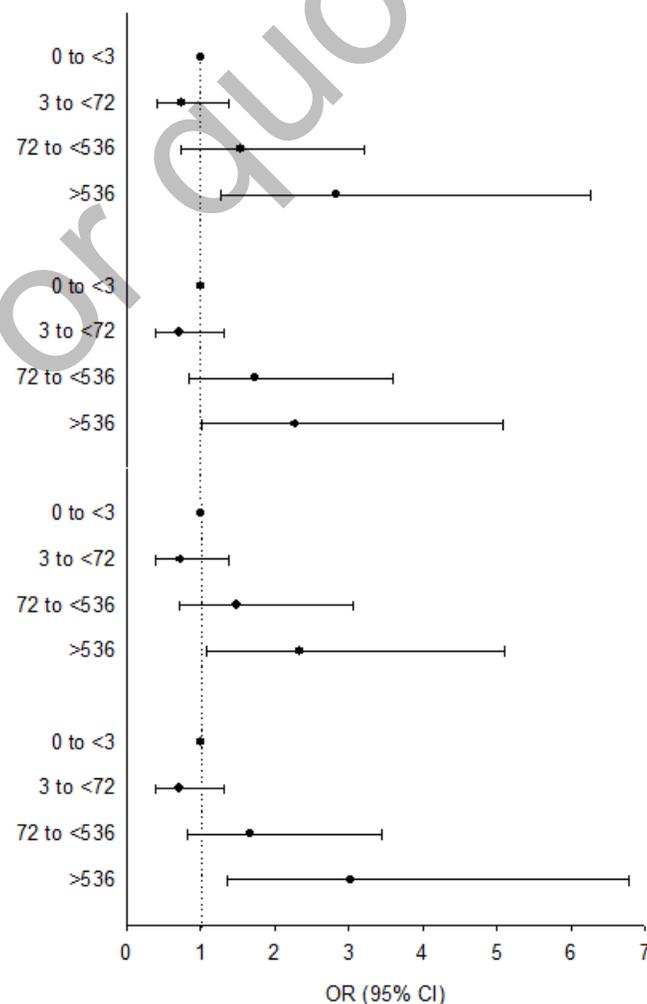
- Cumulative REC, lagged 15 years
- Main model, adjusting for smoking status and packs/day, work location, history of respiratory disease, history of high risk job for lung cancer

DEMS REC
($\mu\text{g}/\text{m}^3\text{-yr}$)

DEMS ALT REC 1
($\mu\text{g}/\text{m}^3\text{-yr}$)

DEMS ALT REC 2
($\mu\text{g}/\text{m}^3\text{-yr}$)

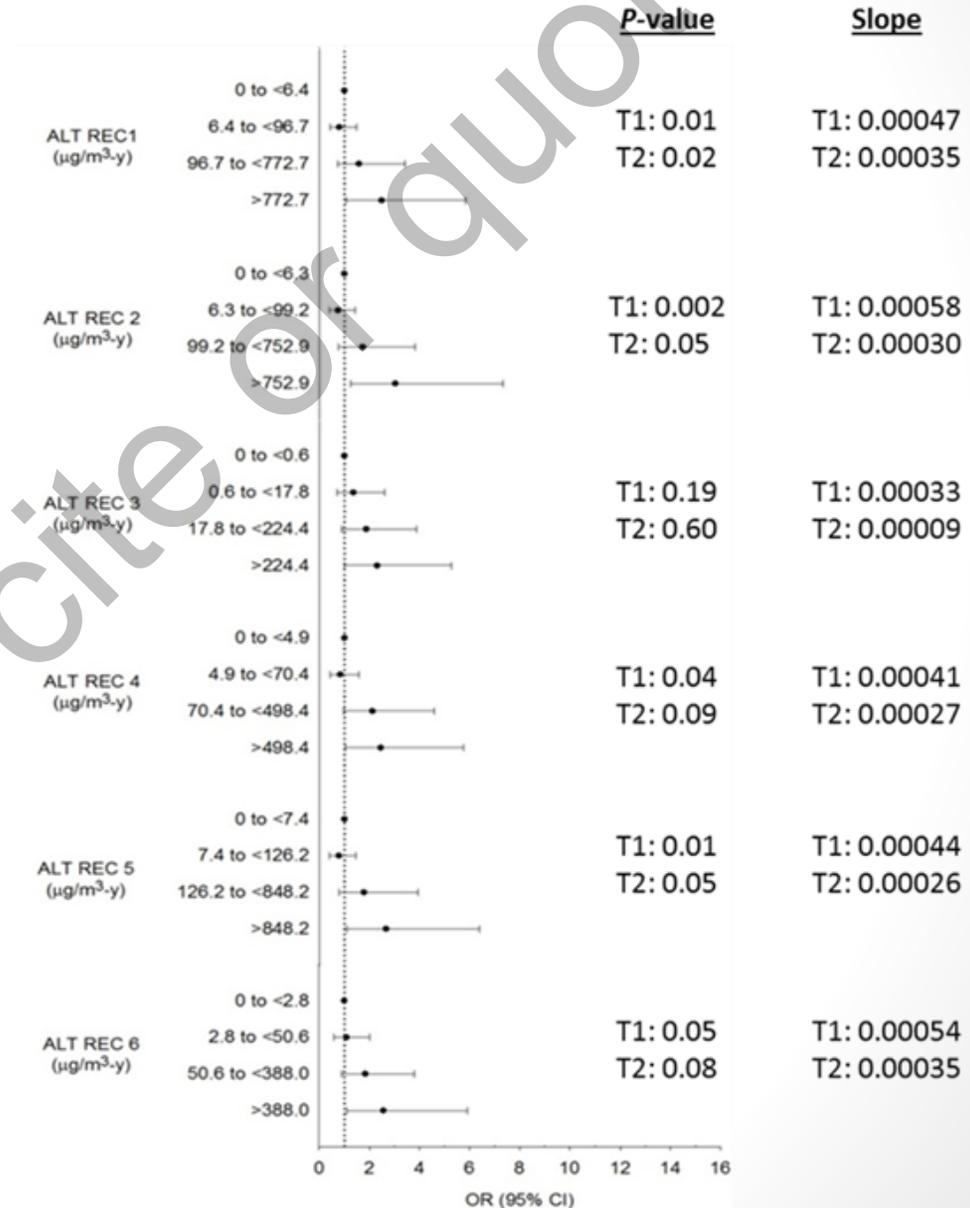
DEMS ALT REC 3
($\mu\text{g}/\text{m}^3\text{-yr}$)



How sensitive are lung cancer Odds Ratios to Alternative Exposures?

Crump et al. (2015) Table III

- All subjects
- Cumulative REC, lagged 15 years
- Model adjusted for smoking status and packs/day, work location, first respiratory disease, body mass, numbers of smokers in home
- No adjustment for radon



Miners Study Exposure Assessment: Panel Evaluation

Strengths

- Extensive collection & use of available data
- The basis for the construction of the model was logically sound and replicable
- CO the best choice available for a surrogate for historical trends
- Many validity and sensitivity analyses were conducted by the authors and external consultants

Limitations/Uncertainties

- Evidence of limited bias in both directions
- Exposure levels during earlier time periods may have been underestimated, but magnitude is uncertain

Research needs for Quantitative Risk Assessment (HEI 1999, 2002)

Evaluations?

DEMS Truckers

Better measures of exposure

- Measures of diesel constituents

✓

✓

- selection and validation of a chemical marker of exposure to the complex mix of diesel exhaust emissions.

✓

✓

- Specific biomarkers of diesel exposures, health outcomes, and susceptibility are needed.

✗

✗

Better models of exposure

- Exposure models may include data from personal monitors, area monitors placed where diesel exposure is likely to occur, and current and historical data regarding emission sources.

✓

✓

- In any such modeling effort, the effects of environmental tobacco smoke should be removed as completely as possible.

✓

✗

- Reliable estimates of past emissions and of factors affecting historical exposures in a range of settings are needed to improve the characterization of uncertainties, both quantitative and qualitative, in historical models of exposures.

✓

✓

Design needs for new studies of exposure-response

- Exposures should be adequately and accurately characterized with respect to magnitude, frequency, and duration, rather than solely by duration of employment.

✓

✓

- The exposures considered should be close to levels of regulatory concern, including a range of exposures to provide a base for understanding the relation between exposure and health effects.

✓

✓

- Errors and uncertainties in exposure measurements should be quantified where possible;

✓

✓-

- These should be fully reported to users, and taken into account in both power calculations and exposure response analyses.

✓

✓-

- Cigarette smoking must be controlled for in any study of risk factors for this disease.

✓

✗

- Smoking histories obtained for a cohort study subset that uses a case-control or case-cohort design

✓

✗

Considerations for Future Quantitative Risk Analyses for Both Studies

- Uncertainty in the levels of exposure in the earlier time periods of the studies when no measurements were available
- How important are alternative assumptions about historical emissions rates to historical estimates and to risk?
- All alternative models should be subject to same degree of scrutiny and validation
- Differences in exposure metrics (REC vs SEC), including consideration of other sources

Recommendations for Future Analyses for Use of Data for QRA

- Sensitivity analyses of DEMS to assess the potential impact of under (or over) estimation of exposure due to changes in both surface and underground engine technology and other changes
 - Challenge: what is the reasonable range for historic underground exposures?
- Sensitivity of Truckers to model assumptions for using background levels (ambient COH) as basis of model
 - Challenge: does ambient COH account for regional differences, changes in engine technology and fuels that might impact near field truck emissions historically

Report of the HEI Diesel Epidemiology Panel (Part II): Diesel Epidemiology and Lung Cancer

Conclusions and Recommendations

Daniel Krewski, Chair HEI Panel
University of Ottawa

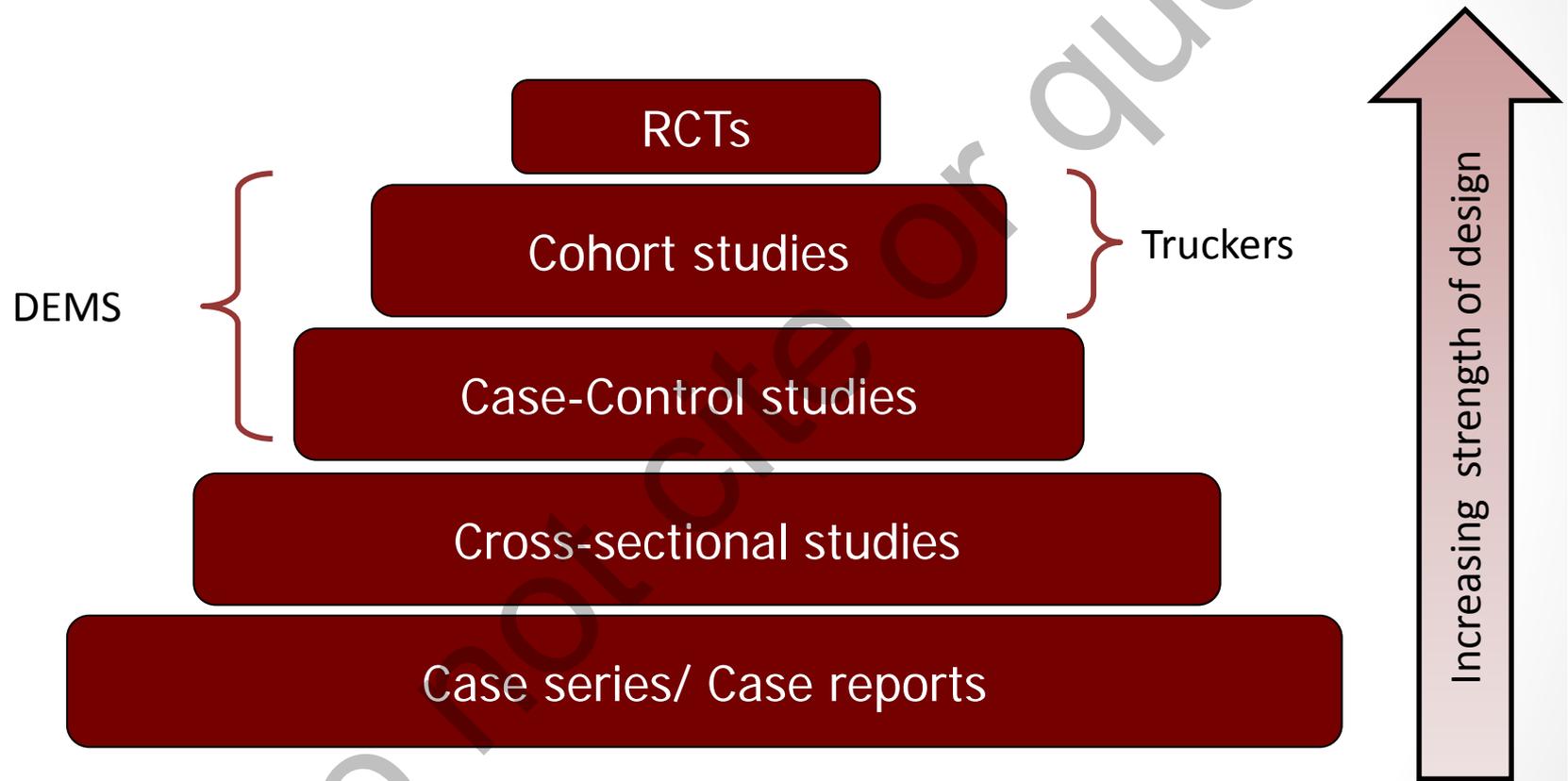
Outline

- Re-cap of the Panel evaluation process
- Strengths and limitations of epidemiological studies relative to the evaluation criteria and research needs identified in 1999 by HEI
- Other questions that have been asked (mine by mine, only underground workers)
- Overall conclusions about the studies
- Recommendations for future risk assessments

Re-cap: Panel evaluation process

- Internal Panel Deliberations April 2013 to September 2014
- Public Workshop and Presentations – March 6, 2014
- Broad based Panel evaluation criteria for epidemiologic studies and their value for risk assessment
- Panel analyses of the DEMS analytical data sets and exposure data

- ✓ **A study design** that is clearly documented and scientifically justified to test the study hypotheses...



- Within each level the quality of the studies can vary depending on its specific design features and conduct.
- RCT= randomized controlled trials

✓ An analytical approach that is appropriate to the data and hypotheses...

- Control for major confounders, by design and analysis
 - Smoking (DEMS)
 - Radon (DEMS)
 - Occupational hazards
 - Other risk factors
- Multiple modeling approaches
 - Cox proportional hazards modeling
 - Logistic regression
 - Continuous parametric models
 - Others

The Panel Conducted Analyses of Two Major Potential Confounders in DEMS: Smoking and Radon

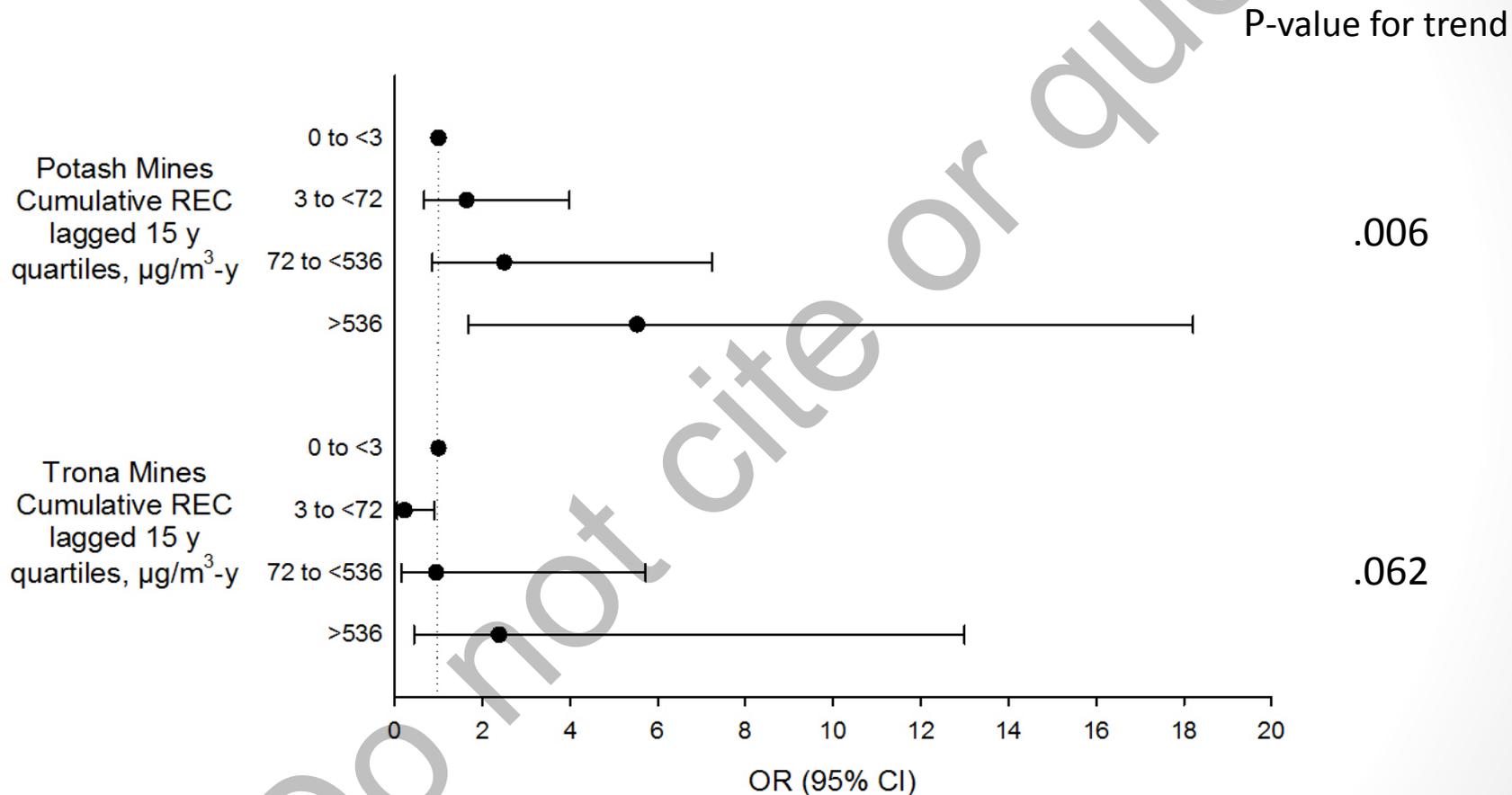
- Although there are many candidate confounders for lung cancer, the Panel concluded that there was no evidence indicating significant confounding that would invalidate the application of the Truckers or DEMS studies for quantitative risk assessment
- The most salient issue for future quantitative risk assessment would be the ability to understand the implications of any gaps (i.e., smoking and radon) on the degree of uncertainty in the exposure-response relationship

Other questions that might be asked...

- DEMS
 - Does the type of mine matter?
 - What is the risk experience of the miners who only worked underground and were likely to be most highly exposed?

Does the type of mine matter?

Analyses by the DEMS Investigators



Odds ratios and 95% confidence intervals for cumulative REC lagged 15 years, by mining facility without adjustment for radon (Silverman 2012, Table 7)

Does the type of mine matter?

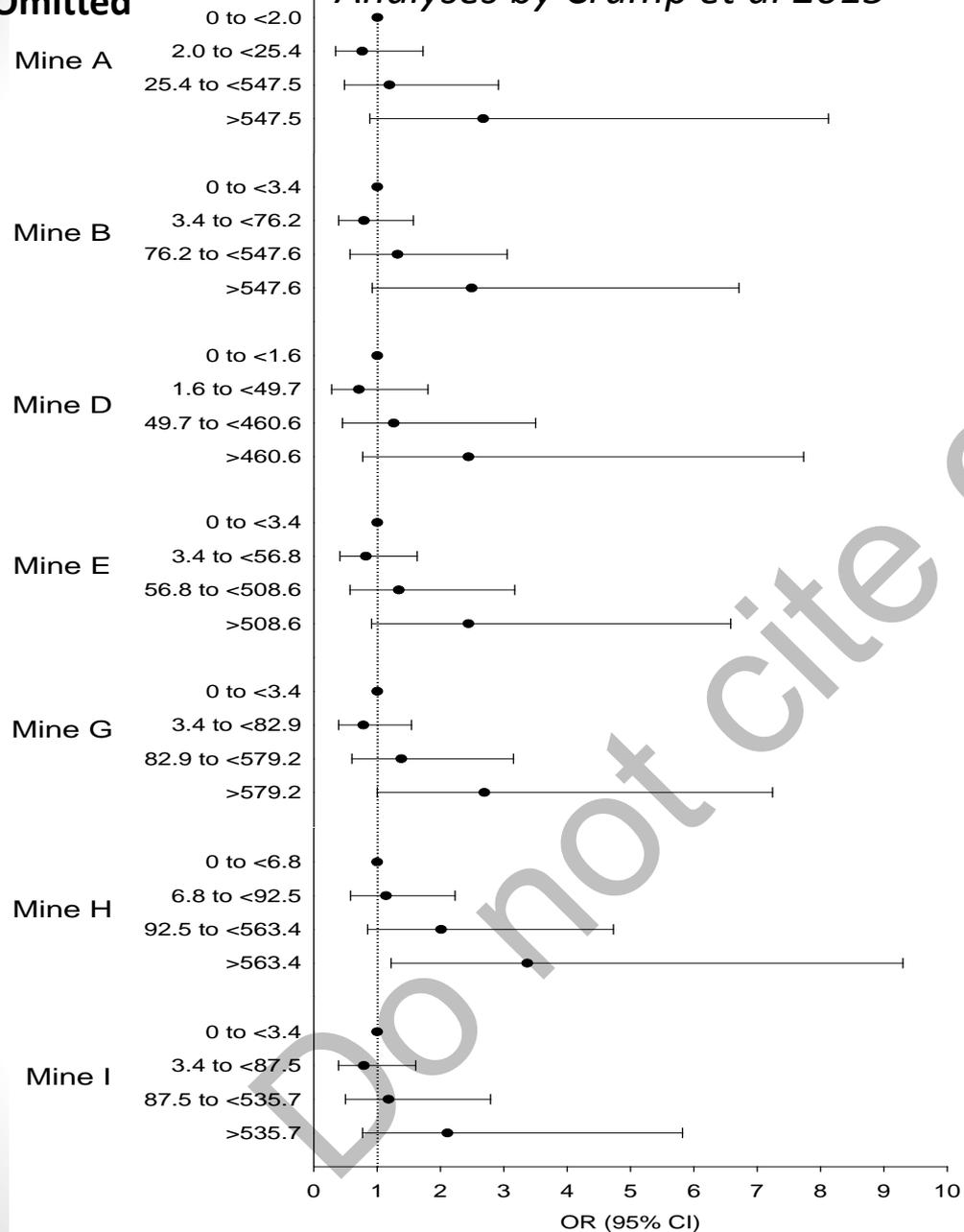
Analysis by Moolgavkar et al 2015

- 3 stage clonal expansion model
 - Time-varying exposure (Monthly average REC)
 - Significance test for fit of model: 2X log likelihood ratios
- Proportional hazards models
 - Log cumulative REC, lagged 15 years
 - Significance test for coefficient: p-value
- **Both models: significant results only for limestone mine and for complete cohort**

Does the Type of Mine Matter?

Analyses by Crump et al 2015

Mine Omitted



Mine Type

T-1 Trend
P-value

Limestone

0.02

Potash

0.02

Potash

0.03

Salt

0.03

Salt

0.02

Trona

0.03

Trona

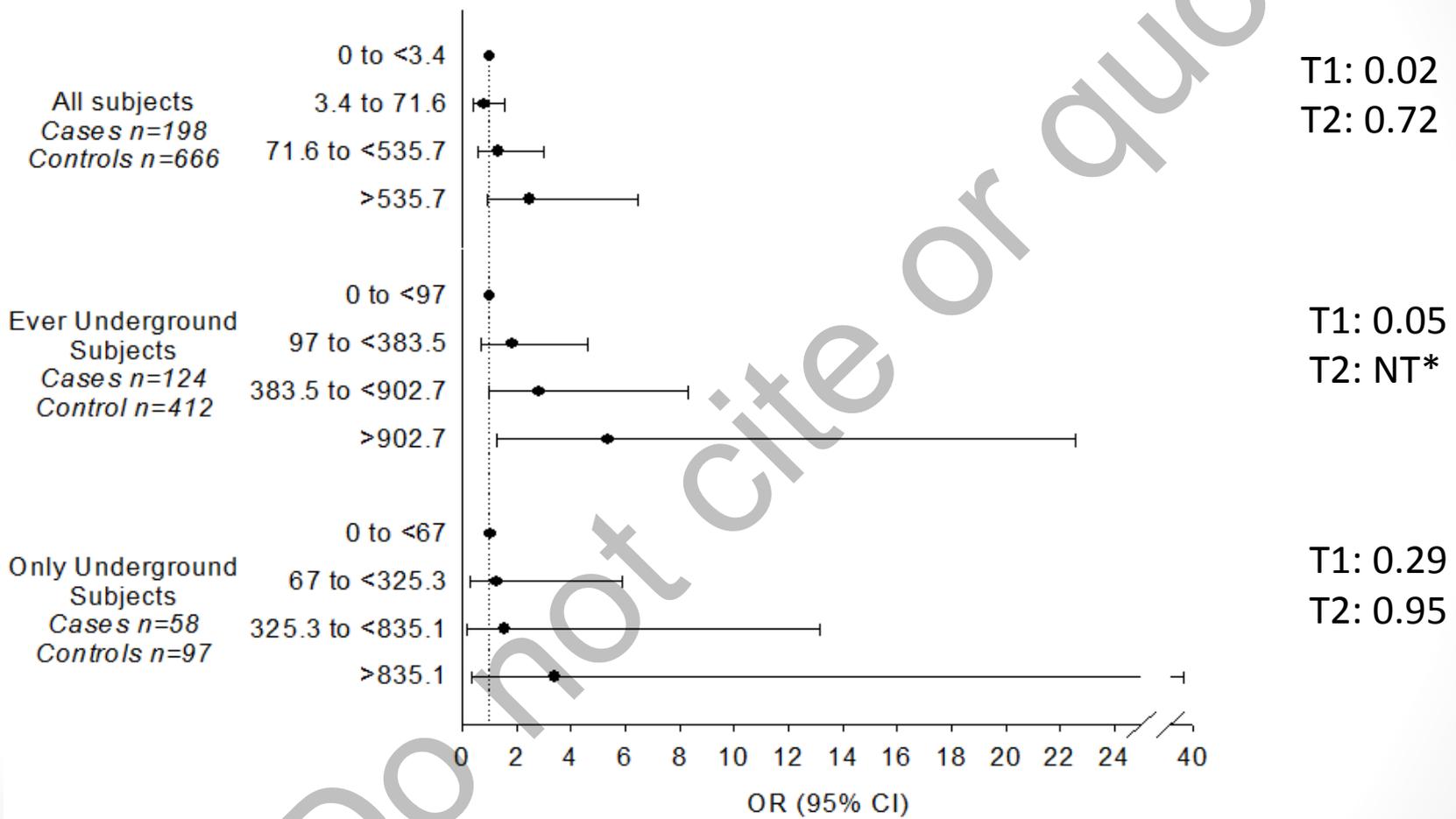
0.06

Cumulative Exposure Lagged 15 Years, **adjusted for radon "with radon" models**, for all subjects after omitting data from a single mine (Crump et al 2015, Table VI). Same test for trend as Silverman et al. 2012

Does the Location of the Workers Matter?

Analyses by Crump et al 2015

**Tests for Trend
p-value**



Odds Ratios and Trend Tests Based on Cumulative Exposure Lagged 15 years, Adjusted for Radon, by work location (Crump et al 2015). T1 test- average exposure; T2 – Continuous exposure assignments

*NT: Negative trend (not significant)

Other questions that might be asked...

DEMS

- Does the type of mine matter?
 - *There is little evidence in a careful mine-by-mine analysis of the case-control study that any one mine could explain all effects (although one analysis of the cohort data suggested that the mine with the highest level of exposure [Limestone mine A] had somewhat higher risks)*
- Does the location of workers matter?
 - *Effects seem consistent across different groups of miners*
 - *Nonetheless, results become less significant when one moves to the smallest group of miners (i.e. those who only worked underground)*

Overall Conclusions

- The HEI Panel found that the epidemiologic information that has accrued since the previous panel reported on this issue in 1999 is both relevant and informative.

Do not cite or quote

Overall Conclusions

- The Panel concluded that the DEMS and the Truckers studies, individually and collectively provide useful new information that advances our understanding of the relationship between the exposure to diesel exhaust experienced by the workers in those studies and their risk of lung cancer.

Translation from study to target population via quantitative risk analysis

What is the observed risk of lung cancer?



Risk characterization: modeling, assumptions, adjustments uncertainties:

- Population demographics
- Differences in smoking, other risk factors
- Levels and timing of personal exposures over a lifetime
- Changes in emission levels and composition

What is the predicted risk of lung cancer?



Other relevant data methods, and analyses

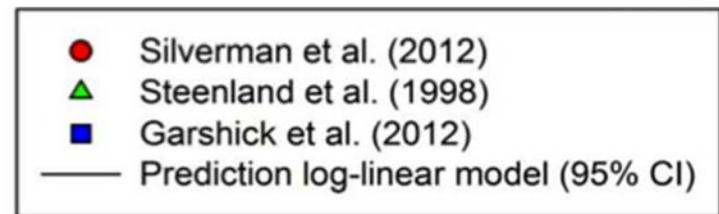
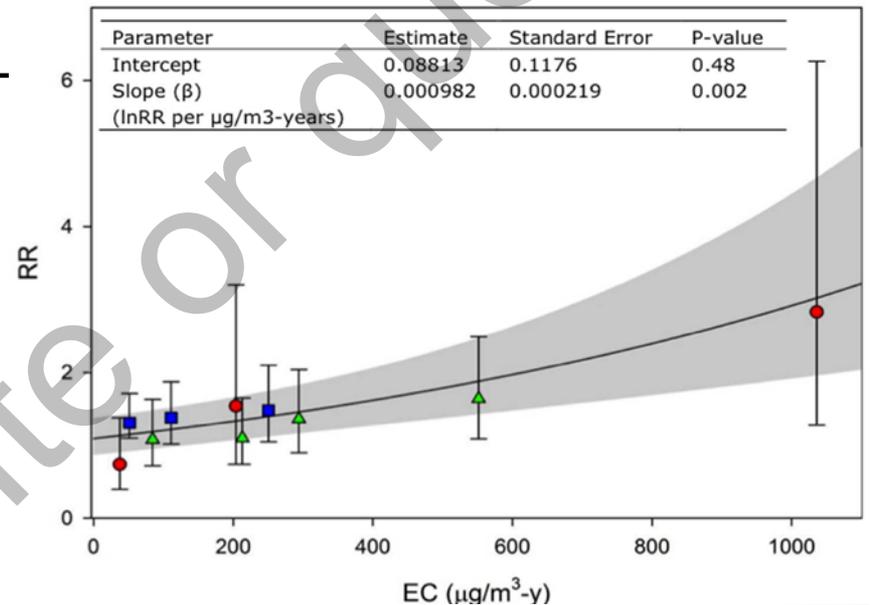
Recommendations:

For future risk assessments

- Sensitivity analyses with respect to historical exposures in both the DEMS and Truckers (see slide 23 in DEMERS presentation for details)
- More in-depth evaluation of a broader set of appropriate modeling approaches for projecting cancer risk over time
 - differing approaches to describing temporal patterns of exposure and risk
 - alternative flexible exposure-response models
 - further exploration of the applicability of biologically motivated models (including approaches to model validation)
- Consideration of possible effects of gender, ethnic, age, and susceptibility

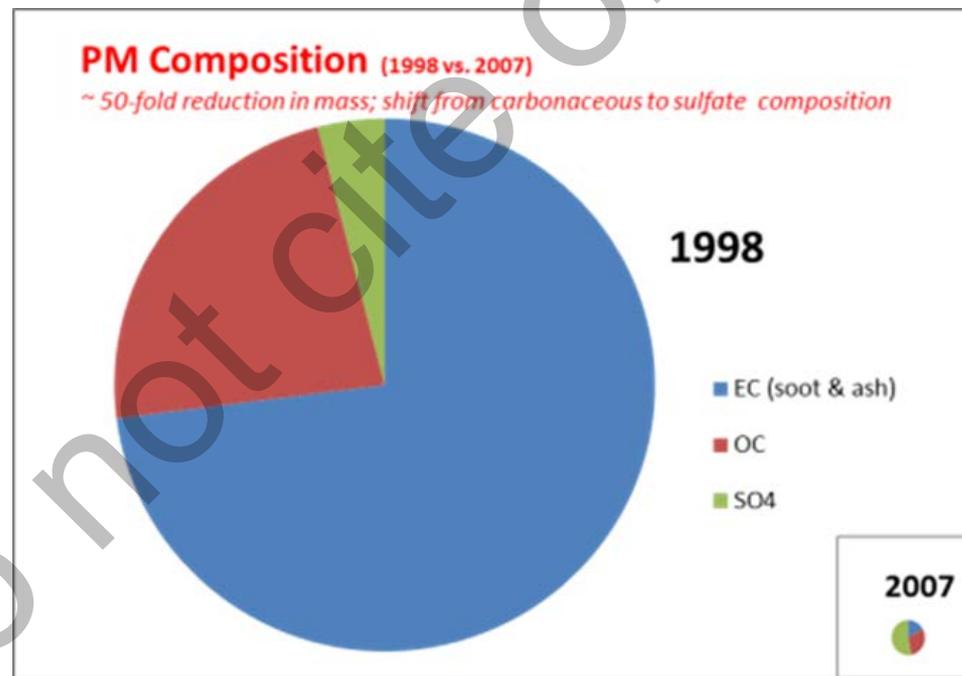
Recommendations: Additional Exploration of Combined Analyses

- Vermeulen et al. 2013 meta-analysis is one example.
- Other issues for consideration include:
 - Analyses with pooled data
 - Common standardized treatment of all data sets
 - Common exposure lags
 - Common covariate adjustments
 - Harmonization of different exposure metrics (REC, SEC, EC)



Recommendations: For future risk assessments

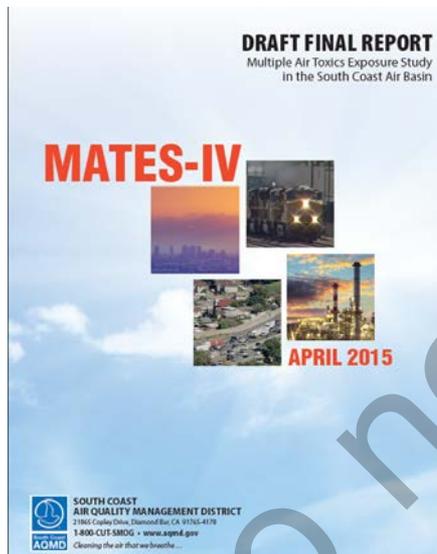
- Consider expected changes in the composition and toxicity of diesel exhaust



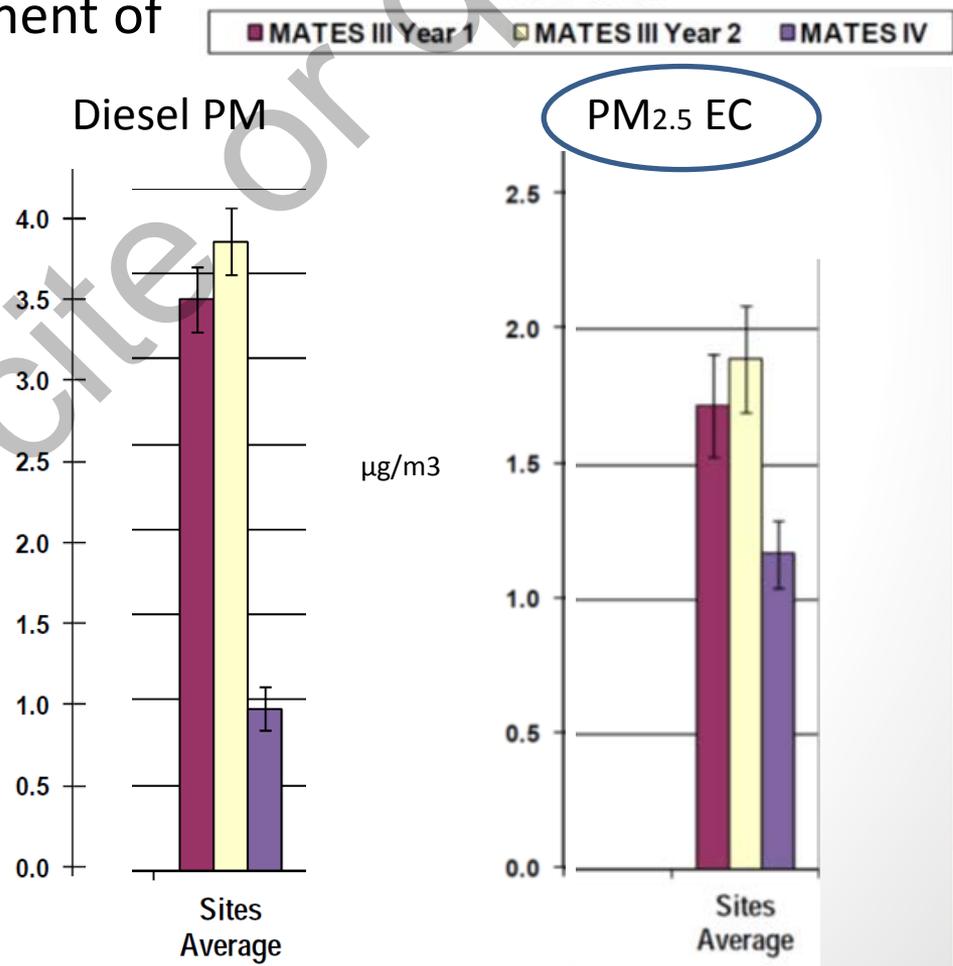
Advanced Collaborative Emissions
(ACES Project)

Recommendations: For future risk assessments

- Address declining diesel DPM and contributions to EC component of PM_{2.5} (1986-2015)



Los Angeles Basin



Overall Conclusions

- The Panel concluded that the data from the studies is sufficiently robust to develop quantitative assessments of human lung cancer risks, and
 - with support of other relevant data, methods, and analysis, to estimate risks at lower concentrations than observed in occupational studies, and
 - to characterize uncertainties in resulting risk estimates.

Current Status and Next steps

- ✓ Draft report completed and sent for external review
- ✓ All reviews received and transmitted to Panel
- ✓ Discussed twice by the Panel
- Report will be revised and published in months following the Annual Conference

Acknowledgements

HEALTH EFFECTS INSTITUTE:

DIRECTOR OF SCIENCE – RASHID SHAIKH

PROJECT MANAGER – KATY WALKER

PRINCIPAL SCIENTIST – AARON COHEN

REVIEW SCIENTIST – KATE ADAMS

RESEARCH ASSISTANT – ADAM CERVENKA

PUBLISHING – CAROL MOYER

UNIVERSITY OF OTTAWA:

NAGARAJ YENUGADHATI

YUANLI SHI