Goals of Today's Talk

Comment on Issues in Controversy

Interpret Cal-EPA's Analysis in Terms of an Overall Uncertainty Distribution

Indicate How an Analysis Based on My Own Judgments Might Differ

Major Issues in Controversy

"Threshold" Question--Can the current database be reasonably used to estimate the carcinogenic potency of diesel particulates, with appropriate qualitative and quantitative descriptions of the associated uncertainties?

- How much residual qualitative uncertainty should we have about whether diesel exhaust has some amount of carcinogenic activity in humans?
- How much uncertainty should we have that there is a true "cancer potency"--a linear incremental contribution to extra cancers caused by low dose diesel exposures?
- How have diesel particulates changed over the years, and what does this suggest for qualitative and quantitative changes in carcinogenic activity?

Dawson vs. Crump Analysis of the Railroad Worker Data

- Who is right?
- Is it possible to do better, and if so how?

A Tale of Two Clerks and an Engineer

	Crump Adj. Resp. Particulate Exposure Estimate	Dawson Diesel Excess Exposure Estimate
Clerk A--Age 60 in 1980; 5 years selling tickets, 35 years in a city department store	5*33 $\mu g/m^3$ = 165 $\mu g\text{-}yrs/m^3$	0
Clerk B--Age 60 in 1980; 20 years selling tickets, 20 years in a city department store	20*33 $\mu g/m^3$ = 660 $\mu g\text{-}yrs/m^3$	0
Engineer C--Age 60 in 1980; 10 years driving locomotives; 30 years in auto assembly work	10*88 $\mu g/m^3$ = 880 $\mu g\text{-}yrs/m^3$	10*50 $\mu g/m^3$ = 500 $\mu g\text{-}yrs/m^3$

Information on Likely Background Rural/Small Town Respirable Particulate from Spengler et al. (1985)*

City	Group	N	Mean RSP ($\mu g/m^3$)	SE
Kingston	Personal	133	42	2.5
	Indoor	138	42	3.5
	Outdoor	40	17	2.7
Harriman	Personal	93	47	4.8
	Indoor	106	42	4.1
	Outdoor	21	18	4.0
Total	Personal	249	44	2.8
	Indoor	266	42	2.6
	Outdoor	71	18	2.1

	Smoke exposed			Non-Smoke Exposed		
	N	Mean	SE	N	Mean	SE
personal	71	64	5.5	178	36	1.6
indoor	80	74	6.6	186	28	1.1

*Spengler, J. D., Treitman, R. D., Tosteson, T. D., Mage, D. T., and Soczek, M. L. "Personal Exposures to Respirable Particulates and Implications for Air Pollution Epidemiology" Environmental Science and Technology, Vol. 19, No. 8, pp. 700-707 (1985).

Probability-Tree Approaches for Analyzing Uncertainties

Toward a Fair Overall Analysis and Presentation of Uncertainties in the Cancer Potency for Diesel Exhaust

Choice of data set(s) for quantitative projections

Choices among statistical and biologically-based models of dose response relationships

Characterization of exposure amounts/time patterns

Statistical uncertainties in fitted parameters (random errors)

Characterizing the effects of various sources of potential systematic error in estimating parameters

My Interpretation of Cal-EPA Analysis

Characterization of Exposure Amounts/Time Patterns

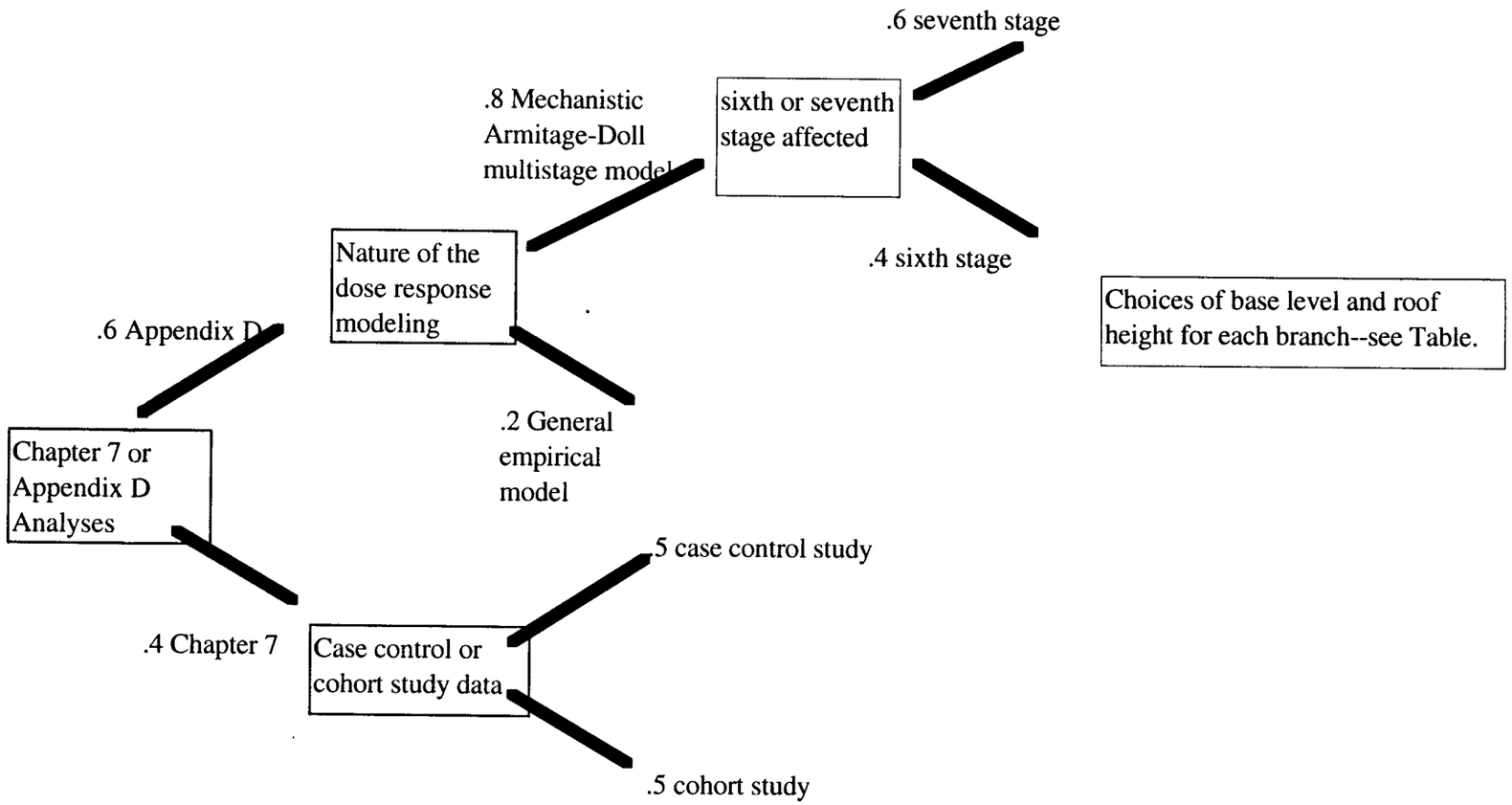
Base (1980) Excess Diesel Particulate Exposure of Train Crews over "Unexposed" Clerks

Base Excess Exposure ($\mu g/m^3$)	Weight
40	30%
50	50%
80	20%

Height of the "Roof" (Ratio of 1959 Excess Train Crew Exposures to 1980 Train Crew Exposures)

Height of "roof"	Weight
1	5%
2	20%
3	50%
5	20%
10	5%

"Tree" Diagram for the Weighting of Different Choices of Dose Response Models and Data Sets for Estimating the Cancer Potency of Diesel Particulates

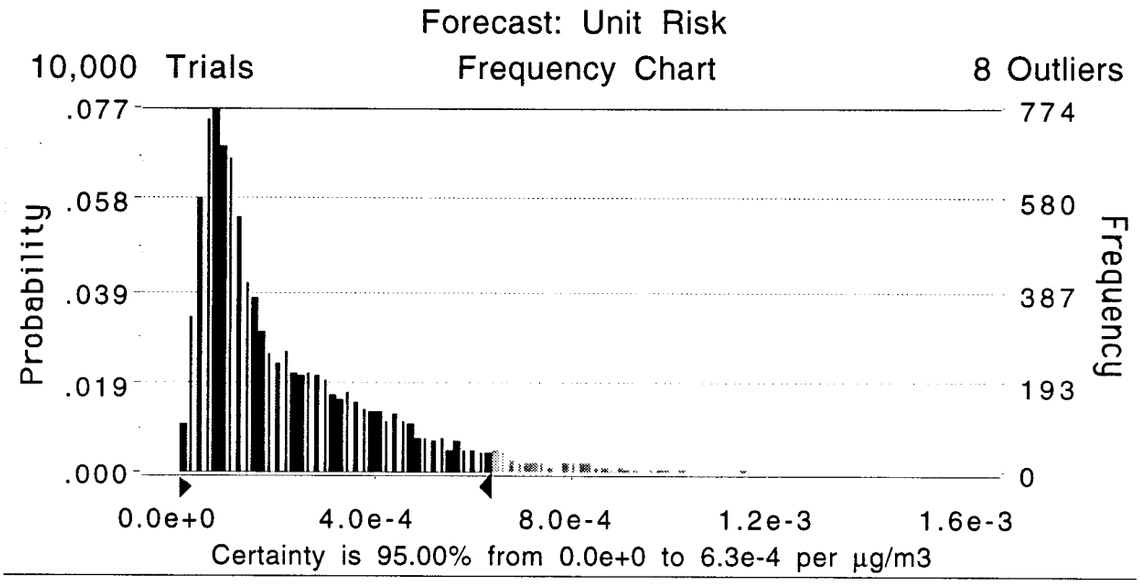


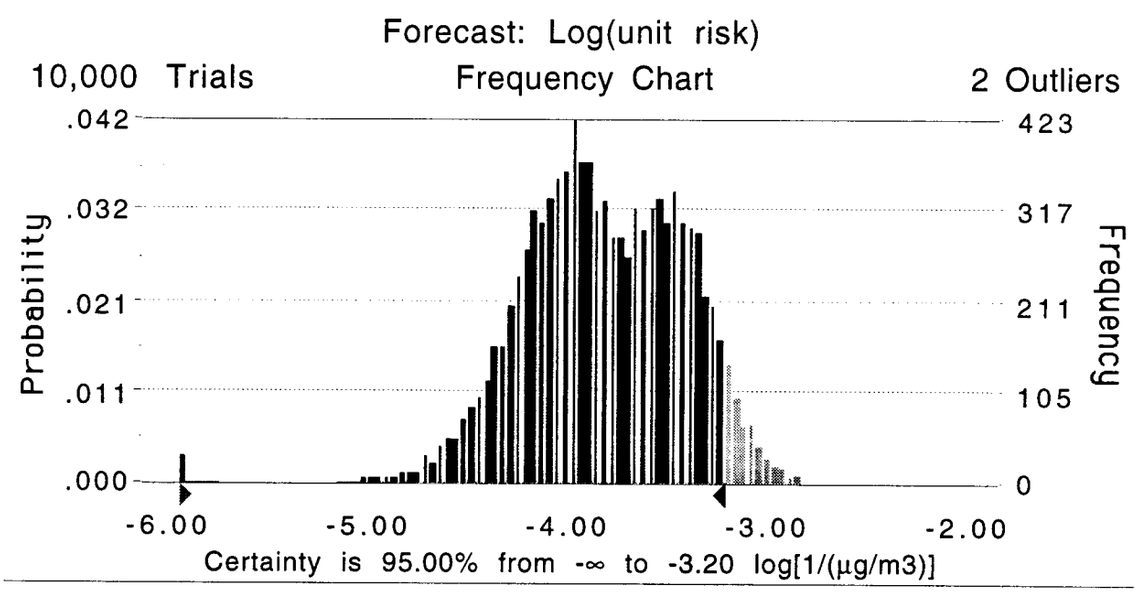
Statistical Uncertainties in Fitted Parameters (Random Errors)

q1 (ug/m^3)^-1

	MLE	95% LCL	95% UCL	MLE-95% LCL	95% UCL-MLE	Indicated Standard Error	Std Error /MLE
I. Case-Control study (1987a) using published slope coefficient for hazard on years of exposure to diesel exhaust (Section 7.3.3)							
A. Ramp (1,50) pattern of exposure	9.1E-04	2.9E-04	1.5E-03	6.1E-04	6.3E-04	3.8E-04	0.415
B. Roof (2,40) pattern of exposure	7.0E-04	2.3E-04	1.2E-03	4.8E-04	4.8E-04	2.9E-04	0.413
C. Roof (3,50) pattern of exposure	4.1E-04	1.3E-04	6.9E-04	2.8E-04	2.8E-04	1.7E-04	0.413
D. Roof (3,80) pattern of exposure	2.5E-04	8.2E-05	4.3E-04	1.7E-04	1.7E-04	1.1E-04	0.413
E. Roof (10,50) pattern of exposure	1.4E-04	4.5E-05	2.3E-04	9.4E-05	9.5E-05	5.7E-05	0.413
II. Cohort study (1988) using individual data to obtain a slope for hazard on years of exposure to diesel exhaust (Section 7.3.4)							
A. Ramp (1,50) pattern of exposure	6.2E-04	2.4E-04	9.7E-04	3.8E-04	3.5E-04	2.2E-04	0.360
B. Roof (2,40) pattern of exposure	4.8E-04	2.1E-04	7.5E-04	2.7E-04	2.7E-04	1.6E-04	0.344
C. Roof (3,50) pattern of exposure	2.8E-04	1.2E-04	4.3E-04	1.6E-04	1.6E-04	9.5E-05	0.344
D. Roof (3,80) pattern of exposure	1.7E-04	7.5E-05	2.7E-04	9.8E-05	9.8E-05	5.9E-05	0.344
E. Roof (10,50) pattern of exposure	9.4E-05	4.1E-05	1.5E-04	5.3E-05	5.3E-05	3.2E-05	0.344
III. Cohort study (1988) applying time varying concentrations to individual data to obtain a slope of hazard on exposure (from Appendix D)							
A. Ramp (1,50) pattern of exposure							
1. general multiplicative model with age-at-start-of-study and U.S.rates as categorical covariates	7.9E-04	3.6E-05	1.2E-03	7.6E-04	4.1E-04	3.6E-04	0.448
2. 6th/7-stage model with age-at-start-of study as categorical covariate	2.4E-04	9.7E-05	3.8E-04	1.4E-04	1.4E-04	8.6E-05	0.363
B. Roof (3,50) pattern of exposure							
1. general multiplicative model with age-at-start-of-study and U.S.rates as categorical covariates	3.3E-04	1.6E-04	4.7E-04	1.6E-04	1.4E-04	9.1E-05	0.279
2. 6th/7-stage model with age-at-start-of-study as categorical covariate	8.1E-05	2.8E-05	1.3E-04	5.2E-05	5.4E-05	3.2E-05	0.399
3. 7th/7-stage model with age-at-start-of-study as categorical covariate	9.0E-05	4.7E-05	1.3E-04	4.3E-05	4.1E-05	2.5E-05	0.283
C. Roof (5,50) pattern of exposure							
1. 6th/7-stage model with age-at-start-of-study as categorical covariate	5.1E-05	1.8E-05	8.3E-05	3.3E-05	3.3E-05	2.0E-05	0.390

Results of a Probability-Tree Characterization of Cal-EPA's Current Analysis





Results of a Probability-Tree Characterization of Cal-EPA's Current Analysis

	Run #1 (10,000 trials)	Run #2 (10,000 trials)
Mean	2.3E-04	2.3E-04
% Tiles:		
5	3.4E-05	3.4E-05
10	4.7E-05	4.6E-05
50	1.5E-04	1.5E-04
90	5.0E-04	5.1E-04
95	6.3E-04	6.6E-04

Toward an Analysis Incorporating Some Additional Considerations

Use of Spengler et al. (1985) data to estimate "background" non-cigarette respirable particulate exposures of train crew members, and therefore re-estimate "base" excess exposure level distribution (including uncertainty due to possible imperfect representativeness of existing measurements)

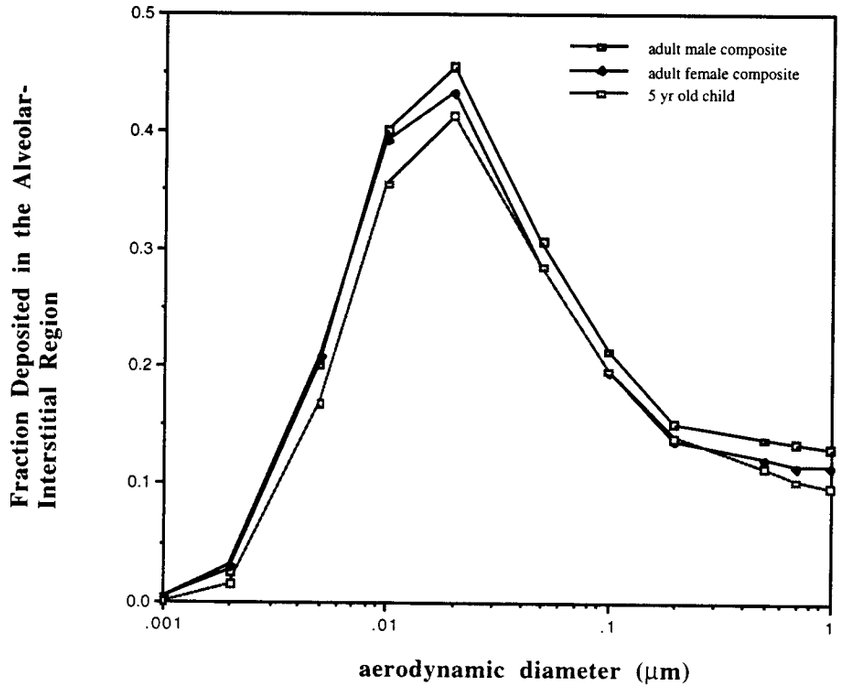
Continuous, rather than discrete representation of some parameters (e.g., base level, height of the "roof")

Some weighting of other relevant sources of information

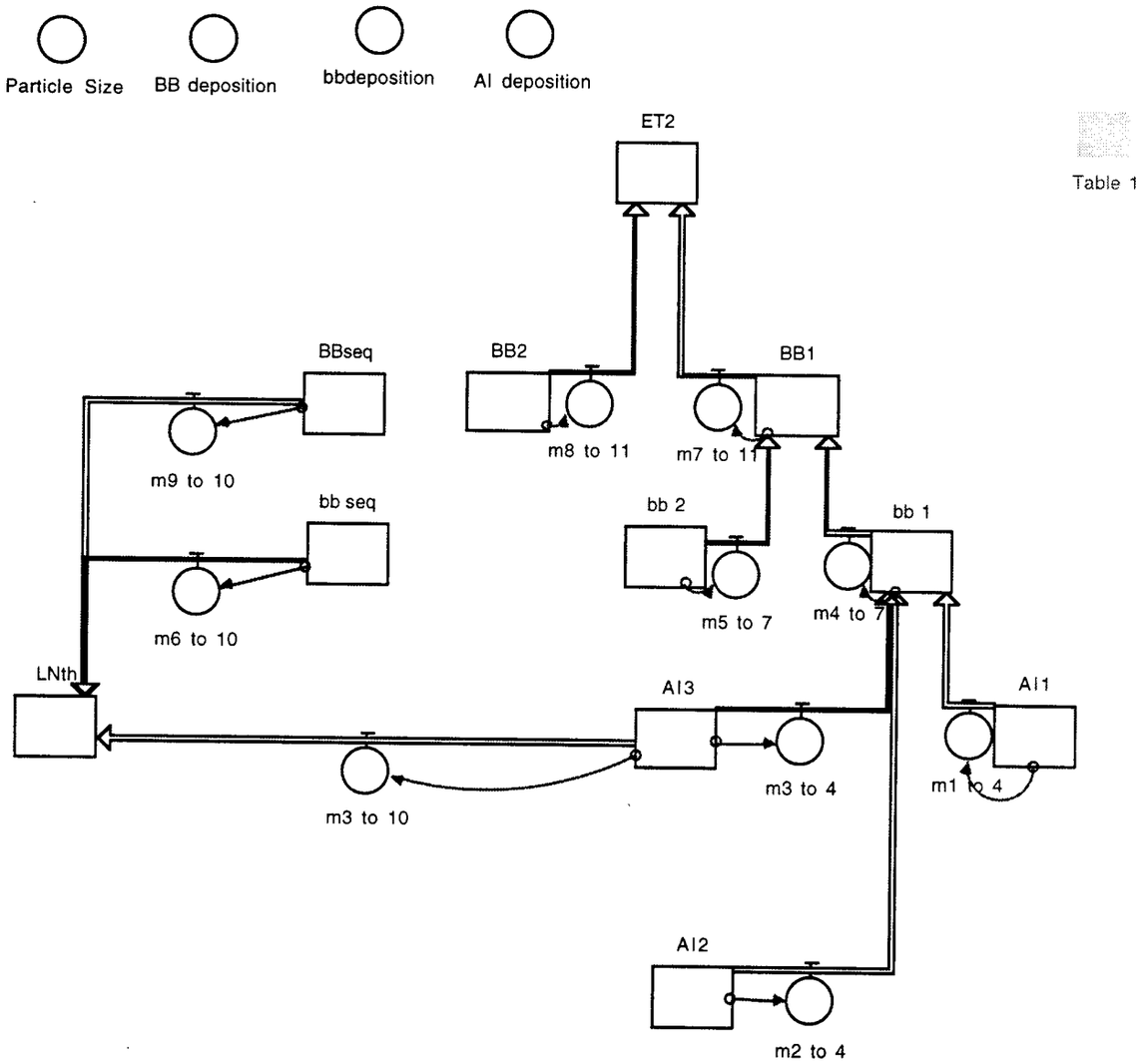
- Meta-analysis results, with uncertainty in exposure levels
- Animal data, with analogies for the rat/human lung cancer potency comparisons for radon progeny and possibly cigarette smoke
- Comparative mutagenic potency data from in vitro systems

Distribution of likely relative potency of "new" diesel particulates, with a tendency toward smaller particle sizes

Activity-Composite Estimates of ICRP Model Alveolar-Interstitial Lung Deposition for Different Population Groups



ICRP Model of Particulate Elimination from Different Lung Compartments



Three Statistical Problems

"Errors in variables" problem

Risk heterogeneity/saturation problem

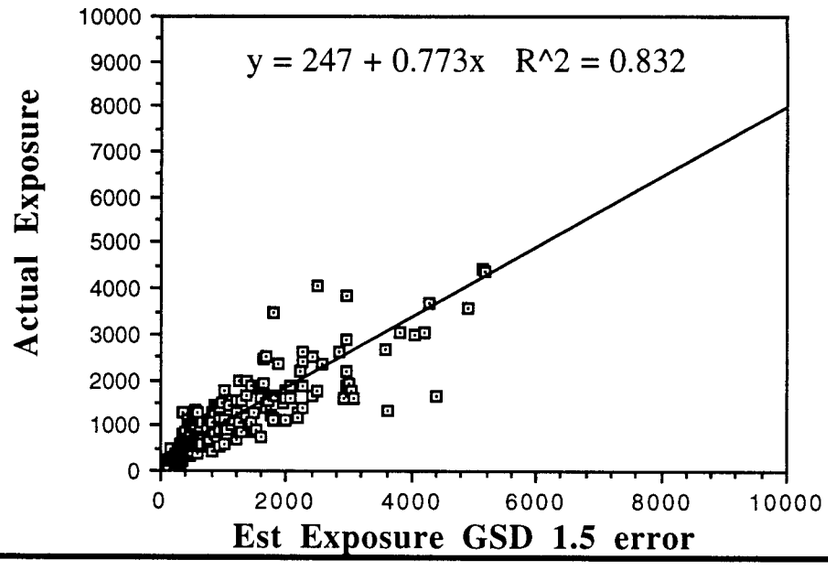
Adverse selection with dose and smoking with time since exposure tends to change average remaining doses and susceptibility of survivors within groups

"Errors in Variables" Problem

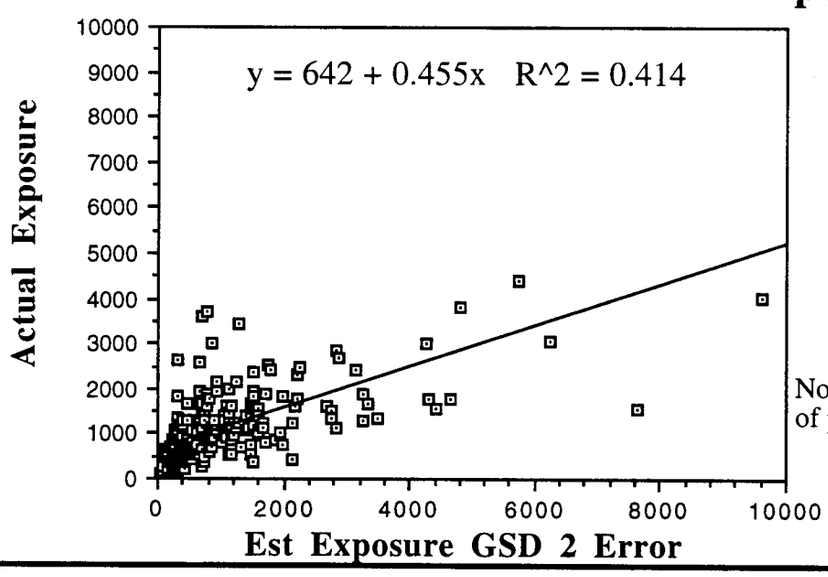
Uncertainty in the estimated exposure levels leads to misclassification and bias toward a lower slope in the relationship between exposure and risk.

Conventional regression approaches assume that the average exposure within a dose group is known without error.

GSD 1.5 Error--Actual vs Estimated Exposure

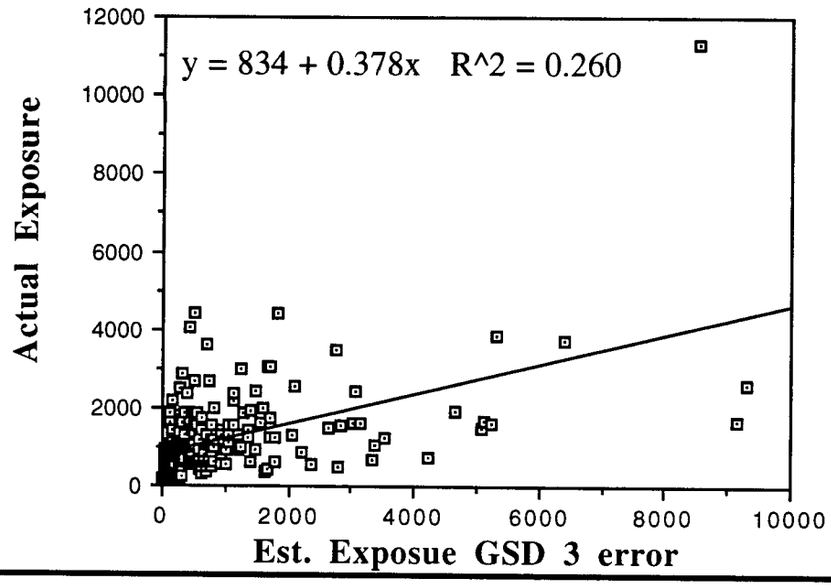


GSD2 Error--Actual vs Estimated Exposure

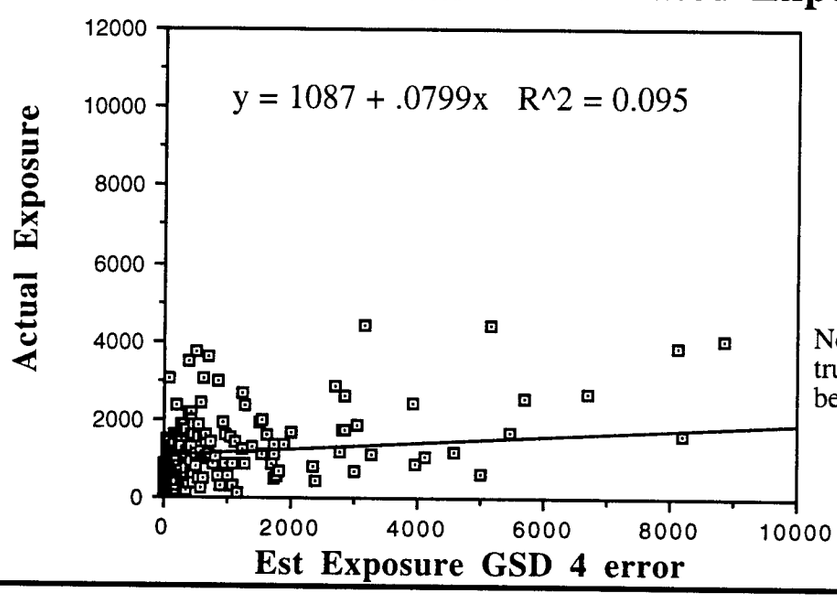


Note--some truncation of points beyond 10,000

GSD 3 Error--Actual vs Estimated Exposures

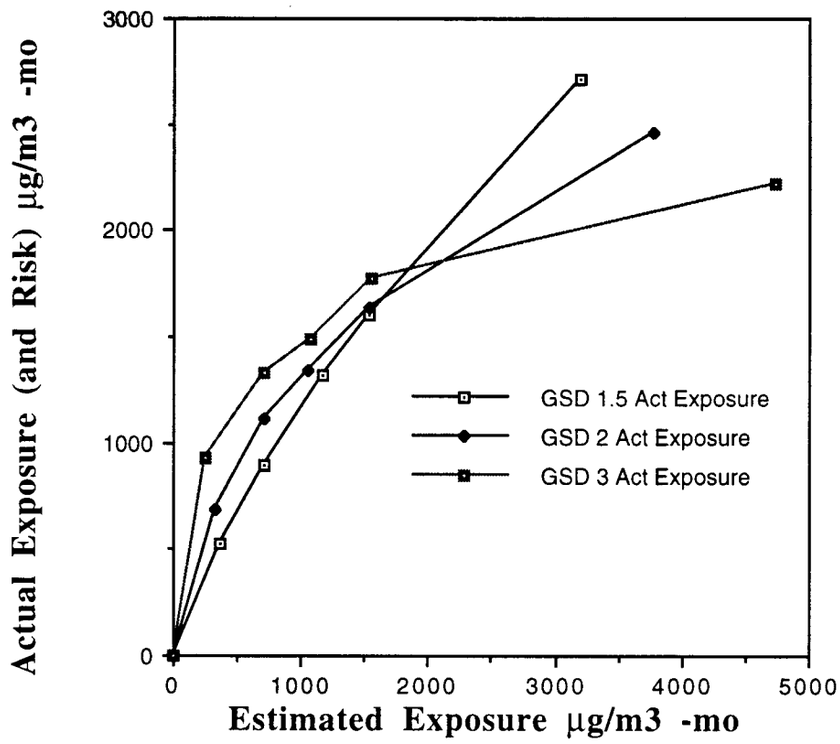


GSD 4 Error--Actual vs Estimated Exposures



Note--considerable truncation of points beyond 10,000

Simulated Effects of Various Amounts of Uncertainty in Individual Dose Estimates for Dose Response in 6 Categories



Risk Heterogeneity/Saturation Problem

People within exposure groups differ in

(1) actual individual dose

(2) dose-enhancing confounders (e.g. cigarette smoking) and

(3) other susceptibility factors

Average "background" lifetime risk of lung cancer is relatively high (about 6%).

There is not much room above this for differences in susceptibility and exposures to have their full effect before there is a significant truncating effect from the fact that only one lung cancer can be counted per person.

Adverse Selection with Time

Higher mortality among heavy smokers from causes other than lung cancer will tend to truncate the years of exposure (and therefore the cumulative dose) of the most at-risk individuals with the greatest accumulated internal dose.

Deaths of the most highly exposed and susceptible people over time will lead to a reduction in the average exposure and susceptibility for the survivors within exposure categories.