

A Probability-Tree Interpretation of the California EPA's Analysis of the Cancer Risk from Diesel Particulates

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Abstract

The Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency has recently published an extensive draft analysis of the carcinogenic potency of diesel particulates. However in that document the results are primarily summarized in the form of a sensitivity analysis of the risk projections to the different choices of modeling assumptions that were made, and the overall range of values considered by the authors to be plausible.

The present report supplements this presentation with a weighted distributional analysis of the combined effects of the sources of uncertainty studied by the Cal-EPA researchers. A probability-tree model is defined to represent assessments of the relative plausibility of different choices of (a) the data sets to be analyzed, (b) mathematical model forms, (c) patterns of likely past exposure for the principal human epidemiological studies, and (d) statistical sampling uncertainties. The relative weights at various nodes of the probability tree were assigned to represent the views of the Cal-EPA analysis team, as expressed in their document, and supplemented with some private conversations with members of the team.

Based on the assessment of the weights in the model that are most consistent with the Cal-EPA's discussion, the upper 95% confidence level for diesel cancer risk, which appears to be most relevant to notification requirements under California's "Proposition 65" law, is about 6.5×10^{-4} per $1 \mu\text{g}/\text{m}^3$ of continuous lifetime average diesel particulate exposure. The corresponding mean "expected value" estimate of risk, relevant for comparative analyses of the benefits and costs of control efforts, is about 2.3×10^{-4} per $\mu\text{g}/\text{m}^3$ of lifetime average diesel particulate exposure. A sensitivity analysis of the effect of varying different weightings in the model over a relatively extreme range indicates that it is difficult to construct a plausible reading of the Cal-EPA document that would come to conclusions for mean or 95% confidence level more than 2.5-fold different from the estimates given above.

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Introduction

In February of 1998, the Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency published an extensive revised draft analysis of the carcinogenic potency of diesel particulates, along with much other information on potential health effects of other types (Dawson et al., 1998). The carcinogenic risk estimates were summarized in the form of an overall range in the 95% upper-confidence limit (UCL) potency values calculated from two epidemiological studies using different approaches (last column of Table 1, from Table 1-1 of the Cal-EPA document), with some further comparisons to results of projections from animal and other data.

Table 1

Cal-EPA Upper Confidence Limit Cancer Potency Estimates for Diesel Particulates For Different Choices of Human Data Set and Modeling Assumptions

Data Set and Dose Response Modeling Approach	Base Level ($\mu\text{g}/\text{m}^3$), and Exposure Pattern (Height of “Roof”)¹	95% UCL Cancer Unit Risk ($\mu\text{g}/\text{m}^3$)
Garshick et al (1987a) case control study, Analyzed in Sec. 7.3.3 using published slope coefficient for hazard on years to diesel exhaust	Base 50, ramp 1	1.5E-3 ²
	Base 40, roof 2	1.2E-3
	Base 50, roof 3	6.9E-4
	Base 80, roof 3	4.3E-4
	Base 50, roof 10	2.3E-4
Garshick et al. (1988) cohort study, analyzed in Sec. 7.3.4 using individual data to obtain slope for hazard on years of exposure to diesel exhaust	Base 50, ramp 1	9.7E-4
	Base 40, roof 2	7.5E-4
	Base 50, roof 3	4.3E-4
	Base 80, roof 3	2.7E-4
	Base 50, roof 10	1.5E-4
Garshick et al. (1988) cohort study, analyzed with a general multiplicative model	Base 50, ramp 1	1.2E-3
	Base 50, roof 3	4.7E-4
Garshick et al. (1988) cohort study, analyzed with a biologically-based Armitage-Doll multistage model	Base 50, ramp 1	3.8E-4
	Base 50, roof 3	1.3E-4

¹The “Base” levels here refer to the excess of train rider exposures to cigarette-smoke adjusted respirable particulates over those of the clerks who were assumed to be exposed only to background non-diesel particulate matter. The “ramp” refers to an assumed pattern of exposures in which a simple linear increase in exposures between 1945 and 1959 (by 1959, diesel locomotives had nearly completely displaced other types of engines in use) followed by constant exposures thereafter until the time of the measurements in the early 1980’s. The “roof” pattern

also assumes a linear rise with the introduction of diesel engines until 1959, but to a larger peak level, followed by a linear decline with improvement in engine technology and operation to the level of the measurements in the early 1980's. The height of the "roof" (e.g. "roof 2"; "roof 3" represents the assumed ratio of 1980 exposures to 1959 exposures

²Note: The notation 1.5E-3 means $1.5 \times 10^{-3} = 0.0015$.

Cal-EPA's summary ranges of UCL's (and, elsewhere in the document, Maximum Likelihood Estimates--MLE's) serves the purpose of informing the reader of the sensitivity of the risk projections to the different choices of modeling assumptions that were made, and the overall range of upper-confidence-limit values considered by the authors to be plausible. However this type of representation does not capture the authors' judgments as to how likely the different possibilities are. It also does not convey a "bottom-line" overall probability distribution taking account of all the uncertainties that the authors have studied.

A more condensed summary probability distribution could achieve a clearer communication of likely risks, and has at least two potential types of specific applications. Contingent on the acceptance of Cal-EPA's set of analytical assumptions and the weights given different combinations of assumptions,

- It would provide a way to make arithmetic mean "expected value" estimates of diesel particulate risks and the potential benefits of different control options. Such estimates are most appropriate for juxtaposition of the costs and benefits of measures that might be taken to change human exposures to diesel particulates in either occupational or environmental settings (Arrow and Lind, 1970; Hattis and Anderson, 1998 in press).
- It would allow calculation of defined upper confidence limit estimates of cancer risk as a function of exposure (e.g., "based on the analysis, one can be 95% confident that the lifetime cancer risk per lifetime exposure to 1 µg/cubic meter of diesel particulate is less than ----.") Such estimates are needed, for example, to decide

when the risk notification requirements of California's "Proposition 65" law are triggered.*

This report develops a "probability tree" model to reflect as closely as possible the views expressed and implied by the Cal-EPA analysts about the relative likelihood of different possible choices at various stages in the estimation of the cancer potency of diesel particulates. The intent of the initial analysis here is to reflect the Cal-EPA analysts' views, rather than those of the author of this report, because (1) the Cal-EPA analysts have done a very extensive and sophisticated study of the basic scientific and statistical merits of different analytical approaches, the quality of data fits, and other considerations that cannot be easily replicated, and (2) the draft Cal-EPA analysis as it stands is most recent official expression of the likely risks of diesel particulates that seems likely to be considered relevant for interpretations of California law. The reader is cautioned, however, that although the model presented here has been constructed to reflect the views of the Cal-EPA team with the aid of the official risk document as supplemented by a limited number of private conversations with members of the team, the specific probability estimates carry no official endorsement from the California Environmental Protection Agency.

The presentation below is in four sections. The first will document the basic structure of the model, and its development. Then there will be a short section describing the implementation of the model in an Excel spreadsheet for Monte Carlo simulation* run using the "Crystal Ball" system (Decisioneering, Inc., Denver Colorado) for iteratively running many individual "trials" of the model. The final sections will then show the results of duplicate runs

* California's Proposition 65 statute is intended to promote public health in part by imposing a duty for manufacturers of consumer products to warn the public of carcinogenic and reproductive hazards in their products that, under reasonably "conservative" risk assessment rules, are judged to pose "significant" risks (1/100,000 on an individual lifetime basis, as defined in the statute).

* A Monte Carlo simulation is a simple way of calculating the distribution of some outcome parameter (in this case the lifetime cancer risk per $\mu\text{g}/\text{m}^3$ of lifetime exposure to diesel particulates) given distributions for several input parameters. On each "trial" of a Monte Carlo simulation, the computer chooses a random value from the specified distribution for each input parameter and calculates the resulting value of the outcome parameter(s). After many individual "trials" have been done, the accumulated set of values of the outcome parameters is assembled into an overall distribution.

of 10,000 “trials” each for a couple of different forms of the model, do some sensitivity analysis and discuss the results. Full documentation of the model structure and one of the runs can be found in appendices.

Development of the Model

Nature of the Model and Approach to Model Construction

Some years ago, the author participated as one of six expert informants in the development of a probability tree for analysis of the cancer potency of chloroform from available animal bioassay data (Evans et al., 1994a). The probability-tree model developed here is in the tradition of that effort and other work by the same group (Evans et al., 1994b), although with some simplifications.

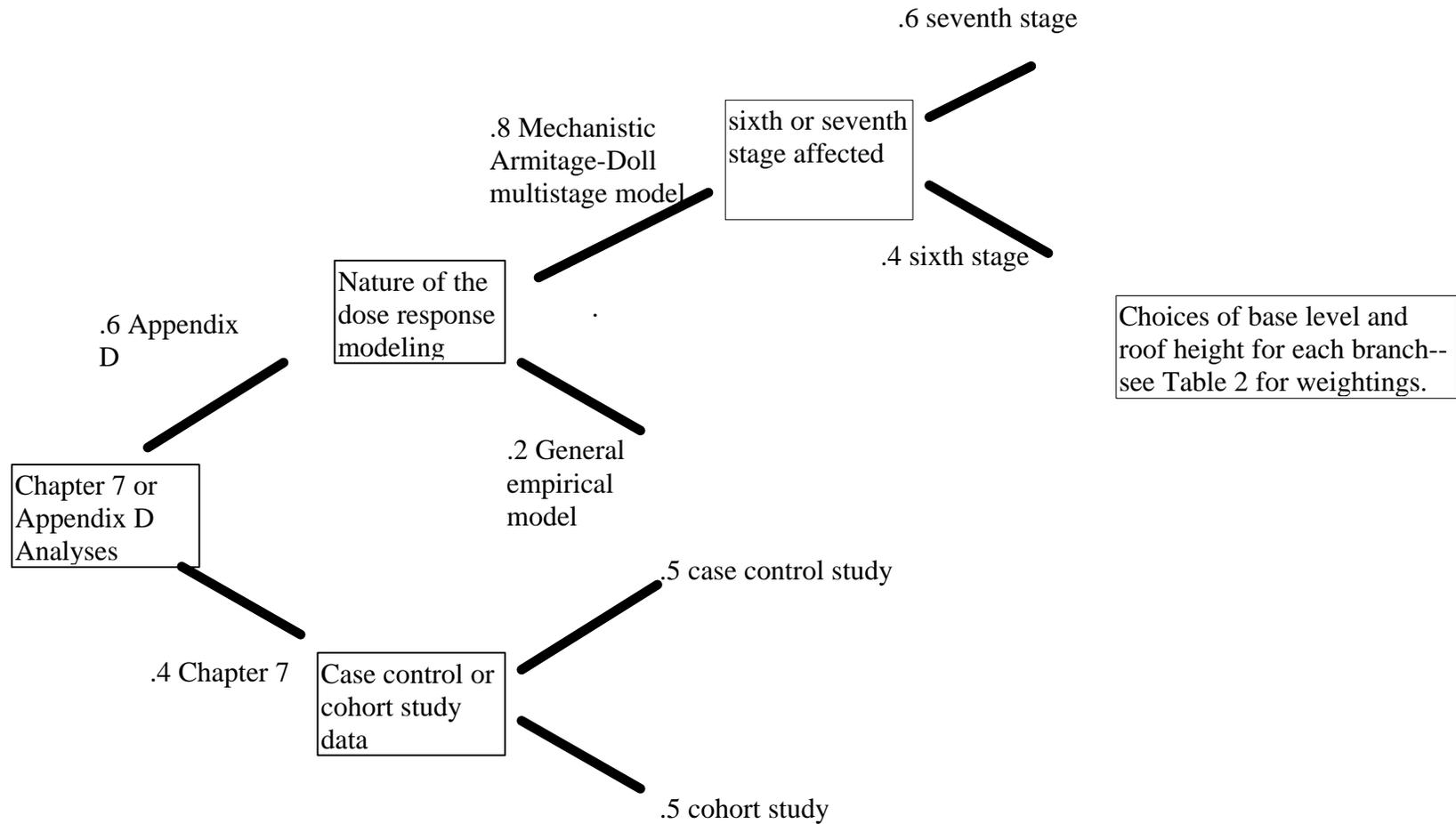
A probability tree is simply a structured series of questions (referred to as “nodes” in the jargon of the field). The questions can take the form of which data set(s) to use in estimating human risks, which mathematical model forms to use in representing dose response relationships, and subsidiary assumptions such as how to express the dosage of the toxicant (e.g., mg/kg body weight, mg/surface area, etc.) For each question, the expert informant(s) are asked to provide their individual judgment(s) about the relative likelihood of different available choices to follow in further quantitative analysis of the risk under consideration.

For the simple analysis reported here, the extensive documentation available in the Cal-EPA report made it relatively straightforward to construct the basic sequence of analytical choices. Initial values for each node were generated prior to the first (June 1997) informal conversation with a member of the Cal-EPA team based on the presentation in Dawson et al. (1997), including observations there of preferences on mechanistic grounds and on grounds of the relative quality of model fits. Then these numerical assignments were updated in a series of subsequent telephone conversations. With the publication of the February 1998 version of the Cal-EPA document, the earlier probability trees were simplified to exclude projections from the available animal data (following Cal-EPA’s decision not to include the animal-based estimates

in their stated range of estimated human potencies), the choices of different “base” levels (1980 excesses of train rider exposures over those of unexposed workers) were added to the tree, and the number of values for the height of the “roof” was expanded from the simple “ramp” (roof =1) vs roof 3, to include roof 2, roof 5, and roof 10, as indicated by the presentations in Table 1 above and Table 2 below. The overall structure of the tree is given in Figure 1.

Figure 1

“Tree” Diagram for the Weighting of Different Choices of Dose Response Models and Data Sets for Estimating the Cancer Potency of Diesel Particulates--February 1998 Perceptions



Animal Vs Human Data as the Basis for Human Risk Projections

Previous versions of the Cal-EPA document included some calculations derived from the carcinogenesis bioassay experiments in rats in their final summary risk range, although they clearly placed much greater weight on the projections from human epidemiological data. In the current summary of the range of risk projections, however, only human-derived risk estimates are included. The animal-based calculations are still present in the document, but are clearly retained mainly for background perspective. Accordingly in the current stochastic representation of Cal-EPA's weightings presented here, no weight has been assigned to the animal-based risk estimates.

Choices in the Projection of Risks from the Human Epidemiological Data

Chapter 7 Analyses vs Analyses Presented in Appendix D

In earlier versions of the Cal-EPA document there was a clear distinction between the risk projections developed in Chapter 7 in comparison to those presented in the Appendix section. Formerly, Chapter 7 used risk analyses previously published by others to infer unit risks for diesel exhaust--whereas the completely original analyses done by Cal-EPA itself were presented in the Appendices. The distinction in the current document is less clear cut. The Chapter 7 projections are still based in part on analytical work and methodology published by others, and arrive at quantitative conclusions primarily in the form of excess risk per year of exposure (for the train-riding workers who were deemed "exposed") following those earlier efforts. But the current analyses in Chapter 7 also incorporate substantial new work by Cal-EPA itself to refine those estimates, and express them using the same range of exposure pattern assumptions as is used in Appendix D. Additionally, Cal-EPA has now made it clear that it tends to favor the Appendix D analyses, referring to them as likely to be more accurate in that they incorporate more sophisticated models of carcinogenesis and other assumptions that Cal-EPA considers more likely to be appropriate (Dawson et al., 1998, p. 7-27). To recognize this

expressed preference, a weighting of .6 has been assigned to the Appendix D analyses, leaving .4 to be split among the two sets of risk projections (from the case control vs the cohort study, respectively) that are presented in the main text of Chapter 7.

Mechanistic Armitage-Doll Model Vs a General Empirical Epidemiological Model

The Cal-EPA document emphasizes that the Armitage-Doll multiple mutation model of carcinogenesis has a strong foundation in what is known about the process that leads to cancer in humans. It is now well established that cancer is the end result of a series of changes and/or rearrangements in the information coded in DNA* in individual relevant cells/cell lines (probably a small minority of relatively undifferentiated “stem” cells). This model differs from the general epidemiological model in internal construction and in the biologically-based weighting of exposures experienced at different ages, relative to the general model which simply adds up cumulative exposure up through a relevant time period. The Armitage-Doll model is therefore to be preferred on first principles (Dawson et al., 1997, p. E-7; Dawson et al., 1998 p. D-8). In addition, it turned out that models constructed on this basis fit the Garshick et al. lung cancer data somewhat better than the standard general empirical epidemiological models used

* For a general discussion of older evidence see Vogel, F. and A. G. Motulsky (1979) Human Genetics--Problems and Approaches Springer-Verlag, New York, pp. 326-329; Fialkow, P. J. (1977) "Clonal origin and stem cell evolution of human tumors," In Genetics of Human Cancer (Mulvihill, J.J., et al., eds.) 439. Raven, New York; Knudson, A. G. (1973) "Mutation and Human Cancer," *Adv. Cancer Res.* 17, 317-352; Knudson, A. G. (1977). "Genetics and Etiology of Human Cancer," *Adv. Hum. Genet.* 8, 1-66. More recently molecular biologists have made significant progress in characterizing exactly which kinds of changes in which specific genes are involved in producing specific types of cancer in people. See, for example, Weinberg, R. A. "The molecular basis of oncogenes and tumor suppressor genes." *Ann N Y Acad Sci* 758:331-338 (1995); Weinberg, R. A. "Oncogenes and tumor suppressor genes." *CA Cancer J Clin* 44: 160-170 (1994); Yunis, J. J. (1983) "The chromosomal basis of human neoplasia," *Science* 221, 227-236; Hoel, D. G. (1985) "Epidemiology and the Inference of Cancer Mechanisms. *Natl. Cancer Inst. Monogr.* 67, 199-203; Fischinger P. J., and V. T. DeVita, Jr. (1984), "Governance of science at the National Cancer Institute: Perceptions and opportunities in oncogene research," *Cancer Res* 44, 4693-4696; Modali, R., and S. S. Yang, (1986), "Specificity of Aflatoxin B1 Banding on Human Proto-Oncogene Nucleotide Sequence." In Monitoring of Occupational Genotoxicants Alan R. Liss, Inc. There is considerable reason for optimism that advances in biomarkers based on these mechanistic insights may lead to important changes in cancer epidemiology in the next decade or so-- Hattis, D., Review of "Biomarkers and Occupational Health--Progress and Perspectives, M. L. Mendelsohn, J. P. Peeters, M. J. Normandy, eds.," Science, Vol. 271, p. 770, Feb. 9, 1996.

for comparison (Dawson et al., 1997, pp. E-9 through E-11; Dawson et al., 1998 pp. D-12 through D-13). Therefore the model incorporates a 0.8/0.2 weighting in favor of the Armitage Doll model.

Sixth or Seventh Stage Affected for the Multistage Model

The Cal-EPA document presents risk estimates for both the sixth and seventh stage affected within the Armitage-Doll Multistage model. The statistical fit in this case was slightly better for the unusual seventh-stage-affected alternative. Therefore this portion of the probability tree reflects a 0.6/0.4 split for the seventh Vs the sixth stage affected.

Relative Weighting of the Case Control vs the Cohort Study Data as the Bases for Risk Projections in Chapter 7

The discussion in Chapter 7 (pp. 7-31 to 7-32) expresses both strengths and weaknesses of the Garshick et al. (1988) cohort vs the Garshick et al. (1987) case control study data. (These two studies have no overlap in the lung cancer and other deaths included, and therefore are regarded as substantially independent as sources of information on likely risk). The case control study has the advantage of explicitly controlling for cigarette smoking.* On the other hand, the cohort study data included larger numbers of deaths and were moreover available with the full details of individual ages and other characteristics studied. This allowed the cohort data to be subjected to detailed analyses using various mechanistic and other models (e.g. in Appendix D), whereas the case control data were evidently only available in the published group aggregate form with less detailed information on individual ages, etc. In recognition of these articulated strengths and weaknesses and discussions with a member of the Cal-EPA team, the model assigns equal weight to the two studies in the context of the Chapter 7 branch of the probability tree shown in Figure 1.

Patterns of Exposure Concentrations Over Time--a "Ramp" Pattern vs a "Roof" with Various Heights

* In the event, Garshick et al. (1987) report that estimates of relative risk from diesel exposure are very similar with and without control for smoking, implying that the exposed and unexposed groups are relatively similar in smoking-related lung cancer risks.

Available measurements that have been used to characterize the exposures of the railroad workers in the Garshick et al. study were made in the early 1980's--after the end of the relevant period of exposures for both the cohort and the case control study. The "roof" and the "ramp" terms refer to two related hypothesized patterns for the exposures of the railroad workers between the first introduction of diesel locomotives in the mid-1940's and 1980.

The "ramp" pattern is constructed by assuming a simple linear increase in exposures between 1945 and 1959 (by 1959, diesel locomotives had nearly completely displaced other types of engines in use) followed by constant exposures thereafter. This is regarded as a "lower bound" on actual exposures of railroad workers, giving rise to higher estimates of risk than those generated by the alternative "roof" exposure patterns, which Cal-EPA considers to be more likely.

The "roof" pattern also postulates a linear increase in railroad worker exposures between 1945 and 1959, but ending at a point in 1959 that is higher than the 1980 measurements. This is because of

- (1) data suggesting that historical exposures to NO₂ in shopworkers may have been an order of magnitude larger than those toward the end of the exposure period. A conversation with Dr. Hammond indicated that an appreciable portion of this is likely have been accounted for by improvements that were subsequently made in ventilation, but some portion (perhaps 2-3 fold) is likely also to have been attributable to higher emissions from the locomotives,
- (2) perceptions by knowledgeable observers that locomotives became progressively cleaner (less smoky) over the course of the 1960's and 1970's (Dawson et al., 1997, p. E-2) and
- (3) some numerical observations and reasoning recently provided by a railway industry expert (Keller, 1998), which suggest a roof height of 9.

In the current document, several different sets of projections of risk are made incorporating different “heights” for the roof--expressed as different hypothesized ratios of 1959 exposures to exposures prevailing at the time of the measurements (assumed equal to the end of the epidemiological follow-up period in 1980). A height of 3 (that is, an assumption that 1959 average exposures were three times the 1980 exposures) is the central value that is used most frequently in Cal-EPA’s projections, and is considered most likely by the Cal-EPA team, on the basis of conversations with two members of the group. The lower part of Table 2 shows the model weightings of various heights of “roof” (and the “ramp,” which corresponds to a “roof” of 1).

Alternative Assumptions About the “Base” Excess Diesel Exposure of Train Riders over Unexposed Clerks

The uncertainty in the “base” exposure level of the train riders perceived by the Cal-EPA team derives in part from the imperfection of the available “respirable particulate” measurements as a proxy for diesel exposures. Essentially the issue is, how much of the approximately 80 $\mu\text{g}/\text{m}^3$ of measured cigarette-smoke adjusted respirable particulate represented real diesel exposure, and how much was toxicologically less relevant “background” exposures to very different particles entrained from soil or indoor dust by the wind or otherwise resuspended by mechanical action?

The size distribution of authentic diesel particles, as measured by Hallock et al. (1987) in repair sheds as part of the railroad workers’ study in addition to many other research groups, has a mass median diameter of about 0.2 microns (millionths of a meter).* In contrast to this, the cyclone device used for segregating “respirable particulates” for the Woskie et al. (1988)

* Measurements of the exhaust particles from more modern diesel engines, which put out smaller densities of total particulates per unit volume, indicate some shift in the mix of particle sizes toward even smaller sizes. This is to be expected because the .2 μ particles are themselves the result of agglomeration of even smaller “nuclei” size particles, together with condensation of hydrocarbons from the vapor phase. Because the agglomeration is a second-order process (involving collisions between particles) it is less efficient, leading to a smaller mix of particle sizes as the initial density of particles per unit volume is reduced (Kerminen et al., 1997; Health Effects Institute, 1997; Bagley et al., 1996).

measurements allowed inclusion of 50% of much larger particles--4 microns--in the measured mass. Particles of this size or a little less would be expected to include substantial amounts of miscellaneous dust kicked up by the wind or (indoors) suspended by mechanical or other processes. This led to readings of an appreciable background level of "respirable particulate" in the Woskie et al. (1988) measurements, even for clerks, for whom the authors believed there was no detectable extra diesel exposure over what would be expected for members of the general community or similar workers outside of the railroad industry. [This judgment that the clerks were essentially unexposed is reinforced by indoor and personal respirable particulate measurements

Table 2
Probabilistic Characterization of Alternative Exposure Patterns--Base Amounts and Heights of Roof

Base (1980) Excess Diesel Particulate Exposure of Train Crews Over “Unexposed” Clerks

Base Excess Diesel Exposure ($\mu\text{g}/\text{m}^3$)	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%

made by Spengler et al. (1985) in non-smoke exposed residents of two small rural towns (bottom of Table 3).]

[In addition to likely differences in chemical composition between resuspended particles and diesel particles, the mechanically suspended particles of a few microns in size have a substantially different distribution of sites of deposition in the lung, with substantial implications for the time the particles remain in the lung after deposition. Generally, the larger particles can be expected to be deposited to a much greater extent on the mucus lining of the trachea and larger bronchi, where they will be relatively rapidly swept up by the action of cilia to be eventually swallowed to the gastrointestinal tract. By contrast, smaller diesel-size particles tend to be deposited to a greater extent (a little over two-fold for the comparison of 0.2μ to 3μ particles) in the alveolar-interstitial region of the lung, beyond the immediate reach of the mucociliary escalator. Clearance from the alveolar-interstitial region is by a much slower process involving ingestion by macrophages followed by slow ameboid migration of the macrophages to the bronchi where they then can be swept up by a continuous layer of mucus (International Commission on Radiological Protection, 1994). Simulations based on the ICRP lung model indicate that particles deposited in the alveolar-interstitial region can be expected to have mean residence times in the lung over fifty times those of particles deposited in the tracheobronchial region.]

As can be inferred from the presentation in the upper portion of Table 2, Cal-EPA essentially took a bounding approach in representing the uncertainty in their analysis attributable to this factor. At the high end, they chose to do calculations assuming a “base” train rider diesel exposure of $80 \mu\text{g}/\text{m}^3$ --essentially making no subtraction for “background” non-diesel exposures for the train riders. 20% weight was given to this possibility in the uncertainty model. At the low end, Cal-EPA derived a value of $40 \mu\text{g}/\text{m}^3$ by subtracting the full cigarette adjusted respiratory particulate exposure seen in the unexposed group from the $80 \mu\text{g}/\text{m}^3$ observed for the train riders. Cal-EPA team members consider this possibility more likely than the high extreme value and accordingly it was given a weight of 30% in the uncertainty analysis. Finally, Cal-

EPA's central value of $50 \mu\text{g}/\text{m}^3$ is given the remaining 50% of the weight in the uncertainty model. One

Table 3
Information on Likely Background Rural/Small Town Respirable Particulate from Spengler et al. (1985)*

City	Group	N	Mean RSP ($\mu\text{g}/\text{m}^3$)	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).

alternative to this choice that might be suggested for a further refinement of the analysis is to consider that the train riders' "background exposures" might be more realistically estimated from the rural outdoor background levels observed by Spengler et al. (1985) (see Table 3). Subtracting 17-18 $\mu\text{g}/\text{m}^3$ as background from the 80 $\mu\text{g}/\text{m}^3$ observed for the train crew members would lead to a central estimate of about 62 $\mu\text{g}/\text{m}^3$ for the "base" (1980) exposures.

Representation of Uncertainties from Statistical Sampling Errors in Estimating Carcinogenic Potency from Specific Sets of Data

The analysis that led to the specification of sampling uncertainties in estimating cancer potency factors is given in Table 4. The first three numerical columns of this table show the Maximum Likelihood Estimates (MLE) of the diesel unit risk/potency estimates, and 95% lower and upper confidence limits, respectively. It can be seen that in most cases the 95% confidence limit estimates of diesel potency are within two-fold or so of the MLE's. This means that there is not a great deal of purely statistical sampling error type uncertainty in these risk estimates. What there is for nearly all cases is symmetrical--which indicates that simple counting uncertainty* probably is an important factor in these estimates. Given this observation, the model represents this sampling error with normal distributions centered on the MLE's and with standard errors calculated as the mean of estimates from the upper and lower 95% confidence levels [e.g., the standard error inferred from the high end = (95% UCL - MLE)/1.645]. For the one case where the comparisons of UCL and LCL with the MLE indicate appreciable asymmetry (the general multiplicative model within the Appendix D calculations), two normal distributions are used--one for the region above the MLE and the other for the region below the MLE. For the small number of trials where negative values would be randomly selected from normal distributions, the model substitutes an arbitrary low potency value (1 E-6 per lifetime 1 $\mu\text{g}/\text{m}^3$).

* If one makes repeated counts of a substantial number of independent events--such as radioactive disintegrations in a series of equal time periods or lung cancers in a population with defined exposures and ages--the distribution of such counts is described by a Poisson distribution. If the number of counts is reasonably high, the Poisson distribution is well approximated by a normal distribution with a standard deviation equal to the square root of the number of counts.

Table 4
Statistical Uncertainties in Fitted Parameters (Random Errors)

$q_1 \text{ (ug/m}^3\text{)}^{-1}$							
	MLE	95% LCL	95% UCL	MLE- 95% LCL	95% UCL- MLE	Indicated Standard Error	Std Error /MLE
<u>I. Case-Control study (1987a) using published slope coefficient for hazard on years of exposure to diesel exhaust (Section 7.3.3)</u>							
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
<u>II. Cohort study (1988) using individual data to obtain a slope for hazard on years of exposure to diesel exhaust (Section 7.3.4)</u>							
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
<u>III. Cohort study (1988) applying time varying concentrations to individual data to obtain a slope of hazard on exposure (from Appendix D)</u>							
<u>A. Ramp (1,50) pattern of exposure</u>							
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
<u>B. Roof (3,50) pattern of exposure</u>							
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	8.1E-05	2.8E-05	1.3E-04	5.2E-05	5.4E-05	3.2E-05	0.399

categorical covariate								
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

Model Implementation and Simulation Procedures

The initial (unnumbered) page of Appendix A shows the setup of the spreadsheet for the most recent variant of the model. The equations within the various cells are documented in the three remaining pages of Appendix A.

The basic key to implementing the model is the definition of an “overall model selector” cell (in this case cell A57) that determines which model will contribute the diesel potency estimate on each specific trial. In the Monte Carlo simulations, this selector cell is defined as a uniform (flat, or rectangular) distribution that simply chooses a random value between zero and one on any specific trial. Then, depending on the value selected, a series of nested “if tests” (cells A58) picks out the appropriate model whose randomly selected statistical uncertainty value will be used as the bottom line risk estimate for that trial. Similarly, three other uniform distributions (in cells A25, A35, and I50) provide for weighted random selections of all combinations of base level, height of roof, and which side of the MLE will be used for the one model with indicated asymmetric sampling uncertainties. MLE potency estimates and standard errors for combinations of base level and height of roof that are not explicitly covered in Table 4 were derived by interpolation with the aid of exposure “Area Under the Curve” calculations for various roof heights using the equation in cell H25. The formulas for these interpolations are given in cells H41-H42, H46-H47, H49, I41-I42, I46-I47, I49, and I51-I52.

The basic model was run twice in simulations of 10,000 trials each using different initial seed values for the random number generator. Details of the results of the first model run and the mathematical forms used for the distributional assumptions are provided in Appendix B.

Results and Sensitivity Analysis

Table 5 and Figure 2 summarize the replicate results of the model runs for a number of selected percentiles of the confidence/uncertainty distribution and the mean “expected values”. It can be seen that there is little difference in the results of the parallel runs for each model. The

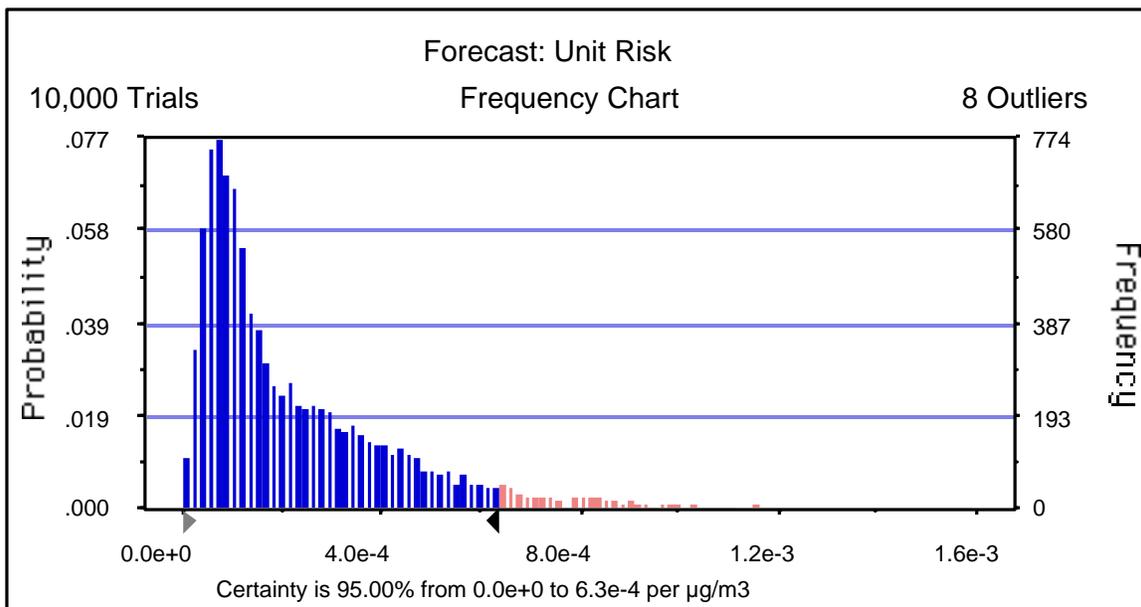
Table 5**Uncertainty Distributions for the Unit Risks of Lifetime Exposure to 1 $\mu\text{g}/\text{m}^3$ of Diesel
Particulate Matter--Results of Two Parallel Runs**

	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

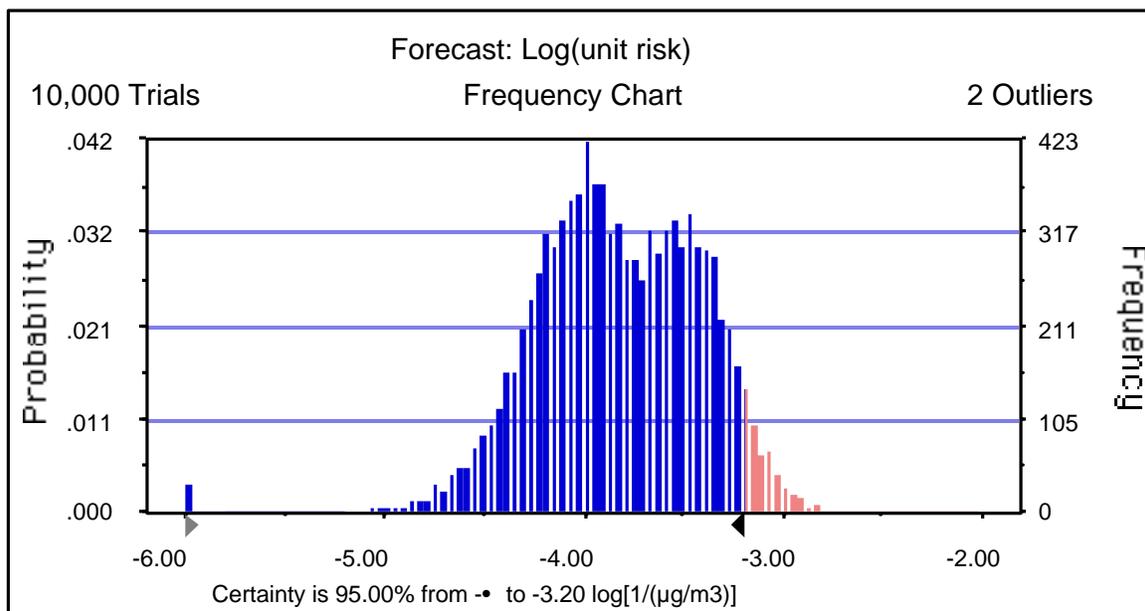
Figure 2

Uncertainty Distribution for the Unit Risks of Lifetime Exposure to 1 $\mu\text{g}/\text{m}^3$ of Diesel Particulate Matter--First Model Run

Linear Plot



Logarithmic Plot



10,000-trial simulation runs are evidently enough to reduce the errors in statistical sampling so that they are modest in relation to the other potential sources of imprecision in the analysis.

Overall, this representation of the uncertainties indicated in Cal-EPA's analysis reflects a considerable range of diesel carcinogenic potency estimates--as any fair statement of our current understanding must. A 90% confidence range (from a 5th percentile to a 95th percentile) spans a nearly 20-fold range. At the 95% confidence level, which appears to be most relevant to notification requirements under California's "Proposition 65" law, the indicated risk is approximately 6.5×10^{-4} per continuous 70-year "lifetime" exposure to $1 \mu\text{g}/\text{m}^3$ of diesel particulate. A corresponding mean "expected value" estimate of risk, relevant for comparative analyses of the benefits and costs of control efforts, is 2.3×10^{-4} .

It can be seen in the lower part of Figure 2 that when viewed on a logarithmic x-axis the uncertainty distribution captured by this analysis is grossly bimodal (two main humps) centered at about 1×10^{-4} and 3×10^{-4} . It is likely that the two humps correspond roughly to the distinction between the centers of distributional calculations based on the Armitage-Doll model vs the other methods of risk projection, with the Armitage-Doll model giving rise to the lower mode.

It is not inconceivable that different observers, or even different members of the Cal-EPA team, could read the Cal-EPA document as implying somewhat different weights for the various nodes in the probability tree represented in Figure 1 and Table 2. It is therefore of interest to do some basic sensitivity analysis on the results--to bound the "set of not-clearly-incorrect answers." To create these bounds, Table 6 shows the effects of relatively extreme possible variations in the five principal choices in the analysis:

- 1) The relative weighting of Chapter 7 vs. Appendix D analyses. The "low" bound model variant gives only a 10% weight to the Chapter 7 analyses, whereas the

“high” bound model variant allocates 90% to this choice in comparison to the “base” allocation of 40% weight to Chapter 7.

Table 6**Sensitivity Analysis--Effects of Bounding Changes to Different Weightings in the Model^a**

Model Variant	Median (50th Percentile of Confidence/ Uncertainty Distribution)	Mean	95% Upper Confidence Limit
Base Case (Figure 1 and Table 2)	1.5E-4	2.3E-4	6.5E-3
Combination of 5 assumption choices leading to low risk predictions	6.6E-5	9.6E-5	3.0E-4
Combination of 5 assumption choices leading to high risk predictions	4.7E-4	5.6E-4	1.3E-3

- 2) Within Chapter 7, the relative weighting of projections based on the cohort vs the case control study data. In the base model these are given equal weight. For the “low” and “high” bound models the cohort study is allocated 75% and 25% respectively of the overall weight given to Chapter 7.
- 3) Within Appendix D, the relative weighting of the Armitage-Doll vs the General Empirical Model projections. For the “low” model, this weighting is raised to 90%, from 80% in the “base” model. For the “high” model, the Armitage-Doll weighting is reduced to 50%.
- 4) Weightings of different values for the “base” diesel exposure of the train crew in 1980. For the “low” model variant, the allocations are:
 - 40 $\mu\text{g}/\text{m}^3$ --10% weight
 - 50 $\mu\text{g}/\text{m}^3$ --45% weight
 - 80 $\mu\text{g}/\text{m}^3$ --45% weight

^a The results in each line are based on runs of 10,000 trials for each case other than the base case.

For the “high” model variant, the allocations are:

40 $\mu\text{g}/\text{m}^3$ --45% weight

50 $\mu\text{g}/\text{m}^3$ --45% weight

80 $\mu\text{g}/\text{m}^3$ --10% weight

5) Weightings of different values for the height of the “roof”

For the “low” model variant, the allocations are:

1--1% weight

2--10% weight

3--40% weight

5--40% weight

10--9% weight

For the “high” model variant, the allocations are:

1--30% weight

2--30% weight

3--30% weight

5--9% weight

10--1% weight

In my judgment, each of these choices for the “high” and “low” bound models represents a very extreme reading--probably well beyond the weightings that would be selected by members of the Cal-EPA team in each direction. It can be seen in Table 6 that even the results of these combinations of relatively extreme choices would be expected to change the resulting risk distributions by only about 2.5 fold in either direction from the base model projections.

Discussion

It should be understood that the modeling results presented here do not represent all conceivable uncertainties in the estimation of cancer risks from diesel particulates that might be

considered potentially significant by different expert informants. For example, all of the estimates presented here presuppose that cancer risks from diesel particulate exposures are linearly related to exposure down to the levels present in ambient air in California communities. Arguments can be made for this, either on the basis that the action of diesel particulates is likely to have at least some mutagenic component, or on the basis of likely interactions between the effects of these small particles and other particulate lung carcinogens present in the environment (Crawford and Wilson, 1996; Hattis, 1997). However, it is only fair to recognize that there is not yet a complete consensus of expert views on this particular point. And there are other modeling choices that different analysts might wish to represent with different weights or different model structures to capture various mechanistic and statistical views. However, the goal here has been simply to accurately reflect the views of one important group of analysts at Cal-EPA, on the set of uncertainties that they themselves have explicitly studied in their published work. In follow-up work, the author will offer a separate distributional analysis based on self-generating weightings of the uncertainties represented in this document and a few other sources of uncertainty. In particular, this follow-up analysis is expected to feature continuous rather than discrete distributions for naturally continuous parameters such as base level and the height of the “roof”, and some weighting of results from the recent meta analyses including other epidemiological studies of lung cancer risk in other groups of workers with occupational exposures to diesel particulates (Dawson et al., 1998, Appendix C and Chapter 7; Bhatia et al., 1998).

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