MEETING

OF THE

SCIENTIFIC REVIEW PANEL ON TOXIC AIR CONTAMINANTS

CALIFORNIA AIR RESOURCES BOARD

MILBERRY CONFERENCE CENTER

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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9:30 A.M.

Janet H. Nicol
Certified Shorthand Reporter
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APPEARANCES

MEMBERS PRESENT:

Dr. John R. Froines, Chairman
Dr. Paul D. Blanc
Dr. Craig V. Byus
Dr. Gary D. Friedman
Dr. Stanton A. Glantz
Dr. Peter S. Kennedy
Dr. James N. Seiber

REPRESENTING THE CALIFORNIA AIR RESOURCES BOARD:

Mr. Robert Krieger, Associate Air Pollution Specialist, Stationary Source Division
Mr. Bill Lockett, Deputy Ombudsman, Northern California
Ms. Genevieve Shiroma, Chief, AQMB

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT:

Dr. George Alexeeff, Chief, Air Toxicology & Epidemiology Section
Dr. John Budroe, Staff Toxicologist, Air Toxicology & Epidemiology Section
Dr. Stanley V. Dawson, Staff Toxicologist, Air Toxicology & Epidemiology Section
Dr. Michael Lipsett

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P R O C E E D I N G S

CHAIRMAN FROINES: Okay. Well, in some respects I am -- can you hear me in the back? In some respects I'm sorry to be sitting in this chair. I think the panel suffered by Jim Pitts' retirement after so many years of really great work as chair of this panel. So I think that the first thing I want to say is as the chair for this meeting that we all owe a debt of gratitude to Jim and he did a remarkable job over the years and he'll be a tough act to follow.

Secondly, I want to introduce two new members of the panel.

I can't tell if this has -- this has a ringing sound to me. Does it have a ringing sound to you? What can we do about that? It's okay?

First person is Dr. Peter Kennedy, who fills the oncologist position. Dr. Kennedy is a member from Southern California, which is terrific for those of us who are also from Southern California, and creates a little balance in this panel. Dr. Kennedy took his first degree in Harvard College and then his medicine degree at Baylor University.

So welcome to the panel.

The second member is Dr. Paul Blanc, who fills the position as occupational physician. Paul is with the Center for Occupational and Environmental Health in the Division of

Occupational Medicine at UC San Francisco. So I think with diesel, Paul's role is going to be particularly important, given his research interests in the area, pulmonary medicine.

I think that, needless to say, that we are now embarking on a process with diesel exhaust which represents the most important set of substances that I think we will have had to address since this panel was established in 1983. I think the issues have potentially significant impact. I think there is considerable scientific controversy. And I believe that there is in some respects a degree of scientific uncertainty as well that will be necessary to deal with.

So I think that the issue of diesel is going to be a difficult one. It is, given the importance of diesel in this society, it's going to be a very important process that we engage in, and so I think we need to take this particular chemical very very seriously and proceed as carefully as possible.

I hope as questions arise people will raise them. I hope that this particular meeting is intended as a briefing. It's intended as a way in which the panel can learn more from the staffs of ARB and Cal EPA, about the fundamental issues associated with diesel exhaust, about the scientific underpinnings for their conclusions, and about

the basis for the decisions that have been made thus far, as well as making us aware of the uncertainties that still need to be addressed.

This meeting, as I say, is a briefing. I hope that we will learn a great deal. It seems to me incumbent upon this panel to ask as many questions as possible to determine what are issues that we think are unresolved or uncertain or need further clarification or are simply questions that require being answered, because I assume that at the next meeting or in a meeting at the latter part of the year, early next year, that we will formally take up the document for consideration.

So we are not taking up the document today for formal consideration. We are simply again having a briefing session.

But I think that we need as a panel to give advice and counsel to the two staffs so that when the document is brought back to us in December or January that the staffs have had the benefit of major input from the panel and so when we begin to consider it, hopefully some of the issues will have been resolved in that process.

I made some other notes, but I think I'll save them. Why don't we get started, rather than my giving a lengthy presentation. I think that will get us off the ground.

MS. SHIROMA: Thank you. Good morning, Dr. Froines, members of the panel. My name is Genevieve Shiroma. I'm chief of the Air Quality Measures Branch at the Air Resources Board. My branch is responsible for implementing the Toxic Air Contaminants' Identification Program, specifically the exposure portion of the program.

Also with me is Robert Krieger, of my staff, who is lead on the exposure portion of these documents.

We are here today, as Dr. Froines indicated, with staff from the Office of Environmental Health Hazard Assessment to review, to present an overview and staff report on our draft document, the "Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant."

I'll be providing a short introduction, and then I'll turn the presentation over to Robert, who will give an overview of the Part A, the report, and the major comments we've received.

Part B will be discussed by Drs. George Alexeeff and Michael Lipsett, with the OEHHA.

At the end of our presentation, I'll go over the anticipated schedule. And along the way feel free to ask questions.

By way of introduction, as you know we have a Comprehensive Toxics Program in California. The program was created by AB 1807 in 1983, which initiated a program for

the formal identification and control of air toxics of statewide importance in California.

The program separates risk assessment, which is the identification of substances, that's the phase we are in now, from risk management, the control of the substance. And we have the definition of toxic air contaminant up on the screen, an air pollutant which may cause or contribute to an increased mortality or a serious illness or which may pose a present or potential hazard to human health.

One of the first steps in the identification portion of the program, the risk assessment portion, begins with prioritization of substances of importance in California. We consider the potential risk to public health, amount or potential amount of emissions, exposure, usage in California, and persistence in the atmosphere.

Now, this next slide shows the process for identification and control of air toxics in California. Again, we are in identification phase.

Once a substance is selected for evaluation, we at the ARB are responsible for preparing the Exposure Assessment Report, or the Part A.

The OEHHA is responsible for the Health Assessment portion of the report, or Part B.

The draft reports are distributed for public review and comment. Public workshops are held where

interested parties can discuss issues with the staff and members of the SRP.

After the public comment period and workshops, staff of the ARB and OEHHA consider the comments and revise the report accordingly.

We then submit the report to you, the panel. You review the report for determining whether sound scientific knowledge, methods and practice were used.

If you are satisfied with the report, you prepare findings and submit them to ARB.

Once the Scientific Review Panel findings are received, a public hearing is scheduled, and a staff report is released for a 45-day public comment period before a hearing before the Air resources Board.

At that hearing, ARB decides on a regulation to formally identify a substance as a toxic air contaminant.

Upon that action, the ARB staff then begins the second phase of the program, the risk management phase. Again, in that phase there is a needs assessment looking at the need for or degree of further controls, there is extensive public outreach and opportunities for public comment, and we work closely with other governmental entities such as the air districts.

Next slide.

We entered diesel exhaust into the program in

1989. We assessed that there indeed was a potential health effects with widespread exposure in California. The IARC had listed diesel exhaust as a probable human carcinogen. US EPA had begun evaluation and in 1994 did investigate it as a number one probable. And overall, diesel exhaust met the Health and Safety Code criteria regarding potential risk exposure, use and persistence.

Now, with this, I'm going to turn the microphone over to Robert, who will give an overview of the Part A exposure assessment.

Yes, Dr. Froines.

CHAIRMAN FROINES: Just one other point about this list of things. As far as I know, diesel exhaust is currently listed as a carcinogen known by the State's experts as a compound known by the State's experts to cause cancer under Prop 65? That's correct?

MS. SHIROMA: Yes, that's correct. Yes.

At this point, I'll turn the microphone over to Robert, who will give an overview of the Part A exposure assessments and, again major comments we have received.

MR. KRIEGER: Thank you, Genevieve.

And good morning, members of the panel.

Can't hear? Test, test. Does this work a little better? I'll just have to speak up. We'll trade microphones.

Okay. As Genevieve indicated, in the next few slides I will be giving you a brief overview of the Exposure Assessment of Diesel Exhaust Report, a summary of the major comments, and our proposed revisions to the report.

Diesel exhaust entered the AB 1807 identification process in October of 1989.

In March 1990, ARB sponsored a conference on the risk assessment on diesel exhaust.

On June 17th, 1994, the initial draft report was released to the public for a six-month comment period at a public briefing.

Our first public workshop was held on September 14th, 1994.

And on January 29th and 30th, 1996, the OEHHA-ARB Health Effects Institute National Institute of Occupational Safety and Health, the World Health Organization, and the US EPA, sponsored a Human Health Study Workshop.

The revised draft report was released to the public in a briefing on May 9th, 1997, for a 100-day comment period.

Yes?

CHAIRMAN FROINES: Do the new members of the panel have copies of that January workshop?

MS. SHIROMA: No.

MR. KRIEGER: No.

CHAIRMAN FROINES: Could you make them available, because I think they're important scientifically.

MR. KRIEGER: Copies of the presentation will be given out.

We held our third public workshop recently on July 1st of 1997.

I will begin my overview of the exposure assessment by beginning with the properties of diesel exhaust.

Diesel exhaust is a complex mixture of gases, vapors and particles, has several thousands of constituents. Some of these substances are known human carcinogens, such as arsenic and benzene, and includes over 40 substances listed by the US EPA as hazardous air pollutants and Air Resources Board as toxic air contaminants. The majority of these diesel exhaust particles are less than one micron in diameter.

This slide shows the 40 compounds that are toxic air contaminants.

Sources of emissions of diesel exhaust.

About 36,000 tons per year are emitted into California's atmosphere each year, and this is based on 1995 Emissions Inventory. The majority of these emissions come from on-road vehicles, or about 59 percent; other mobile sources, 36 percent; and the remaining five percent come

from stationary source.

To characterize exposure to diesel exhaust, we are using particulate concentrations. To estimate outdoor exposure concentrations, we used receptor modeling techniques, including chemical mass balance results from several studies, ambient PM 10 monitoring network data, and the 1990 PM 10 Emissions Inventory.

The ARB used the 1990 PM 10 Emissions Inventory for the basis for calculating the statewide exposure to diesel exhaust PM 10, because it would best represent the emission sources in the years when the ambient data were collected for the chemical mass balance studies.

From the results of this analysis, we estimate that Californians are exposed to outdoor concentrations of diesel exhaust PM 10 of 3.0 micrograms per cubic meter in 1990.

DR. FRIEDMAN: Could you define PM 10?

MR. KRIEGER: Particulate matter ten microns and less in diameter, less in diameter.

DR. FRIEDMAN: All sizes?

MR. KRIEGER: All sizes.

DR. SEIBER: Robert, could you explain why you have to do this estimate? In other words, the State collects PM 10 data around the clock day in and day out for throughout the year, and but that's particulate matter from

all sources. So really diesel is a part, somewhere around, what, six, eight percent, eight percent of the total?

MR. KRIEGER: Yeah. If we're just looking at Emissions Inventory only, it's about actually four percent of the PM 10 total inventory.

DR. SEIBER: Four percent. And what's the other 96 percent?

MR. KRIEGER: 96 percent can either be dust, wind-blown dust is the little larger size particles, other secondary formation, NOx particulate, sulfate, other combustion sources. And --

MS. SHIROMA: Manufacturing.

DR. SEIBER: I think it's kind of important to see that this is a part of the bigger hive and roughly five, ten percent, I saw several numbers in the report which is the contribution from diesel to this total PM 10 load in the atmosphere.

MR. KRIEGER: That's correct.

DR. SEIBER: Of course, it's higher if you're near a freeway and so on.

MR. KRIEGER: That's true.

We've also estimated in 1995 and future year concentrations and these were based on prior Emissions Inventory estimates.

In 1995, the estimate is 2.2 micrograms per cubic

meter.

And in 2010, the estimate is 1.7 micrograms per cubic meter.

And the reduction that you see up there is due to largely in part to the adopted regulations requiring the emission reductions from diesel fuel and engines.

DR. BLANC: Do you have some data now to suggest that your estimate that you made earlier of what the 1995 anticipated levels would be have borne fruit? I mean, part of the problem here or the challenge is that this is such a drawn out and lengthy process that you began drafting a document in the early 1990s and now it's 1997, and certainly some things have evolved since that time.

I think that to continually raise the specter of, well, what about 1996, what about 1997, would be to put you in sort of a blind loop where you could never, given the requirements of development of the criteria document, never have data that was current enough.

So that's not what I'm suggesting, but given the time frame that you were working in, I think it would be possible to comment on whether or not that estimate is consistent with preliminary data that you might have from 1995.

Or another way of saying it, it's sort of counterproductive in your document to predict what future

1995 levels will be, ignoring the fact that the document is likely to be finalized long after 1995.

MR. KRIEGER: That's true. We realize that's the problem in all these documents that we're doing, when times matter.

We are continually updating our exposure document to include -- and we're going to update even some of these exposures for 1995 -- to include the most recent Emissions Inventory.

Since the May version, we've already updated it once because we have a new Motor Vehicle Emissions Inventory, in fact, 7-G, that we've included, that also adjusted these numbers. So this is the most recent numbers that you see right here.

In the future, we also plan on doing 1995 total exposure estimates as well. You'll see it. I'll explain it later in the future slide.

CHAIRMAN FROINES: Will that be available in the final document that we receive in December?

MR. KRIEGER: Yes. Yes.

DR. BLANC: I would be satisfied with seeing a footnote that said since the drafting of this document we now have the 1995 data, which show the level as 2.3 or 1.9 or 2.1, or whatever it is. I'm not saying that you have to go back and rewrite and rewrite, but on the other hand I

think it would be best not to ignore the lapse of time factor.

DR. GLANTZ: Do you have any idea why these concentrations are going down?

MR. KRIEGER: Primarily because of the majority is going down because of the diesel fuel regulation in 1993. The majority of the jump from 1990 to 1995 is due to not only the fuel regulation in 1993, but also emission standards that have been implemented during those years, agent standards.

DR. SEIBER: In one of your drafts it showed that the emissions, on-road emissions, have decreased to about half in 1995 what they were in 1990. That's fairly dramatic.

And, again, picking up on the point, I think the big drop that we'll see is from '90 to '95.

Maybe you can comment on whether that's going to continue on as a trend, given the present system or is that pretty much have we leveled out at that emission level?

Maybe you don't have the information.

MR. KRIEGER: By 2010 it does drops. It steadily goes down, but not a dramatic drop, as you can see, because of the growth and the vehicle mass travel and the fleet makeup.

CHAIRMAN FROINES: Our job is, of course, is to

look at the health effects and risk assessment emissions as well, but it would be interesting if you ever had anything that you could give the panel that talked about alternative fuels and new diesel technology, just for our background reading that would be very nice, because it seems to me that in the long run diesel technology, alternative fuels and other approaches are going to become very important as we try and address the diesel issue.

MR. KRIEGER: Okay. Yes, we can provide that to you.

Near source exposure. We've also done a near source estimate in the May 1997 draft. This was done near a freeway in LA. Well, actually the Long Beach Freeway. Concentrations near this freeway we estimated to be three times that of the ambient air.

This slide just shows that our outdoor exposure estimates compare well with work that was done by other researchers.

DR. SEIBER: That's from all over the United States; right?

MR. KRIEGER: That's correct.

DR. SEIBER: That's not California specifically?

MR. KRIEGER: A few of those were California, just the elemental, the rest were from the nation.

Okay. In response to comments on our initial

draft report regarding that we should account for the time spent indoors, we added an analysis which estimated indoor and total exposure, and this is in the May 1997 draft.

We used estimates of the outdoor population weighted ambient diesel exhaust particle concentrations in the model, the California Population Indoor Exposure Model, or CPIEM, that can estimate indoor air exposure and total air exposure, which accounts for the amount of time spent indoors and outdoors.

The CPIEM was developed under a contract to ARB to improve estimates of population exposures to toxic air contaminants. The model uses relevant data such as distributions of California building air exchange rates, activity patterns data, and air concentrations of diesel exhaust particles as inputs to develop indoor and population exposure estimates across all the environments.

We estimated indoor concentrations in 1990 to be 2.0 micrograms per cubic meter, with a total exposure estimate of about 2.1 micrograms per cubic meter.

We also planned as --

DR. GLANTZ: Could you just explain the difference between indoor exposure and total exposure?

MR. KRIEGER: The indoor exposure is specifically in indoor environments, specifically in closed environments. The total exposure includes the activity that you would

spend normally indoors in an environment for a specific time of day and outdoors. So the total exposure is the integrated exposure of the indoor and outdoor exposure, based on your activity patterns.

DR. FRIEDMAN: You said that for 1990?

MR. KRIEGER: For 1990, that's correct.

DR. FRIEDMAN: So we compare that with the 3.0 and that is outdoors. Is that a general principle that is assumed that usually the exposures indoors are about two-thirds of what you'd expect outdoors?

MR. KRIEGER: Yes. For diesel particles, yes.

We also plan, on another similar note, we plan to calculate indoor and total exposure estimates based on 1990 -- 1995, excuse me, in the next draft of the report, so you'll be seeing that as well.

Now, an update on the CE CERT study. The question of old versus new diesel fuel has been posed prior to our release of the first draft in the identification back in 1994. We determined then that while the total emission exhaust mass has changed over time, the complex nature of the exhaust remains with its various toxic constituents. We therefore have proceeded with our efforts towards identification of diesel exhaust.

However, in response to concerns expressed about whether the thumbprint is similar between old versus new

fuel, we contracted a study with the University of California at Riverside, College of Engineering, Center for Environmental Research and Technology, or CE CERT, to conduct a study to test old, pre-1993, and new reformulated diesel fuels compare their chemical compositions of different fuels on the exhaust from the heavy-duty diesel Cummins engine.

Since that time, CE CERT has established a Technical Advisory Committee made up of representatives from oil companies, engine manufacturers, ARB and OEHHA to provide technical assistance on this project.

Testing began December of 1996 and the preliminary results will be available within the next few weeks.

At this time, we can tell you that the testing of the engines met all the standard testing protocol.

The results are being QA/QC'd at the present time with the Technical Advisory Committee planning to meet by the end of this year to review these results.

DR. FRIEDMAN: Could you explain some of the jargon you used, the QA/QC?

MR. KRIEGER: Quality assurance, quality control.

DR. FRIEDMAN: Could you explain what you mean by that in this context?

MR. KRIEGER: Mainly, I'm not specific to the whole protocol on this, but quality assurance/quality

control generally is a series of checks to make sure that the data that is being produced in this study is handled properly from the point that the engine is testing the results, to the point it's analyzed in the lab and the point where we get the results. So it's a whole step rise progression to make sure there's certain checks along the way.

DR. FRIEDMAN: On the quality of the data, the raw data or on the calculations?

MR. KRIEGER: Yes. The quality of both -- both the quality and the calculations of the data.

DR. SEIBER: Is the -- remind us who the Technical Advisory Committee, who is it composed of?

MR. KRIEGER: Some of the companies represented is the oil companies.

MS. SHIROMA: Arco and Chevron.

MR. KRIEGER: Arco and Chevron. And Engine Manufacturers' Association. Members, representatives from those associations.

MS. SHIROMA: Cummins.

MR. KRIEGER: Cummins. I have a list of them. I can provide those to you, but I don't know all of them.

DR. SEIBER: They funded the study and now they're going to review the results or how is that --

MR. KRIEGER: We fund it, to CE CERT. CE CERT is

under contract from us to do this study. CE CERT established the Technical Advisory Committee.

MS. SHIROMA: With our concurrence.

CHAIRMAN FROINES: Are there -- there are representatives from Cal EPA and OEHHA and ARB?

MR. KRIEGER: Yes.

CHAIRMAN FROINES: On the committee?

MR. KRIEGER: Yes.

CHAIRMAN FROINES: Are there academic investigators?

MS. SHIROMA: UC Riverside.

MR. KRIEGER: Yes. UC Riverside. Actually the CE CERT study, they have co-contractors, UC Davis is doing part of the study, and UC Riverside. Actually Janet Areus (phonetic) is one of the researchers, and Norm Kado and Pablo Comato from UC Davis.

CHAIRMAN FROINES: Are you looking at, for example, how the mix of polycyclic and nitropolycyclic aromatic hydrocarbons have changed?

MR. KRIEGER: Yes. This is a very intensive study dealing with not only with polycyclic aromatic hydrocarbons, the PAHs, but also the nitro PAHs, the nitrosamines. We have a whole list of the compounds.

MS. SHIROMA: Mutagencity.

MR. KRIEGER: Mutagenicity as a model.

CHAIRMAN FROINES: I think we should get a copy of the protocol that you have, because clearly there is a potential change in risk depending on the changes in the composition and amounts of various subspecies. And so that would be interesting for us to have and be aware of.

MR. KRIEGER: We'll provide you a copy.

CHAIRMAN FROINES: I don't mean to be too technical, is that direct-acting mutagenicity or is it enzyme-catalyzed mutagenicity, do you know?

Because the problem with the Riverside people is they tend to look at direct acting.

MR. KRIEGER: I believe it's direct-acting, but I'm not sure on that.

DR. BLANC: They're just doing Ames testing?

CHAIRMAN FROINES: No, not necessarily. That's not one of the problems historically.

MS. SHIROMA: We'll send the panel members a packet of information about the study and the protocol and makeup of the advisory committee.

DR. SEIBER: Given our panel -- John, the panel, I think, is scheduled to meet in December. Would this study be concluded to the point where we'd have a presentation or have the result before that December meeting?

MS. SHIROMA: Protocol-wise, we need to finish QA/QC and then discuss the results with the Technical

Advisory Committee, and then we'd be able to come to the panel. I don't think we would be at that point by the December 10 meeting, but by a January -- is that right, Robert?

MR. KRIEGER: Yes. By January. Actually we're looking at times in December for the TAC, the Technical Advisory Committee, to meet, to discuss the results. So after that time, or at that time, we could provide you some --

MS. SHIROMA: But why don't we take a look at their schedules and see if we can't provide for their being able to meet before the December 10 meeting.

CHAIRMAN FROINES: If there are major changes in composition, that has health implications as well. George may not want to address that, but it's something we'll have to think about that about once we see the results.

DR. BLANC: Will that study also address the potential redistribution of particle size that occurs in the newer engines and the newer fuel?

MR. KRIEGER: Yes, it does. It includes particle sizes all the way from .1 up to 2.5 microns.

CHAIRMAN FROINES: Go ahead.

MR. KRIEGER: In summary, diesel exhaust, as I mentioned, is a complex mixture of gases, vapors and fine particles.

Emissions of diesel exhaust PM 10 in California are estimated to be approximately 36,000 tons per year, and the majority of the particles are less than one micron in diameter.

MS. SHIROMA: Next slide.

MR. KRIEGER: As mentioned before, projected diesel exhaust outdoor ambient concentrations decreased from 3.0 micrograms per cubic meter in 1990 to 1.7 micrograms per cubic meter in 2010.

The California outdoor annual average ambient concentration in 1990 is estimated to be 2.2 micrograms per cubic meter.

Our near source estimate can be up to three times that of ambient air concentrations.

And, finally, we have considered a person's daily activity and exposures to different environments to estimate a total exposure concentration of 2.1 micrograms per cubic meter.

Now, I'd like to present some of the major comments we received on the May 1997 version of the report.

The first one deals with exposure calculations should include the vapor and gas phase constituents.

The second one is a discussion of atmospheric transformation products should be enhanced.

CHAIRMAN FROINES: Bob, are you going to go

through each one and then go back to each one?

MR. KRIEGER: Yes. I'll respond in the next few slides.

No. 2, comments, discussion of atmospheric transformation products should be enhanced in the report.

No. 3, the characterization of uncertainty of exposure analysis including near source estimates are lacking.

And the last one is the form of the identification.

Based on these comments we received, we plan on rewriting the executive summary to clarify exposure analysis methodology.

We also plan to include additional information from existing data to enhance our discussion of the vapor gas phase of diesel exhaust into our report.

We will also incorporate additional studies in the Part A and executive summary on the potential mutagenicity and carcinogenicity of the PAH and nitro PAH compounds. Actually, some of this is already mentioned in our Chapter 5, but we're going to move this up into the main part of our text and the executive summary.

DR. SEIBER: Robert, particularly on the middle bullet of that slide, will that come from the CE CERT study, that vapor phase composition particulate? Will there be new

data, we haven't see the protocol, but is that part of the CE CERT study, is that your main source of new information, do you anticipate?

MR. KRIEGER: We will -- we're anticipating, well hopefully we'll use that information, but we also have previous information, existing data, that mentioned -- talk about the vapor and gas phase of diesel exhaust that we can use in our report.

So there is some existing data out there.

MS. SHIROMA: CE CERT will help.

MR. KRIEGER: CE CERT will definitely help.

We also will be moving some of our discussions under the certainties in our exposure analysis from the appendices to the main text of Part A and the executive summary.

We also plan, like I mentioned before, it's not on this slide, we plan to add the indoor and the total exposure estimates for 1995.

And we are looking at how we can better describe and characterize the toxic components of diesel exhaust.

This concludes my presentation. If there are any questions --

CHAIRMAN FROINES: Can we go back to the third bullet. We will incorporate additional studies into Part A and executive summary on the potential increases in

mutagenic and carcinogenic PAH and the nitro PAH compounds.

Can you say a little bit more about what you intend to do and what the sources of information are?

MR. KRIEGER: There are a few sources that we haven't included into our report and one is a UCD study that dealt with the vapor and gas phase mutagenic compounds from diesel exhaust.

CHAIRMAN FROINES: UC Davis?

MR. KRIEGER: Right. UC Davis.

And they examined actually the vapor and gas phase, the mutagenic properties from diesel exhaust from old and new fuels too. This is kind of like a pilot study before the May CE CERT study. So that data hasn't been incorporated into our report. That data will be incorporated.

CHAIRMAN FROINES: Isn't there data from Janet and Roger Atkinson on the same --

MR. KRIEGER: Yes. We are actually going to take a look at all the data they have in the studies that they have and we have now. But right now I have a stack of reports from actually UC Riverside that talks about the mutagenic and carcinogenic compounds in diesel exhaust and we're going to look at it, and also incorporate it in the report.

DR. BLANC: How will you deal with the changing

emphasis at the national level on particulate matter 2.5 micron and less? Most of your emphasis here has been on exposures to PM 10 particular matter, ten micron or less.

It would seem that given the new emphasis on the national level it might be useful as a parallel to the question that was asked earlier or a suggestion that it be emphasized the portion of particulate exposure contributed by diesel in the overall PM 10, that it be useful to talk about the overall contribution to PM 2.5, because it's my impression that given the particle size distribution, in fact, proportionally it will become even more important if you look at 2.5. Am I correct in the assumption?

MR. KRIEGER: Yes. You're correct. We actually are going to add or expand our discussion on that PM 2.5, and specifically addressing the proportion of diesel exhaust. It actually goes from four percent from the PM 10, to a little over seven percent for the portion of 2.5. You would think it would go much higher, but from your Emissions Inventory, that's what we've come up with, seven percent. But we're going to add that into our next draft, the discussion on the proportion, realizing that over 93 percent of the diesel exhaust particle is smaller than one micron, so we're all going to --

MS. SHIROMA: Throughout the report.

MR. KRIEGER: Throughout the report we're going to

clarify.

DR. BLANC: Then it would also, I think, be important to, in the same sense that people are asking you to put in caveats about how there may be uncertainty in some of your estimates, I think it would be important for you to put in caveats, and in fact, your estimates may be overly conservative, because as emphasis, which is to ultrafine particulate effects, that is to say the effects of particulates not only that are less than one micron, but less than .1 micron, and as the proportion of those particulates becomes more important from diesel, then in fact you may be overly conservative in the contribution of the exposure.

And I think if you're going to be forced to put in caveats about your uncertainties in one direction, I think you should put in your caveats in the other direction as well.

MR. KRIEGER: Okay.

CHAIRMAN FROINES: The percentage of --

DR. BLANC: I would actually -- let me follow up one thing.

I would actually appreciate some modeling or a table in your revised version which said if we look at ambient particulate air pollution at this level, this is the proportion and if you look at it at this level. Because of

the particle distribution I think you can do that and you can look at two models, one with the pre-1993 fuel and one with the post-1993 fuel.

If you want, I think if you drew a graph, what you would see is as you talk about the size of the particle that you care about, the proportion contributed by diesel exhaust will go up linearly.

So if our health concerns in the second section, in fact, are to a certain extent related to ultrafine particulate, then indeed the issue of the diesel fuel becomes more important, not less important.

CHAIRMAN FROINES: That's particularly true if you consider the cancer effects and non-cancer effects become -- is an issue which I think will come up today, so we won't start talking about it now, but the implication of what Jim and Paul are saying is that we need to understand better the nature of that size distribution and then to think later about its relevance to health.

MR. KRIEGER: Thank you. Yes, we will look at that, put that table in our report, in our analysis.

DR. SEIBER: Are you ready to wrap up the exposure part?

MR. KRIEGER: Yes.

DR. SEIBER: I have a question that really kind of cuts across the exposure and health, so this -- I'm going to

bring it up now.

If you sum up what's known on the concentrations of individual chemicals and diesel exhaust, can you account for the observed biological effects of the total mix? I think the answer in the report is, no, you can't, but there's some missing fraction.

Is there any hope that we can get to a better material balance, so to speak, for want of a better term, in getting back the individual chemicals?

We had a hard time with environmental tobacco smoke. I'm sure we're going to have a hard time with this one too.

Could you comment on whether we have a reasonable chance at making some kind of a summation based on individual chemicals or is it just too far separated, the total effect as opposed to what you would sum from individual compounds?

MS. SHIROMA: I think that -- and you'll hear more from the OEHHA presentation, that in looking at the health studies, in looking at a causal effect from the exposure to diesel exhaust as a complex mixture.

Now, on the other hand, as we go about updating and revising our diesel exhaust exposure, it's particularly at a point when we take a look at the CE CERT data, which is looking at, I believe, at least 150 different constituents.

It will be very very insightful to see what constituents are there before and after and amounts and so forth. And perhaps an exposure assessment looking at those specifics can be fruitful.

But, again, the health studies are looking at exposure to diesel exhaust as a complex mixture. So I will leave it to George to discuss that future.

DR. SEIBER: Sort of like doing a principal component analysis where you go back and you say, okay, I can explain 90 percent of my effects with these seven compounds or something. And my guess is it's going to be very difficult, but I just wondered if you're thinking along that line and trying to fill in some of those gaps.

DR. GLANTZ: You know, the way I read that, I mean, I agree with Jim, I think that's a worthwhile thing to do, but I wouldn't be surprised that the reason that the toxicity you see associated with the diesel exhaust is more than the sum of the individual chemicals may reflect interaction effects. And the fact that when you have two or three compounds present, the net effect is more than the sum of the effects of the compounds separately. That's another possibility.

DR. SEIBER: You have got the particle itself.

DR. GLANTZ: Right. Right.

CHAIRMAN FROINES: Well, if I can weigh in here,

it just so happens in my bag of tricks here, I've a paper by Paul Howard and Fred Beeland (phonetic) from the National Center for Toxicologic Research, called "The Effect of Co-Pollutants on Metabolism of DNA Binding of Carcinogens," and in this paper they show that pyrene and nitropyrene will enhance DNA formation, DNA adduct information with 1,6-dinitropyrene. And some other compounds actually reduce the amount of DNA adduct formation.

So it's clear, it seems to me, because these things require metabolic activation and there are competitions for enzyme sites that there will be potential competitive interactions or other types of interactions that might occur in a toxicokinetic context, but having said that, and being aware that those interactions are possible and do exist and there's evidence to indicate that, it still seems to me a useful exercise to do what Paul and Jim are saying, which is to look at the individual compounds, assume additive toxicities and do some risk calculations based on the compounds and the concentrations that we're aware of.

And that I think that we're dealing in a epidemiologic context with the whole ball of wax, so to speak, but it seems to me that that's an exercise that at least acknowledges the fact that we do know something about the identities of rather potent carcinogens in these mixtures.

DR. FRIEDMAN: What you would do if these calculations, based on individual components, came out quite different from what the observed -- the data that one observes from the whole exposure to the whole exhaust product would be? I mean, what does this add to our understanding if it came out quite different, what would you believe?

CHAIRMAN FROINES: That's hard to say, I think.

DR. SEIBER: What I think John meant to include the particles too, not only the chemical compounds, but as it was pointed out, the shifting distribution of particles.

And then the other confounder is you've got vapor versus particle bound, and it's very difficult. What would it do, let me turn it around and say if you were able to explain the toxicity with six or eight or ten factors, then that would in the risk management phase somebody at some point could say, okay, get rid of these six or eight and we've cleaned up our act. It might help in that phase.

And, I don't know, I think it kind of helps us understand the dose response dilemma if we know that it's benzene or anthracene or benanthracene, we know something about their dose response behavior already. I think it adds to the ability to make a good decision.

CHAIRMAN FROINES: In a scientific context, I think that this committee that's looking at the differences

in compounds and it will report, the Technical Advisory Committee will report in December, that's important work, because if there are significant changes occurring in the chemical constituents, that clearly has implications for human health risk.

And so it's useful to know what the differences may be that we're seeing between earlier diesel and more current, and one may not be able to make -- use that in any kind of final risk estimation, but it gives you a better sense of what we're -- what we have out there to address.

So I don't think it's a magic bullet, but I think it's an interesting piece of information.

DR. FRIEDMAN: That helps me understand. I agree with both of you. I think that makes good sense.

CHAIRMAN FROINES: I'm told we need to take a brief break to deal with some technical difficulties.

Is that correct?

Shall we take a ten-minute break?

(Thereupon a short recess was taken.)

CHAIRMAN FROINES: Why don't we get going. We have some people who have to leave, so I'd rather move it ahead as soon as possible.

Genevieve, we did not entirely finish your presentation, I think, the schedule.

MS. SHIROMA: I will do the schedule after George

and Michael are done.

CHAIRMAN FROINES: So for the panel the last page of the document deals with schedule, and so that will come up after the OEHHA presentation.

You might introduce yourself and Michael for the people who are new to the panel.

DR. ALEXEEFF: Good morning, members of the panel and members of the public and the audience. I am George Alexeeff, and I'm chief of the Air Toxicology and Epidemiology Section in the Office of Environmental Health Hazard Assessment and Cal EPA.

And with me is Dr. Michael Lipsett, who is a public health medical officer.

And also with me are a number of other staff members who helped prepare our diesel exhaust report, and as we go through the report if there are questions that I feel I can't answer, I'll try to draw on the staff to help to see if we can get an answer for you today on some of those questions.

Our presentation is kind of lengthy. There's several parts.

The first part is an overview of what is in the document, simply just to indicate what are the major points that we make in the document, and how we got to the current document.

The second portion of our presentation will be to discuss the key comments or issues that have been raised in the public comments submitted and to simply try to elucidate what those issues are, because the issues raised are very complex.

The next slide, please.

In June of '94 we released a draft document and there was a public comment period that was conducted, as well as workshops.

We reviewed the public comments, discussed the issues with many of the commentators. We held a joint international workshop and Dr. Kathy Nauss from HEI is here, who actually helped put it all together. That was in January of '96.

And then we -- I can't see from here. I'm sorry.

And then we conducted additional analyses and made changes in response to the comments in the workshops.

Next slide.

In the draft that we released in May, it was the Scientific Review Panel draft that was the intent. In that draft we updated the literature, conducted a literature search, added some new studies. We reported it closely with the US EPA, consulted the Health Effects Institute, NIOSH, Dr. Crump, and others.

As we mentioned, a workshop has held July 1st. We

received public comments and I'll be discussing the key public comments a little later.

Next slide.

I'd like to just mention the Health and Safety Code from which what we're operating here, because I've had a number of questions from various sorts.

The Health and Safety Code requires us to evaluate the health effects of candidate toxic contaminants. We prepare recommendations, consider all the scientific available evidence. We assess the availability and quality of the data on the health effects, including the potency and the mode of action. We estimate the levels which may cause or contribute to adverse effects.

Next slide.

Now, where it can be established that a threshold exists, the estimate shall include both of the following factors. So there's a threshold.

The exposure levels below which no adverse effects are anticipated --

You know, all the slide is not showing on the projector here and is it too far back? Okay.

CHAIRMAN FROINES: You notice that Paul Blanc is the occupational physician, so he knows about workplaces.

DR. BLANC: I was the AV nerd in junior high school.

(Laughter.)

DR. ALEXEEFF: I can pretty much see from here now.

So where it can be established that a threshold exists, the estimate we provide shall include both the following factors. The exposure level below which no adverse effects are anticipated and an ample margin of safety which accounts for the variable effects in the heterogeneous population exposed to the substance under evaluation which they may experience, the uncertainties associated with the applicability of the data to human beings, and the completeness and quality of the information available on the potential human exposure to the substance.

And this margin of safety we general consider as uncertainty factors that we add in.

Next slide.

In cases where there is no threshold of significant adverse health effects, the office shall determine the range of risk to humans resulting from current or anticipated exposures to the substance.

This is what we generally do for carcinogenic substances. We also did it for the health effects of lead.

I'd like to just briefly --

DR. BLANC: George, can I stop you there for a second?

The implication of what you just said, since lead was the only non-carcinogenic toxic air contaminant prepared for the criteria document report, is that correct?

DR. ALEXEEFF: Well, actually it's a slight difference. Actually lead is carcinogenic, but the key end point, where are the non-cancer end points, and it's the only document which really focuses on non-cancer health effects.

Yes.

DR. BLANC: In that one you also treated a substance that from the point of view of not having a threshold?

DR. ALEXEEFF: Yes.

DR. BLANC: So there's never been a document where a material was evaluated for which there was felt to be a threshold?

DR. ALEXEEFF: There were two documents, acetaldehyde and perchloroethylene, which the primary effects of those compounds were cancer. And the cancer risk assessment was assumed to have no threshold.

In those documents as well they also provided non-cancer end points and in that we assumed a threshold and incorporated uncertainty factor to estimate the level that would not effect the non-cancer health effects.

So we have had documents which have discussed

non-cancer health effects and two chemicals have developed health levels. We will be bringing to the Scientific Review Panel in the future some documents with a couple hundred compounds where we do this kind of analysis, but up to now we have not discussed it extensively in the Scientific Review Panel.

DR. BLANC: But there's no, from what you've said in your previous slide, there's no legislative imperative for having to deal only with primarily non-threshold issues? You have guidelines for how to deal with --

DR. ALEXEEFF: Yes.

DR. BLANC: Do you perceive some institutional reluctance to embark on assessments in the non-threshold -- in the threshold area?

DR. ALEXEEFF: No. None at all. Most of the other work in our department has been in the non-threshold area for a lot of the health standards that we develop for water and in the arena of ambient air quality standards.

So there's no reluctance. It was simply our focus for those chemicals was carcinogenicity, and that seemed to be the end point that would drive the risk assessment and that's simply where the focus was.

There's no reluctance. We were simply trying to deal with the health effects most important to the public health.

DR. BLANC: So it was a perceived public policy reason that led to that focus historically?

DR. ALEXEEFF: As we brought documents to the panel, if issues are raised regarding non-cancer health effects, we tried to address them in the document. So it wasn't -- I wouldn't even consider it a policy. It was simply as we went through each chemical we tried to identify the health effects that were the most important. And the carcinogens -- for the carcinogens except for lead, it appeared that the cancer effect was driving the risk assessments.

DR. BLANC: John, am I being too obscure?

Do you have any historical comments from the panel's point of view?

CHAIRMAN FROINES: No. I think that it's an extremely interesting question. For example, in the occupational standards for formaldehyde, you know that the levels where respiratory and irritative effects occur, occur below that which you would think about when you would regulate for carcinogenesis.

So, in fact, with formaldehyde you could actually in a occupational context, you might set standards that were lower than the non-threshold phenomenon of cancer.

So the issue, I think, is extremely important. And it will come up today when we talk about non-respiratory

effects.

I want to talk about Andy Saxon's work on IG mediated rhinitis and asthma.

So there are a number of issues that will come before us on diesel that I think we have to -- we want to be careful not to over-focus the debate on the narrow issue of the dose response and all the uncertainties, because we may lose the forest of diesel toxicity for the little trees of the debate over the rat lung tumor, for example.

So I think it's important what -- I think what you're saying is extremely important with respect to diesel exhaust.

DR. ALEXEEFF: So --

CHAIRMAN FROINES: Is that in the same vein that you were raising?

DR. BLANC: (Nods head.)

DR. ALEXEEFF: It's simply an area that we definitely want to get into and any assistance from the panel is welcomed.

As I mentioned also, we will be bringing documents to the panel over the next year. The intent right now is to bring one document which will look at health effects for 50 compounds, acute health effects. And another one that could look at chronic health effects for another 120. Those are in preparation and will probably be coming to the panel over

the next year.

We're trying to go back and catch up on some of the chemicals. We focused on cancer and didn't deal with the non-cancer health effects.

So if we can handle it all in one document, it will help us.

Okay. I'll briefly touch on the major topic areas, the toxicokinetics. Some of the issues that came out of these major topic areas, toxicokinetics, the non-cancer health effects, the quantitative risk assessment we conducted on that, genotoxicity and mechanisms of action, the cancer findings on animals in occupational studies and cancer quantitative risk assessment.

The key point in toxicokinetics is we examined lung particle deposition and retention and clearance and chronic exposure of rats to concentrations above 2.5 milligrams a cubic meter can result in particle accumulation due to the exceedance of clearance capacity.

We evaluated the published data and mathematical models for retention and we used empirical lung burden data for the animal quantitative risk assessment.

For the non-cancer health effects we reviewed some of the occupational exposure studies. We felt that the data we saw was insufficient to calculate a reference level.

In terms of the animal data, there are several

studies reporting inflammatory histological changes and we chose one which reported above 460 micrograms per cubic meter in rats exposed for 30 months.

And the next slide.

The next slide summarizes our non-cancer risk assessment on animal data and also compares it with that for US EPA and the World Health Organization.

You can see that each of the organizations focused in each case on rat models, mostly on the Ishinishi study. The primary end point was pulmonary hyperplasia.

The method of analysis was to establish the No Observed Adverse Effect Level, and then to calculate the Human Equivalent Concentration, the HEC.

And then from that to add an uncertainty factor, labeled UF, and then develop the reference level.

And you can see there are a couple of different methodologies employed. One just used a No Observed Adverse Effect Level and larger uncertainty factor. Other methodologies used what's called the Benchmark Concentration, which is where you use the slope of the dose response curve to establish the No Observed Adverse Effect Level, and then add a human concentration.

And then in our analysis we focused on the Benchmark Concentration results and looked at different percentages of response using a couple different models.

If we look at the next slide, please.

DR. BYUS: I have --

DR. SEIBER: I have a question. Go ahead. You're closer.

DR. BYUS: My question is back to this issue of recurring issue with particle size. You may call it diesel exhaust, maybe more specific in various areas, but it turns out that this is the old diesel exhaust, with perhaps not as fine of a particle, will that affect the conclusions you've drawn from these kinds of studies?

In any event, you want to really specify throughout the document what the particle distribution is for the exhaust of all of these studies, so that one can make the comparison later or sooner, if it needs to be done.

DR. ALEXEEFF: Yeah. I agree with you.

I think we tried to do that in our summary tables, but I think that is something we would definitely like to do.

DR. BYUS: That's all.

DR. SEIBER: My question, George, was on the previous overhead. You said that the data are insufficient to calculate a reference level, and then -- that's all right. Then on this one you listed some reference levels; right?

DR. ALEXEEFF: I'm sorry. I was referring to the

human data.

DR. SEIBER: Okay. I just want to make sure I understand.

DR. ALEXEEFF: I'm sorry. We felt that the human data, there was human information on various health effects. However, we were unable to find a quantitative response that would be applicable to the concerns that we have, where we could extrapolate to an environmental exposure.

DR. SEIBER: So all this is based --

DR. ALEXEEFF: So this is based upon the rat.

DR. BLANC: You're talking about chronic responses?

DR. ALEXEEFF: Chronic response.

We didn't evaluate acute health effects, so that would be an area if there was information that we could add.

DR. BLANC: Well, isn't there information from a series of experimental human exposure studies?

DR. ALEXEEFF: I'm not sure if it's quantitative or not.

DR. BLANC: By definition, they're quantitative, because they are controlled human exposure studies.

DR. ALEXEEFF: Well, the ones that -- let me see. We have just a small discussion of this in our document.

And, well, maybe there are studies that provide -- we'd be happy to include any other studies that you're aware

of, but the ones we were aware of when we were finalizing this report were inhalation of small amounts of the particles in examining immunological responses. The actual quantitation, we didn't see it. From the studies we saw, we couldn't see how to extrapolate them to an ambient concentration. Maybe there is --

DR. BLANC: Well, I can see how it would be a problem if you were trying to look at chronic health effects, because you were -- the focus of the review in the draft document was particularly on cohorts of miners with exposure to diesel exhaust from mining equipment. And chronic health effects, such as chronic productive cough, chronic bronchitis. I'm not even sure that I saw pulmonary function data, but there might have been some.

But there are experimental and even actually field studies where people have looked at cross-changes in relation to diesel exhaust exposure, and those studies do quantify the exposure.

And perhaps if you were limiting yourself to -- perhaps that statement about the lack of quantifiable human data refers more to the difficulties of the chronic cohort studies. But I do believe there are at least limited acute inhalation data.

DR. ALEXEEFF: We'll be happy to look at that.

DR. BLANC: Do you agree with the --

DR. LIPSETT: I think -- I think you're referring to some of the studies that are being done in Scandinavia?

DR. BLANC: Yes.

DR. LIPSETT: Yeah. I don't follow -- my involvement really was with the meta-analysis, but I understand that there have been studies where they have looked not at only lung function, but indicators of inflammation in some of those studies.

But I think that when this document was drafted, I'm not sure that any of those have been published at that point, but we can certainly contact Dr. Sandstone to find out what the state of his research is.

DR. ALEXEEFF: We'd be happy with any suggestions you have.

The couple of health levels I mentioned previously, there were non-cancer and even the lead levels were all for chronic exposure, so we really haven't tackled acute health effects in this program, substantially, other than qualitatively.

DR. BLANC: But correct me if I'm wrong, if you were looking at toxic air pollutants that might induce acute decrements in the lung function over a population which include people who already have borderline lung function that would meet your standard for something that you'd be concerned about.

DR. ALEXEEFF: Yes. I'm almost certain it would meet the standard. It's not a restriction on time.

DR. FRIEDMAN: Can you explain a little bit more of the uncertainty factor, what is that used for? Is that to take a fraction of the dose and you have a no effect and then you apply that to get an even lower level just in case you're wrong? And why some people choose 30, 25, 100, how that's arrived at.

DR. ALEXEEFF: Sure. The uncertainty factors -- the uncertainty factor approach has basically come out of roughly the 1970s, the drinking water standards, and various National Academy of Science reports. That's where the whole philosophy came from.

And in those studies and analysis -- and also related to food standards, trying to develop acceptable daily intakes -- and in those standards they were looking at two issues in extrapolating from animals to humans.

The difference in sensitivity between the average animal in a study who are fairly very specifically defined, kept -- other than the exposure, kept healthy, well-fed and comparing it to the average human, which -- the average human. And it was generally thought that a factor of ten would deal with the variability between animals and humans.

Now, that's not to say there aren't cases where the variability is less, but in a public health standpoint,

it was thought that ten would deal with both issues of differences in metabolism, which are generally considered the toxicokinetic issues, and differences in the susceptibility of the response between the two populations, and which is generally considered pharmacodynamics.

Now, so that's one factor of ten.

The other factor of ten generally refers to the differences between the average healthy adult and the type of individual that Dr. Blanc was referring to, the susceptible individual for the end point you're concerned about.

And for many of the analyses that have been done, the variability in the human population is often -- well, it can range anywhere from two to over a hundredfold, just the variabilities, so it's thought that a tenfold, if you can go from the average to the most susceptible, a tenfold will account for most of the differences in the human population.

So those are basically the starting points that you -- that one thinks about when one does this analysis.

If one has more information that will help reduce the uncertainty, you can reduce the uncertainty factor and that's generally the approach that's used.

So in these cases, since we were -- we had -- those uncertainty factors are generally used for when you're starting from an animal study with not much information, to

a human population where you actually know what's going to happen when they're exposed to this chemical.

So as you have more information, you can reduce the uncertainty factor.

DR. GLANTZ: I don't know if you're misspeaking or what, but you've been saying tenfold. Do you mean hundredfold?

DR. ALEXEEFF: For example, if you look at the WHO, W-H-O, the NOAEL approach, that's the standard approach we were referring to where the uncertainty factor is 100 and the uncertainty factor is based upon a tenfold factor from animals to humans, and a tenfold factor within humans.

DR. GLANTZ: Okay.

DR. ALEXEEFF: The addition of either an improved approach over the NOAEL, such as the benchmark dose, the human equivalent concentration, allows one to reduce the uncertainty in the extrapolation and therefore the uncertainty factor reduces.

DR. GLANTZ: Just to clarify it then, when you talk about the uncertainty factor of ten, it's ten for susceptibility and ten for animal to human, and you multiply them together to get a hundred?

DR. ALEXEEFF: Right.

DR. GLANTZ: So the standard uncertainty factor would be a hundred and US EPA pulmonary hypertension is only

30, because it's felt that there's less than the usual amount of uncertainty?

DR. ALEXEEFF: Correct.

DR. FRIEDMAN: Thank you. I appreciate that.

CHAIRMAN FROINES: Which is the benchmark approach here, George?

DR. ALEXEEFF: The ones that say BMC.

CHAIRMAN FROINES: BMC.

DR. ALEXEEFF: Benchmark concentration approach.

CHAIRMAN FROINES: And then the ones below for pulmonary hyperplasia are using the probit analysis?

DR. ALEXEEFF: We're using the two forms of benchmark, a probit and a Weibull.

CHAIRMAN FROINES: I got it. I got it.

I think we should try -- and I'm worried because Stan has to leave at noon, and so we should write down questions for a while to try and move it to a place where Stan can hear as much as possible.

DR. ALEXEEFF: Next slide.

This just summarized what was in that slide over there in terms of the range of the levels.

Go to the next slide.

Just briefly go over the genotoxicity evidence.

There is a lot of evidence on the genotoxicity of diesel exhaust, whole diesel exhaust and especially diesel

exhaust extracts are mutagenic in bacterial assays.

Particles in extracts are mutagenic in mammalian cell assays.

Extracts are reported mutagenic in cultured human lymphoblasts.

Next slide.

DNA extracts induced chromosomal aberrations in mammalian cell assays. However, in vivo studies are negative.

Diesel exhaust particle and extracts induce sister chromatid exchange in mammalian cell assays, but results in vivo are mixed.

Treatments of mammalian cells in vitro have resulted in increase DNA adduct formation.

Rats and monkeys exposed to whole diesel exhaust have shown an increase in DNA adduct formation.

And there are increased levels of DNA adducts have been reported in workers exposed to diesel exhaust.

Again, this slide just summarizes, I mentioned 2.5 about the clearance.

CHAIRMAN FROINES: How many studies have there been positive findings in DNA adducts in the human population?

DR. ALEXEEFF: Do you know?

FROM THE AUDIENCE: Two studies.

DR. ALEXEEFF: Two studies.

FROM THE AUDIENCE: Both Scandinavian --

DR. ALEXEEFF: Why don't you come up to the microphone and introduce yourself.

This is Dr. John Budroe.

DR. BUDROE: There's been two studies, both of them Scandinavian, one with truck drivers and garage workers and one with bus drivers, showing approximately -- the most exposed workers maybe a twofold increase in DNA adducts over controls.

CHAIRMAN FROINES: They look at adducts persistence?

DR. BUDROE: No, they didn't. They were taking samples of the peripheral blood lymphocytes, and just doing an immediate sampling.

CHAIRMAN FROINES: Thanks.

DR. ALEXEEFF: Okay.

DR. BLANC: John, that was your written-down question?

(Laughter.)

CHAIRMAN FROINES: Prerogative of the chair.

DR. ALEXEEFF: I mentioned 2.5 in toxicokinetics as affecting the clearance. You can see it there. Above 2.5 in the rat lung, there are clearly positive studies. There are five important studies that have been consistent.

Below 2.5 or between the range .35 to 2.5, there's not significant increases generally.

Hamster studies in terms of the cancer findings are negative.

And most of the mouse studies have been reported negative.

And similar to the World Health Organization, US EPA presented a comparative analysis of these rat studies and used our standard linearized multi-stage approach. We also used a biologically-based dose response analysis of the modeling data.

And the range of risk we obtained from the animal data was one times ten to the minus five, to three times ten to the minus four.

DR. FRIEDMAN: Is that for lung cancer in humans?

DR. ALEXEEFF: That's an estimate in lung cancer in humans, based on the rat data.

There are many sources of uncertainties with animal studies. The general extrapolation from rats to humans, the relative importance of mechanisms of action for the rat lung, how genotoxicity fits in.

The rat lung has shown a generalized response to inerts. We'll be discussing that in the comments.

The role of particulate overload, chronic inflammatory response, cell proliferation and oxidative DNA

damage is a major uncertainty.

The choice of dose response models and the presence of a threshold.

DR. SEIBER: You're going to come back to that discussion --

DR. ALEXEEFF: We'll come back to that when we discuss the comments, mostly from Dr. Mauderly. We will go into that in detail.

To briefly touch on the epidemiology information, there are 47 occupational cohort case control studies, including truck drivers, railroad workers, dock workers, transport workers, equipment operators.

And we conducted both a qualitative and a quantitative assessment of this literature.

Qualitatively in the report we looked at consistency of the data, the strength of the findings, possibility for bias or chance of the associations, evidence of the exposure response, the temporality of the associations, and the biological plausibility.

Are you going to go into this, Michael?

DR. LIPSETT: Go ahead.

DR. ALEXEEFF: Should I mention this now, or should we just talk about it later?

CHAIRMAN FROINES: Go ahead.

DR. ALEXEEFF: In terms of the consistency I think

you'll see that generally the results are fairly consistent across the studies.

The strength of the findings, the strength is considered weak, that is to say the relative risk is not very large, in about the 1.4 range.

The possibility of bias or chance association with this broad range of studies, both smoking ingested and nonsmoking ingested, the chance of bias, it seems to be very small.

Evidence of exposure response, that's been of interest in this, and the evidence is weak and has been under great question. We'll be discussing that later.

Temporality of the associations, that refers to whether enough time was given to measure the response, that's generally good.

And the biological plausibility, well, as you can see there's a lot of information on genotoxicity that suggests plausibility.

We'll also discuss the rat information as well.

DR. FRIEDMAN: When you talk about bias, does that include confounding?

DR. ALEXEEFF: Yes, Michael will be talking -- Dr. Lipsett will be talking about that.

CHAIRMAN FROINES: I think just to put things in context, George is a toxicologist, so when he looks at

exposure response he's thinking about putting rats into boxes.

Remember, that when you do exposure response in a human population, you're dealing with occupational exposures that are notoriously difficult.

So we have to keep in mind what's weak and what's not weak in terms of the context of the nature of the studies that are being conducted.

DR. ALEXEEFF: Thank you.

DR. GLANTZ: Could I just say, thank you for that written question.

(Laughter.)

DR. GLANTZ: On behalf of the panel.

Can I -- I actually did want to say one thing.

I actually was a little -- in reading the report, I was little bit bothered by what you said on this. Not -- it was all kind of standard stuff, but I actually think that the evidence is stronger for a causal relationship than you put forward, and this -- because these standards that you outline here are sort of the standard standards that epidemiologists use for drawing causal conclusions based just on observational studies.

And I think that there is actually quite a lot of evidence on mechanism and biological plausibility, so rather than just sort of saying, well, there's a weak association,

but it's biologically plausible, it seems to me it should be saying that there's a lot of evidence of toxicity in terms of carcinogenicity and the epidemiological studies pick that up. I mean, it's a difference in emphasis.

And one of the things you had in there, which people say, which just drives me crazy, is, well, the relative risk is below two, and that makes it weak.

That two number to me, is just the number that's been pulled out of the air by various people. In fact, some years ago the tobacco companies were doing polling among scientists to see how long they could sell it to for ETS.

And I think the fact that you don't have a huge increase in individual risk doesn't mean that there's not a relationship there. It just means that the risk increases around what you said 1.4, which to me for an environmental toxin is pretty high.

When you look back at a lot of other compounds that have gone through this process, we have made decisions and recommendations relating to risk assessments where there was no epidemiological data.

And so to me when you look at the evidence on diesel, and there are a lot of genuine issues that need to be addressed in terms of the epidemiology, but it seems to me that it's actually pretty strong.

And what you have here is a reasonably good case

based on the animal exposure studies where you can control everything that there is something going on.

And the fact, given all the problems of assessing exposure in the real human studies, which are -- you were just getting into, the fact that you can see something that's as consistent as you see in the epidemiological studies, I think is pretty strong.

And so I would urge you in redoing the report to kind of be a little more assertive about the value of the epi studies and rather than just dismissing the animal toxicology or treating the animal toxicology sort of one point that addresses the biological plausibility question that the statisticians have raised is to say really that's established a certain amount of -- that's established a certain amount of evidence for carcinogenicity, at least in some environments, and we can detect that reasonably consistently in human exposure studies.

So and that two I would really like to see -- there's two places I found where you talk about it, I just -- that makes me crazy. I think you should just take that out. It's a silly, arbitrary number.

If you go read the literature where people have discussed that, it's clearly the issue of how high the relative risk is, has clearly been done, if it's only in a vacuum, if there's no really meaningful toxicological

evidence.

You've got a lot of toxicology, you've got a lot of epidemiological studies.

So I've been quiet for a long time. Now just write it down --

DR. BLANC: Stan, do you want to, in context just comparatively to the relative risk of cardiovascular disease associated with smoking for example or the relative risk of bladder cancer associated with smoking too, to epidemiological associations which are absolutely established, what's the relative risk?

DR. GLANTZ: The risk for active smoking in heart disease is around two to four and I don't know the bladder numbers.

But, I mean, we've just gone through this whole same debate with secondhand smoke and the risks that you get are sort of comical.

There's a lot of environmental toxins where if you even have epidemiological data, which often we haven't had, you're getting numbers of this range.

And the fact -- and I think that the meta-analysis that you presented at the workshop and it's in the report is actually quite convincing that there is real association that you can pick up in that epidemiology, and that's completely consistent with what you would expect of some of

the toxicological studies and I think that's the way it ought to be framed.

This two number, it's just something that's a public relations number. There's no science to justify that.

CHAIRMAN FROINES: I just want to say one thing and stress it. I think that the consistency across different biological end points is really important to emphasize, because I worry that we break things down into little trees and we look at each one separately, so we say well, there's this genotoxicity, there's this DNA adducts, and these animals, and then there's epidemiology. And actually they represent a total picture of the toxicity of these compounds in a collective sense. And I think it's a mistake not to understand it that in context.

DR. GLANTZ: Yeah. I mean, that's actually the exact same point I'm making is I think we need to really emphasize the sort of completeness of the picture that you have here, and rather than looking in each little bit of evidence kind of in isolation. I realize that epidemiologists think about epidemiology, the toxicologists think about the toxicology.

But I think that the thing that makes this document -- I mean, I don't think it's done yet. I think there's some very important issues that you need to deal

with and I think as it's gone through these drafts it's been getting better.

But I think the thing that makes the case strong and defendable is the consistency across the multiple different ways of looking at it. And everything has its problems. I mean, people aren't rats and they don't live in boxes.

And, you know, with the epi studies there's all the problems of exposure measurement and confounding and when you put it all together you get a pretty consistent picture.

So anyway.

DR. SEIBER: Stan, I just want to follow up a little bit and clarify for my own understanding.

When you look at the 31 studies, I think, that you mentioned in the report that have been done, obviously some show an association, some do not, it jumps around and there are different workers, different exposure levels, and they're very hard to compare. It's really only when you do the meta-analysis that you distill out something that tells us that in fact we do have a causative agent here?

DR. GLANTZ: No. I mean, we should let Michael present, he's the one who did the analysis, but you don't need to do the meta-analysis to detect an effect. A lot of the studies are statistically significant on their own, so

it's not one of these things where you got a whole bunch of negative studies and you pool them and you manage to squeeze out a positive result. There's a bunch that were significant on their own.

And the other thing which I found -- in fact, one other comment, since John wanted me to talk a lot, now, remember which was a mistake, but I think in terms of your -- of the risk assessment, I think you don't make use of the results of the meta-analysis nearly enough. I mean, I realize there's controversy about whether you're better off picking a best study or a meta-analysis. There's pluses and minuses to both approaches.

But, you know, I was very impressed with the meta-analysis and the consistency that was shown and they sliced the studies a whole bunch of different ways to try to deal with the different criticisms that it can raise and it ended up with pretty consistent results.

And I think that to me is a more -- that's a very solid thing that you should do more than bury it in the appendix in the report, because I think if you take that and then if you take your best study approach that you were using, you actually end up with pretty similar numbers and I think that makes both of them stronger.

So, you know --

DR. SEIBER: Probably should go ahead.

DR. GLANTZ: The next slide was --

DR. ALEXEEFF: In the next slide this slide graphs the estimates of relative risk for the smoking-adjusted studies of diesel exhaust in lung cancer.

And on the next slide --

DR. GLANTZ: If I can just talk again, since John has unleashed me.

DR. BLANC: I think unmuzzled would be a better --

DR. GLANTZ: Unmuzzled, whatever.

I mean, the fact is when you look at these things, the smoke-adjusted studies are probably the best ones to look at, because smoking is potentially a confounder here, and if you look at them, all but one of them show an elevation in risk. That to me is pretty compelling.

And a few of them are statistically significant.

And the problem you have when you do these kind of studies is usually they are hideously underpowered because it's hard to get a big enough sample size.

And that's very convincing stuff to me, and not only are all but one of them have relative -- or odds ratios above one, which this of course corresponds to a log of zero, but they're all about the same.

You know, and so you get a very consistent view across all these studies.

And if you look at the analysis that's in the

appendix, Michael Lipsett, who did this, cut it a whole bunch of different ways trying to exclude different categories of studies that could be criticized on different grounds and you quite consistently come up with about the same risk estimates.

So this to me is much more personally compelling than just picking one or two studies and using the one or two epi studies.

But I think there are other people who disagree with that, so my advice in terms of the final risk assessment would be to do it both ways, because you're going to end up with about the same number and I think it gives you a much stronger case for whatever it is you come up with.

DR. ALEXEEFF: The next slide for that graph we showed, this is the summary of the relative risk reported for two different models. And you can see it's 1.43 and the 95 percent confidence level is 1.32 to 1.56, depending upon the study, the model.

The next slide.

Just to briefly summarize, whole diesel exhaust, diesel exhaust particles and extracts have been shown to be genotoxic.

Diesel exhaust exposure induces DNA adducts in rats and monkeys and is associated with DNA adduct

information in humans.

Polycyclic aromatic hydrocarbons contained in diesel exhaust have been shown to be bioavailable in rats and humans.

And evidence in rats suggests particle clearance can be overwhelmed at high exposure concentrations resulting in tumor development.

Evidence for carcinogenicity in rats is sufficient.

Evidence for carcinogenicity in humans has been classified as limited.

In terms of the risks that we calculated, we used the published relative risk from the Garshick, two different studies, the Garshick case control and Garshick cohort studies.

And then we also conducted a reanalysis of the original Garshick cohort data.

We summarized discussions with Dr. Crump, who also did a reanalysis of the Garshick data.

And we expanded discussion of the sources of uncertainty. This is in compared to the previous draft.

The results, in summary, for the case control study, the range of upper bound, 95 percent confidence limit for unit risk, which is the risk per microgram per cubic meter for a lifetime exposure is five times ten to the minus

four, to two times ten to the minus three. And that's based upon two different assumptions of occupational exposure, 125 or 500 micrograms per cubic meter.

In the cohort study where we used the published data, the relative risk -- I mean the risk estimate comes to one times ten to the minus three for the upper bound.

This is calculated using what we called the roof pattern, which I'll be discussing briefly.

In addition to those, using the published data and calculating the risk estimate, we also obtained the individual data for the cohort study and we applied both multiplicative models and some specific biologically-based models to calculate risk estimates.

The next slide.

The range from those models are two times ten to the minus four, to two times ten to the minus three, for again the upper 95 percent upper confidence limit.

In general, the assumptions that we added to the published results resulted in reducing the estimates of risk by about fivefold.

DR. GLANTZ: George, one other question that gets back to the issues people were talking about earlier, is this the point was made that I think it was in 1993 the diesel fuel changed, and so somewhere in there, was that the right year, 1993, and so the mix and what was coming out the

exhaust changed. So was this new diesel or old diesel and does that matter? As a microgram --

DR. ALEXEEFF: This is definitely old diesel and this is definitely older old diesel.

DR. GLANTZ: Really. It's like vintage old diesel.

DR. ALEXEEFF: Right. Because the measurements for these studies were conducted in '81 to '82.

How does that -- and then the exposures that the cohorts received were even earlier than that.

Where I'll mention this there was changes in dieselization of the railroads and there was changes undoubtedly in engine efficiency, reduction in particulates and there are undoubtedly fuel changes over that time period.

DR. GLANTZ: Well, is that -- how -- when I read the report I didn't pick up -- I mean, how do you adjust for that or does it not matter or is the -- I mean, we have heard some discussion earlier that the newer engines actually produce more small particles that might be worse or is something better or, I mean, how -- I mean, how is this a reasonable number to use based on what's out there today or what can you say about that?

DR. ALEXEEFF: Well, basically the -- all the estimates are based upon using the microgram per cubic meter

of particulate as the marker. Okay. So --

DR. GLANTZ: Is this total particulates?

DR. ALEXEEFF: Particulates related to diesel exhaust, yeah, total particulates.

In the sense -- so if one looks at the vapor phase or the non-particulate phase, that is not used in the actual calculations, considered to be fairly consistent among the different fuels. Okay.

Now, so one issue is this size difference of the particles, but that is not taken into account in these calculations.

What we've generally done, and what has been done in both the studies that have been conducted in rats, as well as the studies in humans, is to look at particulate as the marker, and that's the basis of adjustment. So it's not as fine as we would like looking backwards, but that's what we have.

If one looks at some of the studies, for example, in the rats, and if -- well, let's say in the rats, and you look at different types of engines that were used in the study, that did not seem to affect the risk calculated that much. Might have been other reasons for that, we'll discuss later.

But the information that we have does not seem to show that the fuel change has caused the dramatic change in

the risk, except for the fact that particulate emissions have been reduced dramatically and therefore the risk from an individual vehicle or such is reduced dramatically, because the particulate emissions are reduced.

But on a particulate basis, we don't have a difference, as far as we know.

DR. SEIBER: Getting back to the same point on the exposure, when you look at these 31 epi studies and you pick out the ones that have been adjusted for smoking and so forth, are there some that show a fairly clear dose response or is that -- this has been commented on in the letters that there's really no progression in effects with dose, because we don't know what the dose -- we don't know what the exposure was.

Can you comment on that, pick out the best, what you consider to be the best of those studies and what's the strength of the exposure measurements?

DR. LIPSETT: In none of these studies were there any concurrent exposure measurements, industrial hygiene measurements of the cohorts, although in the two studies in which this quantitative risk assessment was based, the Garshick studies, the investigators did do detailed post-hoc investigation of the number of the job classifications, and then they went back and they tried to -- and they classified people as exposed or not exposed, based on what they found

in those subsequent IH investigations.

Now, in general, in these occupational epi studies there was the length of employment was generally taken as a surrogate for exposure, length of employment in a job classification, and depending on what the study design was, they might be classified as exposed or nonexposed or probably exposed versus possibly exposed. There are a variety of different ways of doing this, but in terms of having anything that approaches the kind of exposure measurements that you would get today in a occupational epi study, that those don't exist.

But there are, having said that, there are a number of studies that looking at, say, a group of highly -- or low, medium and high exposed, based on job classification again, there are a number of studies that do find evidence of a dose response relationship.

There are others that look for it, that didn't find it.

And we did discuss this in Chapter 6 in the review of the epi studies there in terms of talking about the biological plausibility. On pages 6-47 to 49, we did discuss this issue about dose response.

DR. SEIBER: There's evidence in some of the studies, not all of them, because you don't have enough information?

DR. LIPSETT: Right. And it's, you know, given the, you know, extensive exposure or the measurement error or misclassification of exposure, I mean, it is -- I mean that tends to bias you against finding a relationship to begin with. Tends to bias towards the null if it's a nondifferential type of classification. That you even see a dose response in some of these, I think, is strong evidence to support a causal inference.

DR. GLANTZ: Go ahead.

DR. ALEXEEFF: Just to add on that, a lot of the comments we received were specifically with regards to the Garshick cohort study. And in the -- I was going to be discussing that later.

But in the original analysis published in 1988, Dr. Garshick indicated what appeared to be a fairly strong-looking dose response pattern. Okay.

In subsequent reanalyses, first by Dr. Crump, Dr. Crump in his reanalyses has concluded, and it's part of our discussion here later, that the dose response trend does not exist.

And in reanalyses by Dr. Garshick of his own data, he suggests that the dose response trend is not as clear as it was in the original publication.

So in terms of that one particular study which seemed to have the strongest information, there's been a lot

of criticism and readjustments and recalculations and we'll be discussing that later.

Or we can discuss it now, whatever. It's a fairly long --

DR. BLANC: I think it's useful to move quickly to some of your responses to the comments that have been made by various critics, because it seems to me we're spending a lot of time going back over again a representation of the original draft document, whereas a lot of the controversy has surrounded criticisms that have been made and it would be useful for me to hear some of the thinking that you all have in terms of addressing the concerns and questions that have been raised.

DR. ALEXEEFF: Well --

CHAIRMAN FROINES: I think that's good, because we are going to lose Stan and in fact I would go to those things that have some of the most quantitative elements to them.

DR. ALEXEEFF: I think that, I don't know if we'll be able to satisfy your questions at this point, because we will -- our intent was first of all let you know what's in this document, and then to let you know what the key criticisms that have been leveled against or provided in response to our document.

We don't have answers to those criticisms at this

time.

Our intent is to go back and to look at those, those issues that are raised. I hope maybe you'll have some information to provide as well.

We were not planning on rebutting those issues. We haven't -- we are still evaluating them.

DR. GLANTZ: I understand that, George, but I think one thing, first, back to what I was saying before about this question of what are you measuring in the exposure.

I think in the document you need to address that point, because it's an obvious criticism that's going to be raised then, and I think you need to discuss if -- just basically make the points you've made here and at least acknowledge the kinds of changes that may have taken place, and you're saying that basically the main risk reduction you're seeing is because of reduction in the total particulate emissions and that's leaving out the fact that the change in the nature of the particulate emissions may make -- given one microgram, are actually more toxic, maybe, because it's smaller particles.

At least you need to talk about that. You may not be able to do anything about it.

But I like to agree with what Paul said, I think -- and I had several discussions with George and the

staff on some of these controversies. I think it would be helpful with the caveat that this is a work in progress to at least outline what the issues are and let the panel offer whatever suggestions they have to help guide you in dealing with them.

DR. BLANC: I'd like to bring up one area before Stan leaves.

DR. GLANTZ: I'm coming back, by the way.

DR. BLANC: I want to hear what you have to say, and I'm going to be gone later, so it's an area that's near and dear to your heart, I know.

One of the responses that was offered in the workshop or the public hearing in September, I guess it was, from Dr. Smith from University of California Berkeley School --

DR. FRIEDMAN: Could you speak more into the microphone.

DR. BLANC: University of California Berkeley, School of Public Health, in terms of the criticisms or the -- it was a critique of the reanalysis of the Garshick study in which he said that the reanalysis was flawed in an important way, because it did not take into account the collinearity between age and dose and years of work experience.

And, Stan, I know that's an area that you've

written about and teach about, and it seems to me to cut to the heart of sort of the fatal flaw in the critique that have been made of the Garshick study.

So to my mind I was very eager to hear back from Dr. Lipsett and others from an epidemiologic point of view of whether they agreed with Dr. Smith's critique and, if so, I think that should certainly be incorporated into the discussion.

And maybe, Stan, you'd care to elaborate on the general principles of this issue.

DR. GLANTZ: Well, why don't we hear what they have to say first.

DR. ALEXEEFF: Okay. Get to the issues. Okay.

I'm just going to mention a couple of things.

I'd like to just mention a couple of things before I get to specific issues.

First of all, obviously you've not reviewed the document formally. We want additional time to revise, particularly the cancer discussion and the cancer risk assessment section in response to the comments that we've received, especially the key ones that I want to outline for you.

DR. GLANTZ: While George is getting the slides, it's also important to note that there are actually two Garshick. There's a cohort study and there's a case control

study, right, and we're talking about the cohort here, right?

DR. ALEXEEFF: These are the five issues that I wanted to get to today. And these are the ways the issues are phrased by the commenters, just so it's clear what the issue is being raised. And I'll just mention them and then I'll be happy to go to either one of these five that we'd like to discuss.

First one is the rat, that the rat lung tumor data should be not used to generate quantitative estimates of human lung cancer risk from environmental exposures.

Second one has to do with the use of the meta-analysis and epidemiologic studies.

Third is the Garshick cohort studies should not be used to generate quantitative estimates of lung cancer risks. That's what we were just discussing that study.

The next is that the Garshick case-controlled study should not be used to generate the quantitative estimates of the lung cancer risks.

And the fifth is that the executive summary should be revised to incorporate more statements on uncertainties and risk characterizations.

So those are the five, I think the five key areas that we would like to focus on if we can today and also in revising the report.

So which one would you like me to go to?

DR. BLANC: Three.

DR. ALEXEEFF: Okay. Pick the most complicated, of course.

CHAIRMAN FROINES: Stan, there's no way that you can -- this is a little bit off the record. There's no way that you can -- would not have to teach today?

DR. GLANTZ: That would be tacky to not show up. I'm sorry. Why don't you take lunch from 12:00 to 1:00.

CHAIRMAN FROINES: The problem that we're faced is that Paul leaves at 1:00.

DR. GLANTZ: That's true.

I think you should just go ahead and then I'll get back and I'll be back around 1:30. I'll talk really fast.

CHAIRMAN FROINES: Why don't you just go in and give them a reading assignment, or bring them here, bring them here.

DR. GLANTZ: We have another few minutes. That's true, we could bring them all here to see statistics in action. That's not a bad item.

DR. ALEXEEFF: I don't think it gets much more complicated than what we're going to talk about.

DR. GLANTZ: That's true. Maybe I'll do that, show up a little early.

Going to be talking about measures of uncertainty.

DR. LIPSETT: George asked me to just go over these Garshick studies just to give you a little bit of a basis for assessing them.

I'm going to be in the way here.

These series were done by a group of investigators at Harvard. Garshick is the lead author on both of them. And they investigated the incidence of lung cancer in male railroad workers with at least ten years of employment.

The basic source of information about these workers was the Railroad Retirement Board records, and so the population base they were looking at was about 650,000 male railroad workers.

In the case control study, they identified cases of lung cancer occurring among these workers during a one-year period, 1981 and '82.

The controls were matched two for one. There are two controls for each one of these cases. They were matched on age and date of death. And they consisted of workers who had died, but had no mention of cancer, suicide or accident on their death certificate.

Additional information was obtained by the decedent's next of kin, including information on smoking.

As I mentioned earlier, these investigators undertook some industrial hygiene measurements, trying to identify which of the different job classifications in the

railroad industry were -- could be considered exposed versus nonexposed.

Then the individuals in both the -- in the case control study were then classified according to what their job classification was initially as being exposed or not being exposed. That's what this analysis was. It wasn't low, medium, high, it was either just exposed or non-exposed.

For the purposes of this analysis they assumed that diesel exhaust exposure began in 1959, which is the year by which about 95 percent of the diesel -- or of the railroad fleet was dieselized, so that the process began earlier. The midpoint was about 1952 in terms of dieselization.

In terms of estimating the risks for relative risk for these workers, they dichotomized the group into those who were lower than retirement age or retirement age or above at the date of their date of death. These risk estimates were adjusted for both the smoking information which they got from the decedent's next of kin and for punitive asbestos exposure, which is also something they looked at in doing their industrial hygiene measurements.

What their estimates of relative risk as exemplified by the odds ratios here were 1.39. This is crude and it's unadjusted for the potential confounders.

And then 1.41, which is adjusted for smoking and asbestos exposure.

Then they tried to model smoking in a variety of different ways, looking at people who have been exposed for at least 20 years, and found that the relative risk was about 1.5. And it really didn't vary too much depending on how they modeled the exposure.

This is only for the younger age group. And the reason that they split this initially into the younger, the group, the railroad one, was that younger group was more likely to have had diesel exposure, assuming that they were -- they would be a starting point of 1959 for diesel exposure.

So that may have included people who actually had exposure prior to that time, but they were the ones who were the youngest once dieselization was completed, were the ones who were likely to have had the longest exposure to diesel.

The cohort study --

DR. FRIEDMAN: Can I ask a question?

Why did they pick death controls. Was that to avoid ascertainment bias? Rather than living people.

DR. LIPSETT: I think that was an issue. It might have been a convenience factor. It wasn't really -- it wasn't something that was discussed in any detail.

DR. FRIEDMAN: Did they collect the smoking data

from the relatives?

DR. LIPSETT: Yes. So that the quality of the information, presumably, was similar for both the cases and the controls.

Okay. In the cohort study, again it's this information also retrieved from the Railroad Retirement Board is 55,000 male workers, age 40 to 60 in 1959, who had at least ten years' work experience at that time, but no more than 20 by 1959.

Again exposure is dichotomized, that the group is either exposed or not exposed.

In this analysis, jobs that had clear asbestos exposure were excluded.

And they had follow-up from 1959 through 1980. This included 19,000 deaths, almost 1700 of which are from lung cancer.

Now, they modeled the incidence of lung cancer. They used two different basic models.

One was whether a person was in a diesel-exposed job in 1959, and when they did this it was the youngest workers had the longest exposure to diesel, as I mentioned earlier, the highest relative risk, and I'll present those in the next transparency, be my last one, and then George will continue with his discussion of the quantitative risk assessment.

And then they also modeled this mortality experience based on years of exposure in particular jobs.

And in this, in this analysis, they did observe a dose response, as Dr. Seiber asked about before. It was a dose response, but only when the four years of -- four years of exposure preceding the year of death were excluded.

In effect, that would have eliminated people who died in the first few years of this cohort, people who were likely to have the least amount of diesel exposure by, at least by under the investigator's assumption.

Okay. This is the -- these are the risks that were observed under the initial model, that is assuming they were exposed in 1959, the youngest group had relative risk of 1.45 and the oldest workers, it was basically no increase or decrease in risk observed.

Okay. Unless there are any questions, I think George --

DR. GLANTZ: I just have one quick question.

So the interpretation that you put on this declining risk with age at the beginning of the study was that in fact the age at the beginning of the study is sort of an inverse measure of exposure?

DR. LIPSETT: Yes. Exactly right.

DR. SEIBER: I didn't quite understand that. They could have been exposed to diesel before 1960 or 1959,

because the dieselization started long before that; is that correct?

DR. LIPSETT: That is correct.

But for the purposes of this analysis they chose to start at a point where the entire fleet was nearly -- or it was nearly the entire fleet was dieselized.

DR. SEIBER: I have a hard time understanding why that declines. Maybe I'm just -- what am I missing?

DR. GLANTZ: I think, and correct me if I'm wrong, I think what they're saying is that the younger workers are going to have more time working in a completely dieselized fleet than the older workers were. So the exposures, the people who were 40 years old in 1959 are going to have more exposure cumulatively than the people who were 60, because the dieselization took time to happen.

Is that -- I mean -- I'm saying that's my understanding.

DR. LIPSETT: I think that's the impression the investigators tried to convey in the paper as well.

DR. SEIBER: Is that enough to show such a dramatic -- that's 50 percent less.

DR. BLANC: It's just the kind of effect I would expect to see. In other words, on average somebody who was 62 years old in 1959, the most possible exposure they could have had to diesel among that group would be ten years.

That would be the absolute most, because you said it started in the early '50s, dieselization.

DR. LIPSETT: The midpoint according to the investigators was '52, so it began earlier.

DR. BLANC: So let's say some of them do, most of them don't and then most of them who are dying of lung cancer are dying anyway, between '59 and '80 are dying fairly soon after the initiation of exposure, so it would be unlikely to be related to it anyway. So you're stacking the deck.

And this is exactly -- were there be to causal relationship, this is indeed exactly the relative risk pattern one would anticipate seeing. It's actually very impressive step-wise pattern of risk.

And echoing what Stan said earlier, the fact that you can even see a relative risk of 1.45, when in fact the best case scenario is those people who are 44 and -- 40 to 44 and 59, haven't had all that much exposure before they die of lung cancer by -- they have to have died by 1980, which means that at the most they're 64 years old, which is on the young side to be dying of lung cancer.

So, you know, we're talking -- this is not a trivial effect.

DR. KENNEDY: There were criticisms made over the retrievability of the death certificate data. Was that in

the cohort study or in the case control study there, particularly for younger patients?

DR. LIPSETT: I think it was in the cohort.

DR. KENNEDY: There were about 20 or 25 percent of --

DR. LIPSETT: I don't remember the exact number, but I have the paper here --

DR. KENNEDY: The data were not available?

DR. LIPSETT: Yeah. I have the paper here. I don't remember the exact percentage. I can provide it to you.

DR. BYUS: I have one simple question. What about environmental tobacco smoke in this system? I mean, chances are, these railroad workers, a lot of them, smoked. I mean, you control for the ones that died that smoked directly, but I would imagine that many of them were exposed to environmental tobacco smoke, even if they didn't smoke primarily, and we know that that has a relationship to lung cancer. So did anybody ever deal with that?

DR. LIPSETT: It may be in some of the sequent analyses that they did, but this is not part of this analysis.

DR. BLANC: You'd have to assume the systematic effect of the people who worked in the diesel jobs in the railroad had more ETS exposure than the people who didn't

and I don't think there's any --

DR. BYUS: I don't know whether that's the case or not, I mean --

DR. BLANC: Why would you even hypothesize such an association?

DR. BYUS: If they were smoking in a confined environment. I don't know how they worked or where they worked. I don't know what the smoking patterns were in diesel exhaust workers. If there were groups of them working inside where smoking was allowed or, you know, I just don't know that. I'm just asking.

DR. LIPSETT: You could make arguments either way with something like that. You could say that for the people who are outside doing manual labor they might not have the time to be able to smoke as much as the clerks who are working indoors. And the clerks in this particular study were the ones who were classified as nonexposed. And yet if you had a scenario like that, then it might cut against it, it would tend to diminish the effect that you would see.

DR. FRIEDMAN: The other point I'd like to make in response to that, I think it's a good question, but usually for a confounder to explain an association, it has to be much stronger and, if anything, the environmental tobacco smoke is a little bit less strong than what we're seeing here. It's more in the range of 1.2 to 1.3, where this is

1.4. And so it would be very unlikely that that could account for this.

DR. ALEXEEFF: Just as a comment, although in Garshick's original presentation, this information he didn't actually use exposure measurements in his calculations. The industrial hygiene data done by members of his group did go back and look at industrial hygiene data and the measure of exposure that we used in our quantitative risk asset was adjusted for ETS.

And in the study it was suggested or indicated that it appeared that the clerks, who were classified as unexposed, were exposed to more ETS, as Dr. Lipsett suggested, than the other workers.

So but probably Dr. Friedman's point is the most relevant.

DR. SEIBER: One last point before we leave this draft, at least for me.

From a statistical point of view, and I'm not a statistician, I'll make that clear at the beginning, would you tell us among those five data, which ones -- give us some kind of exposition on the statistical significance among those five numbers on the right.

DR. LIPSETT: Okay. If in the epidemiologic risks your estimate of relative risk includes the number one, then -- or goes beyond it, it's not statistically

significant. But so that the top two, which don't go down to the number one, with the confidence interval, those would be considered to be statistically significant. The bottom three would not.

DR. SEIBER: Okay.

DR. LIPSETT: Okay?

DR. SEIBER: Thanks.

DR. LIPSETT: Okay. George.

DR. ALEXEEFF: Now I'm going to go through the -- you saw the nice part of the Garshick study, the original published data.

Now, I'm going through some of the issues that have been raised in the comments and the reanalysis and try to indicate, one, sort of all the work that we have done over the past few years, both us and other groups, in trying to understand the data set, and also some of the complexity that goes into trying to determine why analyses of these data sets appear to have conflicting results.

I don't have the answers to why at this point, but I want to show you the progress that we're making.

First of all, you can see here that we had with regards to this comment that this cohort study should not be used for quantitative risk assessment, we had quite a few commentators that made this point, including Dr. Garshick himself, who was the lead author of that, as well as

Dr. Kenny Crump, who was the lead individual on the reanalysis of the study.

CHAIRMAN FROINES: Do you have overheads for that?

DR. ALEXEEFF: Yes.

CHAIRMAN FROINES: Does everybody have the overheads for this?

DR. ALEXEEFF: As we mentioned before, as I mentioned before we did calculations in two ways. Well, many ways, but the two basic areas were on the actual published results, and on the individual data. Just important to keep that in mind as we try to unravel these issues.

The second point to make is that there was exposure data that was used that was developed in '81-83. The information in '81-83 is considered to be very good. The issue comes in play as what were the exposures from 1959 to 1980, which we don't have on real-time information.

This again just summarizes the cohort that Dr. Lipsett mentioned, the 55,000 individuals involved. And you can see here that the -- I better sit down, so I don't block this.

You can see here that there's three different exposure groups. This also is important to keep in mind because the different analyses look at that. We have shopworkers, we have what's called mostly train riders and

then we have these clerks and signalmen.

And this is the ETS-adjusted exposure concentrations that were made for these different groups.

The remainder here was reported to be respirable particulate, but not diesel exhaust particulate, and not ETS.

The other issue to point out here is the shopworkers, they have highest average exposure. At the same time their exposure status is uncertain and the reason is for that is in those shopworkers that worked on diesel engines regularly, they had highest exposure. Those that worked on other activities, that had to do with the actual engines of running a railroad, they had essentially no exposure. So the exposure in this classification can be very high. So that was another area of concern.

This graph here just depicts the dieselization issue that Dr. Lipsett mentioned. Again, we see that it decreased and that in 1959 it appears to have almost a whole fleet was dieselized. And at the same time after 1959 there's discussion in the Woskie article about smoking engines being taken off line, improvements in engine design, efficiency, reduced particulates. It's roughly anecdotal. We don't have quantitative information. But it appears from our impression that there's increased dieselization, and then there's improvement, efficiency in the engines.

On that basis, in our analyses we favored this kind of an exposure pattern, what we called the roof pattern, and these patterns will also become an important issue too. I just want to let you know what we did in our numbers. This reflects the dieselization and this reflects improved efficiency and it's just an exposure assumption for the pattern.

I'll skip the risk estimates.

DR. KENNEDY: George, there was some comments among the reviewers that your estimate of -- estimates of exposure were higher than other models had predicted using that system. Would you comment on that?

DR. ALEXEEFF: Yes. Yes. As a result, we estimated -- our estimate suggests we actually have an exposure factor on the side there, and since the measurements were actually made here, this is the point where the Woskie industrial hygiene measurements were made, and so we were looking at dieselization and then the improvement efficiency. We assumed a factor of three. And so therefore we assumed more exposure of the workers, which resulted in a lower risk estimate, an inverse relationship.

CHAIRMAN FROINES: I think that there's in this population there was likely to have been dermal absorption. And I'll never figure out what that was. It can be quite high. I remember reviewing all the data on PAHs and dermal

uptake and it turns out to be higher than one would be anticipate. So it's a factor which we'll have to think about in the future.

DR. ALEXEEFF: Just as a reminder, this was our risk estimate from the published data, one times ten to the minus three.

And then we used, as I mentioned before, a number of models, general multiplicative models, and a biologically-based model and did a number of analysis and these were suggested over time.

And then the summary of our results on that are shown in this graph here.

Here we have different exposure patterns. This roof and a ramping, which I'll explain, basically doesn't peak up as high, and levels off.

But for the most part with one being the published results, you can see that the assumptions that we're using in biologically-based model here or in our other calculations for the roof pattern, the risks are decreasing in our estimates here. There are less than one times ten to the minus three.

I just wanted to show you what we did, because it will help clarify as all the discussion goes on.

I'll skip the range of risk slide.

And so generally there are the general

uncertainties involved in human -- using a human study for risk assessment.

The use of the appropriate model, whether it's the general model or a multistage model. It's estimating the historical exposure measurements is an issue, what the level is, what the pattern is, and also the classification of the exposure groups. So those are also important issues.

Now, in addition to these general issues, we have the additional issue that Dr. Crump reanalyzed the data for US EPA in 1991. It wasn't actually published until 1994, after the issuance of our documents, which is this time lag thing, but so we didn't discuss it in our original publication.

But in our most recent draft we do discuss what we understood to be the -- first of all, that our analysis differed from those conducted by Dr. Crump. There's been a lot of discussion in workshops. There's been discussion, communications with Dr. Crump. And so it's clear that our analyses, the results of the analyses have differed, the interpretations have differed.

We've made a number of efforts to try to identify what these differences are and what are the differences in the assumptions, the approaches and the results.

And I'll be giving you some information on that to show you the complexity of these issues.

Now, the factors that we identified in the report that we thought were important are these. These are in our Appendix F.

CHAIRMAN FROINES: It's important to stress that this work is work in progress.

DR. ALEXEEFF: This is work in progress and this is what we found at the time we released the report. Since then we have more information, which I'll be discussing some of that here.

These are the factors that we identified.

Controlling for age appeared to be important.

Whether or not shopworkers were incorporated in the analysis.

Whether or not the last four years of the study were included, because there was a dropoff in follow-up in that study.

Measures of exposure, the exposures categories and the method of describing the trend.

Those are the primary areas that we had looked at.

Now, these are -- this is another issue here, the different exposure patterns.

In the original Garshick, the original Garshick study published in 1988, although he didn't have concentrations, this is the exposure pattern that he had assumed. People were exposed as of 1959. We already know

that would happen before that in part, but exposure is not included in the analysis.

And the people were assumed to be exposed equally in that kind of block for train workers.

And the clerks were assumed to be unexposed.

And that's how the relative risks are calculated.

Now, in 1991 in Dr. Crump's reanalysis, he introduced another way of looking at this, and that was called the ramp pattern, and this was in 1991.

And in this case he added this issue of ramping up the exposure from '45 to '59 and then leveling off. So that was another -- so a lot of the calculations are made between these different exposure patterns.

The next issue that's different is Dr. Crump assumed that the clerks were actually an exposed group. That affects the calculations.

Finally, in our report, we have a different yet exposure pattern. Again I mentioned we had this roof pattern which goes up and then comes back down.

And then we have this other pattern, this ramping, similar to Dr. Crump's analysis, except we assumed that clerks were controls, not exposed.

So you can see just on the exposure patterns and who you're classifying as exposed in trying to compare analyses it makes it difficult in trying to resolve what the

differences are.

And the different exposure patterns, the factors that I mentioned, the controlling factors, have various levels of importance and influence in the calculations. And some of them are starting to make sense.

Okay. So I'm going to start going through this in general.

DR. SEIBER: On the clerks, I'm assuming, do people feel they're unexposed because --

(Numerous people enter the room.)

DR. GLANTZ: Excuse me. Just for the record, Dr. Lockett said bring the students here. So you're now being invaded by Biostatistics 183.

And could I just ask, having created this chaos, it was not my idea, could I just ask in the interest of didactic wonderfulness, if when these students get in here, maybe George or somebody could just take a minute and briefly summarize very briefly the Garshick thing again so they can know what we're talking about, since we're depriving them of my lecture --

DR. SEIBER: You mean be your guest lecturer for the day.

DR. GLANTZ: Yeah. George can be our guest lecturer.

Are you looking at me because you're like totally

shocked?

DR. ALEXEEFF: I can honestly say --

CHAIRMAN FROINES: I'm looking at you because I think it illustrates how highly -- how highly we hold you in regard to do this. You had better contribute markedly this afternoon in the various discussions.

DR. GLANTZ: Maybe you can just back up and spend a couple minutes just so the students here know what you're talking about.

DR. ALEXEEFF: I'd be happy to do that.

As I was going to say, I know from experience that I'm trying -- we're going to get into a very complex analysis, reanalysis, reanalysis of the analysis, and probably to have the basic facts under your belt helps to move on.

Okay. Class, students. Okay.

We're going to be -- what we're discussing here is a epidemiologic study on railroad workers conducted by Dr. Garshick in 1988.

And in this study there were 55,000 railroad workers at various ages. They were assigned to job categories. They were followed from 1959 up through 1980. There were 19,000 of them or so died, 1600 from lung cancer.

And the way we understand the exposure, the exposure is first assumed to have occurred from 1959 to

1980.

This slide here shows the report in the actual study of Dr. Garshick in 1988. And what he found was that people that were younger in 1959 had a higher relative risk. That is to say, their risk of contracting lung cancer was increased.

And the logic for this is that the younger folks had more of a chance to be exposed from 1959 to 1980, as well as the few years before 1959.

DR. GLANTZ: And that's because they were just putting diesels in in the '50s.

DR. ALEXEEFF: One of my top five slides here.

I'll just mention this, so you understand the issue here.

There is a large number of individuals that are concerned about using this study in a risk assessment, which is what we're trying to do, estimate the risk to the public from this occupational study. And one of the commentators is the study author himself, Dr. Garshick, as well as Dr. Kenny Crump, who first started working on this for US EPA.

This slide shows the locomotive dieselization up until 1959. So although the original study assumed that people were exposed only from 1959 onwards, clearly there must have been some exposure prior to 1959, but we don't

know how much.

We can make assumptions about the exposure. Assumptions that our department made were that exposure peaked in 1959 and then came back down, and that the peak was roughly three times the levels that were actually measured in 1982.

DR. GLANTZ: George, when you -- how could it peak in 1959 if they were essentially a hundred percent diesel in 1959?

DR. ALEXEEFF: We took in our evaluation there was dieselization occurring, and then in the studies in the industrial hygiene studies, they indicate that the engines were being improved, that poorly-designed engines were taken off the railroad, and as dieselization become more popular the better engines were being used more widely with reduced particulate emissions. So that's the basis of this.

There are studies with other engines, not railway railroad engines, showing how efficiencies did improve over time dramatically.

Those are, when one is trying to estimate what exposure these railroad workers had in order to better quantify the risk, the original study assumed a constant exposure from '59 to 1980.

In 1991 a reanalysis assumed a ramping effect up until '59 and then leveling out.

The difference in this study they also assumed the clerks were exposed, but in the original study they were not considered exposed.

In our document we made two different analyses, one with a peaked roof pattern which went up, as I just mentioned, and a ramping pattern, which also leveled off here. We also assumed the clerks were not exposed to diesel engine exhaust.

DR. SEIBER: That's where I had a question, George.

The assumption that clerks were or were not exposed. Now, I'm assuming that a clerk works in an office near where the railroad yard or is the train station or whatever and somewhere in the report we talked about outdoor versus indoor. That would seem to argue to me, to my way of thinking, that they were in fact exposed, because air filtration isn't perfect, and some of the outdoor air can even use the factor such as the one you developed to correct for that.

So can you comment on this assumption that they're not exposed?

DR. ALEXEEFF: Well, maybe Dr. Lipsett can comment on it. But see if I can make a first shot at it.

In one sense in epidemiologic studies one has to base the risk on some control population. And you

generally, you'll see in some of the slides I'll show later, that you generally choose the population that has the lowest exposure and often that population is set at one or assumed unexposed.

DR. SEIBER: Even though they are by definition you just normalize.

DR. ALEXEEFF: That's one methodological thing that is done with epidemiologic studies.

But in this particular analysis in discussions with one of the authors of the industrial hygiene study, it was -- we discussed this at the scientific workshop in 1986, we were told that the concentrations that I placed on the board that she, Dr. Hammon indicated that it was clear to her that the concentrations were not, for the clerks, were not diesel. Okay.

Now, that's all the information that I have on that, although I think your logic is reasonable.

DR. LIPSETT: George, do you want any response?

DR. ALEXEEFF: You have some additional?

CHAIRMAN FROINES: Just one comment.

I think one can ask Kathy to write a comment about that.

Secondly, though, that if you did think there was a response, then the clerks might also have the ramping effect to where it declined with time. So if you had a ramp

up, you might have to have a ramp down for the clerks as well as for the other. So you'd have to think about it in both ways.

DR. FRIEDMAN: May I? I have a question. Maybe you've explained this, but I think it would be helpful for us to understand that given that there are 30 or 40 studies, epidemiologic studies, why so much attention has been focused on this one.

DR. ALEXEEFF: Well, even in our scientific workshop, which occurred in 1986, in January, although it was lot of controversy about the analyses and reanalyses, it was still felt that in many ways this was one of the best designed studies, and the large number of individuals and the high quality of the health information tabulated on the cohort, because I guess railroad workers, once they joined the railroad, tend to stay with the railroad.

And the way that the health information is organized, it's kept in ways that are well to review it.

In contrast, truck drivers, there's a lot of mix of -- there's differences of how truck drivers may be organized. They all don't report to a central board as in the case of this case, the dock workers.

DR. FRIEDMAN: So it was felt that this had the best data, far better than other studies and in terms of length of exposure and follow-up information?

DR. ALEXEEFF: Probably the exposure information, the size of the cohort, the follow-up for what it's worth, and probably the information that Dr. Blanc pointed out, that the reverse trend is actually a compelling factor of showing a potential dose response. Those all sort of fed into why this study has been looked at so carefully.

DR. LIPSETT: I want to follow up a little on Dr. Seiber's comments about the clerks.

One is you would suggest that they might be in railroad yards and might get infiltration of diesel exhaust indoors and that certainly is true for some of the clerks, but others were in headquarters buildings that were far away from that.

And also one of the implications, say if the clerks were substantially exposed to diesel exhaust, one of the implications of that is that the relative risks that you're getting, they can be looked as kind of reference with relative risk estimates, would end up biased in a downward direction, if that's true, but we don't really have a good sense of that.

DR. ALEXEEFF: Okay. Then as I indicated, there were a number of factors that have been identified thus far that could affect the analyses of this cohort study, how age is controlled for in the models, how whether shopworkers are included, whether the last four years of the study are

included, what measure of exposure is used, the exposure categories, the method of describing the trend.

Now I'd like to get to the heart of the matter here.

What the principal thrust of the comments we've received are, and I'll be focusing on the comments actually submitted by Dr. Garshick and Dr. Crump, because I think those actually get to the key of the issues. And many of the other comments were useful ones. But the key ones for us that are difficult for us or require a lot of attention for us to evaluate and consider are these from these investigators.

Okay. So and I will be trying to present their comments as much as I can from their perspective and not from mine.

Dr. Garshick reanalyzed the original data and the shape of the exposure response relationship was not as positive as originally reported. Therefore, the original published data should not be used.

That's one comment.

DR. GLANTZ: George, do you mean the original published data or the original published results? You're not saying --

DR. ALEXEEFF: The original published results, the exposure response --

DR. GLANTZ: You're not saying there's anything wrong with the data, it's the interpretation you're saying -- I just wanted to be real precise there.

DR. ALEXEEFF: Let's put it this way. The key issue here is the trend, the dose response trend. So in other words the exposure response relationship was not as positive, so the graph we had on there, the slope is not as great. Okay. Or the slope is greatly diminished, as Dr. Garshick puts it.

Therefore he felt that -- Dr. Garshick felt the original published data -- or others would argue, the original published data should not be used.

That was one of the ways we analyzed it.

The next point is that reanalyses by Dr. Crump of the Garshick data concluded that the trend was not present when age was more carefully controlled, and that exposure response was lacking.

Now let me show you what that means.

This Dr. Crump's re-creation of Dr. Garshick's data and this is showing the original results, the 1988 results.

So you can see this is graphically what we saw in that table. And so it looks like a very nice dose response trend. And you can see from this analysis right here that one of the issues of the factors I had of shopworkers -- the

shopworkers, was when you exclude shopworkers you get the same trend. So in terms of for this exposure pattern, the shopworkers, whether you included them or do not include them do not area one of these factors that affects the results.

DR. SEIBER: Just a note of clarification.

Only the last two points we already established in questioning are statistically different from the first three; is that correct? I think that's what --

DR. ALEXEEFF: These are statistically significantly different from one.

DR. SEIBER: One, two and three.

DR. ALEXEEFF: The test of significance is on that one. I don't know --

DR. LIPSETT: Actually, this is a little different from what was -- what I had presented, which was just -- right. It was looking at those particular age groups there. And it wasn't -- well, you're right in that top two in those risk estimates were statistically significant, and in this instance they were -- I'm not sure exactly about the correspondence here to that particular table. I wasn't involved in this part of the analysis.

DR. SEIBER: I thought it was the exact same.

DR. BLANC: They're related, but they're not the same.

DR. ALEXEEFF: This is a re-creation of the visual depiction made in the Garshick study.

DR. GLANTZ: So you've got, just for the students' benefit, on the horizontal axis is how long they have been exposed to diesel exhaust, and the vertical axis is the risk of cancer.

DR. ALEXEEFF: Right. The risk of cancer and the diesel exposure in years.

FROM THE AUDIENCE: What did you do to reanalyze it?

DR. ALEXEEFF: You'll see.

Now, as I mentioned, the importance of this is just to show that Dr. Crump -- and we also have been able to reproduce Dr. Garshick's original analysis, so that's what the importance of that is.

Same time, though, when, as Dr. Crump indicates, when the trend of lung cancer relative risk for duration of exposure --

DR. LIPSETT: George, can I interrupt you for one second.

Dr. Dawson has pointed out to me that these particular points are -- they were not on the table that I presented earlier, but they are in the report and every one of those levels of exposure, one to four, et cetera, are statistically significantly different from zero. They're

all elevated in the statistical relationship.

DR. ALEXEEFF: Okay. Now, this is -- this is part of Dr. Crump's reanalysis of the Garshick, the original Garshick data, using the original exposure pattern of '59 to '80, that block pattern.

And he used a different measure of controlling for age, a measure called attained age, instead of calendar year.

The trend appears to slope off down here. It goes up and then it goes down.

And then he also did the analysis for shopworkers.

So it's the basic issue right here in these analyses and reanalyses is what is happening to the trend, do we really see a dose response or not. Okay.

And that is the issue being raised where -- the issue raised by the commenters is that this is showing there is no dose response trend, therefore a slope of risk should not be calculated.

DR. BYUS: What exactly is attained age? What does that mean? I mean, maybe that's too hard of a question. Briefly, what is it, what's the difference?

DR. ALEXEEFF: Last week in Monterey when Dr. Crump was asked that, he said it was a very technical question. I'm not a statistician.

I don't know, Michael, if you can explain it or

I'm afraid I will make -- it's instead of looking at age as you're getting older from these, it's the age that you attained at the time of the death. So it's another --

DR. GLANTZ: And if I can -- and I know less than you do, but that never stopped me before. My understanding, or maybe, Stan Dawson, do you want to define it? You know what you're talking about.

DR. DAWSON: Attained age is the age that you did the observation. It doesn't matter whether there's a death. You count the deaths and you count the non-deaths at that moment in time, and that's the age at that moment. And it's in contrast the age at the start of the study, which is the other way of controlling for age that was with the previous slide.

DR. ALEXEEFF: See if I can explain this now.

In the original table that Dr. Lipsett showed, he was showing like 40 to 45, 45 to 50, that's age at the start of the study. That's one way to control for age.

In this analysis, we're looking at the age at the time of the observations was being made.

Is that correct?

DR. DAWSON: That's correct.

DR. ALEXEEFF: Okay. This, again, this is the analysis on the original data set and this is the issue that's raised.

DR. GLANTZ: Could I just say something?

DR. ALEXEEFF: Sure.

DR. GLANTZ: This is getting back to the point Paul raised before I went off and grabbed all the students.

One of the criticisms of basically what they're saying here is that if you count how old the people are, the first way you see a positive dose response relationship and if you count it the second way you don't.

And the issue that was raised at the workshop up in Sacramento was that it really shouldn't matter, they're both supposedly measuring the same thing, which is how old the people were.

And the criticism, I think his name was Smith, raised, was that there was a high legal of collinearity between these variables and when you have a lot of collinearity the estimates become very unreliable.

And I've been talking to George and to Stan Dawson and the others and in fact there is a very high level of multi-collinearity and so I think that this is very problematic, actually, this criticism.

And I did a little -- why don't you just overlay the previous slide on this, George.

The scales are a little bit different, but line up the ones.

And, in fact, we all get older and our eyes don't

work.

Line up the X axis too there.

This is a little bit cheating, because if you get the ones together -- poor George is getting astigmatism.

But, I mean, it's a little bit unfair because the axes are a little bit different.

But if you look at these things on top of each other, and in fact if you correct the axes, because I did this yesterday, they are closer together, those results don't look nearly as different. Those are 95 percent confidence intervals, right? Is that right?

They don't look that different.

And in fact if you put them on the same scale they move closer together.

So it seems to me, and I think this is something that requires some further investigation quantitatively, because I just sprung this on George and Stan this morning, but it seems to me that there's no real difference between these two sets of results, and you're just simply looking at sort of the instability that's built into the model specification and a reflection of the collinearity.

And so I don't -- I'm now convincing myself that this controversy isn't the controversy, and it's really just an artifact of the way the models are specified.

As I say, if you correct the scales, these things

get closer together.

So, I mean, this isn't done yet, and this is something that's going to require some more work, but this may be a problem that kind of goes away and is just simply a methodological artifact.

DR. SEIBER: Stan, you're saying one thing, but I'm looking at it and I still see that they're different. What's going on here?

DR. GLANTZ: Well, this is what I should have brought the slides from my statistics class, but what you're getting here is a sampling variable.

And if you look at the confidence intervals, which are the vertical lines, they overlap quite a lot.

So my guess is that the biggest difference is the last point, and I bet that difference isn't statistically significant in fact.

So what happens is when you have a lot of collinearity, which is -- and the common sense definition of collinearity is you put several variables in the equation that are all measuring more or less the same thing, that produces instabilities in the equations, because the whole idea of a multivaried analysis is to separate out what part of the effect is due to factor A or B or C.

If you have -- if you're putting several different measures in that are all basically measuring the same thing,

the computations for the parameters in the model can't separate those effects out. There's not enough difference to see it. So you get unstable parameter estimates.

And there is a lot of multi-collinearity in the way the second model is specified.

So it may be that this thing that looks like a declining risk is just randomness. You know, there's a certain random element to all of this due to the sampling variation and that may be -- there may not really be a real difference. I mean, Gary knows all about this.

DR. FRIEDMAN: I just want to point out, and correct me and let me know if this is correct, even though the years of exposure pattern changes when you do Crump's analysis, it doesn't take away the association of diesel exhaust with lung cancer. Am I correct? There's still the exposed people have a higher rate of lung cancer than the non-exposed, even though the pattern is not as pretty under this; is that correct?

DR. ALEXEEFF: As of last week, and this has changed a little bit, Dr. --

DR. GLANTZ: This is a work in progress.

DR. ALEXEEFF: It's a work in progress.

Dr. Crump indicated he felt that there is no significance between the exposed and the unexposed.

On at the same meeting Dr. Garshick said although

the slope is diminished, he felt there's still an overall difference between the exposed and unexposed.

So there is some discussion along those lines.

DR. BLANC: I want to go back to the issue of collinearity.

In fact, it's an inherent problem in occupational studies if you put age in the model in the way that Crump has done it. You almost invariably have significant, and I mean meaningful collinearity between year of exposure and age, because most people tend to enter occupational cohorts at around the same age and therefore their age, if handled as age at observation or ascertained age, will equal their work life minus 20, because they go into the work force around 20.

So any study -- and I looked at this quite a bit in asbestos-related health effects modeling, will be completely messed up by adjusting for age.

In fact, in that sense, age is a confounding variable. It is something which is the effect associated with age is not the effect of age, it is the effect of age as a surrogate for years of exposure.

And therefore -- and not only that, but I would say that using ascertained age, if that is the correct technical term, is not what is standardly done in these kind of analyses.

And so one of the things that's been troubling me about the criticisms made of the draft document, I would say globally, have been that the recurring theme in all of the areas of criticism have been in a sense asking this document to reject what are typical assumptions made in epidemiologic analyses, in health risk assessment.

In models of carcinogenicity on every single front, the criticisms are asking the Air Resources Board and Cal EPA to sort of reject standard approaches to handling these public health matters and accept alternative hypotheses, and this is just but one example, I think, of a theme, which I find actually quite troubling in the criticisms overall, troubling not because it tends to make me feel the criticisms are valid, but troubling because what's being asked is to set a precedent in a rather bizarre direction.

DR. KENNEDY: Two points.

First question is what happens if you use Crump's methodologic approach in looking at some very obvious problem like the effect of cigarette smoking on lung cancer? What do those groups look like? Can you show that cigarettes don't produce lung cancer?

No response?

DR. ALEXEEFF: I don't have an answer for that.

DR. KENNEDY: Was this the only difference in

Crump's analysis?

DR. ALEXEEFF: No.

DR. KENNEDY: He also used a different control group?

DR. ALEXEEFF: This just gives a sense -- excuse me?

DR. KENNEDY: He also used a different control group?

DR. ALEXEEFF: Not in this analysis. Just starting to unravel the confusion here.

DR. GLANTZ: There's a whole lot of issues.

DR. ALEXEEFF: And I think that in this, when you look at the original Garshick study, the issue of age collinearity appears to be more important than in the other exposure scenarios that we'll be discussing.

But other issues become important in the other exposure scenarios. That is what is made difficult to try to clarify why these results are different.

In males it may be a reflection of the study design, of the study or the analysis approach that makes it difficult to interpret.

CHAIRMAN FROINES: I agree very strongly with Paul Blanc. I think his points are I think particularly true when we're dealing with occupational studies and which would begin to apply approaches by people who that is not their

primary area of study. And so you end up, I think, not understanding some of the complexities about occupational epidemiology.

And I think that's running all the way through this particular debate.

But I think that one of the things we're going to have to do is to expand further on some of the points that we make as we go over the next few months in learning the specific issues.

DR. ALEXEEFF: I think one of the issues that I think would be helpful to us, and I think is that it's not clear to us what are the generally understood principles in this type of an analysis, and maybe that's -- maybe that's one of the issues there.

DR. BLANC: Wouldn't it be fairly easy, Stan, with a simple Monte Carlo modeling to show this collinear effect and what it would do?

DR. GLANTZ: Actually I think they've already -- well, that they're working on that.

DR. ALEXEEFF: That is something --

DR. GLANTZ: I don't mean to be evasive, but I mean I've been talking to George and to Stan and we've been putting a lot of time into trying to figure out what are the differences in these different analyses and what difference does it makes that they did certain things differently.

And one thing that looks important is this collinearity. I mean, the various inflation factor, I think, was 15, which is very high.

And I mean I start to get paranoid when it's four.

And the so -- I mean, one of the things I've been strongly encouraging the staff to do ever since the workshop in July, is to really very carefully work out what are these differences and elucidate them so they could be judged.

And I would hope in the document, in the next draft of the document, the final draft that comes forward, this stuff will all be spelled out in some depth so readers of the panel and the public can understand what these differences are.

I mean, some of them, I don't remember offhand, some of the differences that have been identified don't matter very much.

And then there are a couple of others that do. I mean this is one.

Another one was, I think whether or not you subtract out background, which I think they should do, I mean, I can't believe that anybody did an analysis without subtracting out the background.

But at least it's turning out in getting to the bottom of what these difference are it's not trivial. I mean, you think we're not talking about, you know, trying to

figure out like the internal structure of the sun, but it's these three papers or four papers. And I mean getting -- figuring out exactly what these difference are isn't obvious, but I think that's what they're hoping to do here by making these presentations to the panel.

CHAIRMAN FROINES: I would like to propose, we're having a very good and very long discussion about all the issues, but out of it we should find some action items.

And I think one action item I think we can agree to as a panel is that we would like to follow that recommendation as a panel, that the staff of OEHHA go back and document rather carefully what those differences are in a way that everybody on this panel can understand, because people even beyond the panel need to understand precisely because they are such major issues.

DR. SEIBER: Yeah. I'd like, since we have a member leaving here in a few minutes, I'd like to jump ahead to the December meeting and see if there's some other steps we can take now.

Now, staff is doing, working with Stan Glantz and going over and trying to present, articulate the arguments and give us reasoning where there's difference in opinion.

Another way to get information would be to ask selected people to appear before the panel in December, and I'd like to throw this out as a proposal, we can decide who

those selected people are, that might enrich the argument, and give us better understanding of the issues, perhaps help us reach a decision.

Now, it's just a suggestion, and I feel that this would help me personally and I guess I'd like to hear what the other folks have to say about that at some point.

You may not want to take it up now, John.

DR. GLANTZ: Well, I think we're going to lose Paul and I've got to go. And I don't think that's a good idea. I think that will just confuse matters.

We had the workshop in July. We had the presentations. These issues have been raised. I mean, they've been highlighted.

I have not seen the issues change. I've been to three or some number of workshops on these. The issues haven't changed that much.

I think it's a much better way to proceed is to let the staff continue to work through these issues, put it in writing, circulate it, submit it for public comment, let people comment in writing and then let that package move forward.

I don't think -- they're sufficiently complicated, I just don't think that's going to do anything but confuse matters, frankly.

We've had this discussion several times and I

really think that the way we operate now with people in written responses is much better.

DR. SEIBER: Since it's a work in progress, I think that phrase was used, it seems to me to get the key people who generated the original data --

DR. GLANTZ: That's what the workshop.

DR. SEIBER: That's what --

DR. GLANTZ: But the workshop --

DR. SEIBER: The interpretation of their work is changing with time as we perform these analyses. I personally I would like to look them in the eye and see what they feel about this.

DR. GLANTZ: Well, I'm very much against that.

CHAIRMAN FROINES: Let me make a compromise suggestion. See, when you move from there to here, you become the compromise.

I may ask to go back to your place.

But for at least for this meeting it may be that -- it seems to me that the work in progress has to proceed and that we want the written documentation to come back to the panel with the changes and explanations and details that we've asked for.

And there should be a comment period that follows, clearly, so that then the panel has the opportunity to consider those comments.

I would then argue that perhaps what we could do would be to in a sense plan two meetings. If we can do this logistically, which is not always easy, if there was to be a short meeting, a meeting in which people came and made verbal presentations to comment on what had been written and commented upon written, then that would be all right.

I think, though, that when we take the document up that document should be this group having a discussion to make a final decision.

DR. GLANTZ: Well, based --

CHAIRMAN FROINES: Let me just finish.

All I'm saying is that I would be open to sitting in the meeting that was before that, however, to hear Garshick or Crump or anybody else that wanted to attend, as long as it was scientific. I don't want to go to a meeting which is made up of people who are not going to speak to the issues as scientists. And I'd be willing to go to that meeting.

But then I assert if that meeting occurs, then the final meeting should not have outside testimony.

DR. GLANTZ: You see, you weren't at the workshop and I was. I mean, I went to the other two, or however many there were, and frankly the workshop was useful, because it sharpened a lot of these issues, but I keep -- I haven't heard anything really really new issues raised on this in

about three years, frankly.

And what you're asking for is basically a workshop, another workshop. And if you have another workshop, it's going to be three more months.

And I think at some point you have to bring these things to closure.

The issues were brought forward in the workshop in July.

I think the staff is doing a good job at trying to understand what the issues are, to respond to them, to respond to them in a reasonable manner.

But I think at this point -- I mean if the staff wants to hold another workshop and you want to attend it, I mean, I was there, John was there and Paul was there, I think were the people who actually showed up, and Jim, and Jim Pitts was there, yeah.

I think that we heard these issues and I think the -- I really don't want to establish a precedent of turning these meetings into an open zoo. The purpose of these meetings are with documents that come before us for the panel to discuss.

The issues are too complicated to think that somebody getting up and making a five- or ten-minute presentation is doing to do anything. At that point we need to hear what we think.

Now, if people think having yet another workshop, and you want to come to it to discuss this yet another time is going to add anything, I mean, I guess it will delay it -- it will add three more months to the program because you got to have all this public notice and this, that and the other thing.

I think the issues have been laid before us. The staff is working very hard to try to clarify them. That document will go out for a public comment. People can comment. And we should just read them.

And I -- if the panel wants -- if the panel wants to -- if the panel wants to recommend another public workshop --

DR. SEIBER: You're using the wrong term.

We have a meeting scheduled in December. We've been on opposite sides of this debate, I know, for several months.

I feel that we ought to be able to have commentators come into our meetings under our set of rules and make comments that will help us make a decision.

This is such an important decision.

I personally, I'm not speaking for the rest of the panel, I personally want to have the best information I can, sharpened as well as possible, before I make a personal decision on this.

And that would help me.

There is some new information coming forward. We heard about a CE CERT study that the timing is a little bit off, it wouldn't be done until January, we're talking December. That's new information.

Maybe there's others. Somebody mentioned Allen Smith's input into the process. That might be a person that we can hear from. Could be a helpful comment.

So when I mull all these things over and I'm taking notes and looking at what's known and what's uncertain, I just see a lot of things that need to be clarified.

Maybe the staff's redo of the report will answer all the questions. Personally I doubt it. I think as a panel member I can be helped by having some outside input.

DR. BLANC: I think that your hesitation reflects, I think, the prime point that we're currently at. I think that you should hold off on it until you see what the response is.

Basically all we're hearing today is a reiteration from the presenters of what was already said in terms of questions raised at those workshops.

And what we have not heard, to any sufficient extent, is the response of the staff.

Now, it's possible that once you hear the response

of the staff, you'll still feel that the critique as made was not appropriately addressed.

But I think it's certainly premature to ask for the critique to be reiterated before we've heard the response to the critique.

What we're hearing today is not the response to the critiques, it's the delineation of the critique and that tends to give the impression of reinforcing the critique inappropriately, perhaps, because we're not hearing the thought-out response.

And it may very well be that after we hear the response to the critique there will be other questions raised.

But I think it's really premature to say that and I certainly wouldn't want to embark on a rehashing of the previous critique that was made.

What I want to hear is a well-formulated response from the Air Resources Board and Cal EPA.

And I think our role here today is simply to delineate those areas in which we are most anxious to hear a response.

CHAIRMAN FROINES: Let me, the prerogative of the chair, Stan.

I think that that's -- I agree with you. I think Stan's wrong on this one, as much as he and I usually agree.

I think that in fact there are -- this has been a very substantive discussion with a lot of new ideas being raised. I think we have more substance in this discussion than some of the meetings we've had in the past. And I think it's important.

And so I do think the staff going back and responding to the things, to the issues that we're raising, but also to continue the process of addressing these issues is really quite important.

I think we can have the document prepared. It can go out for comments.

We can then decide if we want to hold a hearing in which others would come and testify before holding the final meeting to deal with the document. And we can decide that a month or two or three down the road from now and we don't need to make that decision right now.

And if we don't -- if we keep arguing this point we'll never get back to the substance, which I think is problematic.

So what I'd like to do is hold this issue, consider it as we've gotten comments, and then consider how to go forward and we can do that.

DR. BLANC: John, can I time check? It's ten after 1:00. Can I assume that we're going to be breaking in about five minutes?

CHAIRMAN FROINES: Yes. Because I just got a note saying George has been on the hot seat for two and a half hours and we can use a break.

DR. GLANTZ: If I can just say one other thing before we break.

I mean, we -- one of the reasons that we're having this meeting today, which is kind of unusual in and of itself to be kind of talking about a document that hasn't been formally put before us, is because to try to give the staff some guidance from this panel about what they ought to be doing.

Because they're getting lots of guidance from the public. They've got public comments, see, these are the comments.

And I think that what they were looking to was to try to get some reaction back from us about what ought to be getting done out of this thing, so that when the document comes to us as an action item they will -- they won't get blindsided.

CHAIRMAN FROINES: They're getting lots from us.

DR. GLANTZ: I'm not saying they're not. That's the purpose of this meeting, is to get some feedback from the panel on these issues, rather than waiting until the finished documents are put in front of us and have somebody say, well, what about this.

CHAIRMAN FROINES: I can argue in fact since --

DR. GLANTZ: It was your idea to have this meeting.

CHAIRMAN FROINES: I would argue that we have a model here today, that is that we should have in a sense a meeting to talk about the science sometimes out of the pressure of finalizing the document. I think that sometimes putting those two things together, and they're always a time crunch, puts us under pressure where we don't have this quality of discussion. And it may be that we should have two meetings a week apart sometimes, to really -- or whatever the timing may be -- but meetings where we can really go at the science as best we can and they get down to decision making. I think it would be more fruitful in the long run.

DR. BLANC: Can I make a couple comments because I won't be here in the afternoon session.

I want to, in terms of giving guidance for this revision, the areas that I see in a more global sense, my take on the document is that it does not give enough emphasis to non-cancer health effects, that reiterating what John said about not losing sight of the forest, that in fact there are two fronts on which arguments can be made.

One is related to human carcinogenesis, the other is related to other human health effects which are quite

serious and in particular relate to issues of at-risk populations, and that it does the document a disservice to so underemphasize those, and that I as a scientific reviewer would be -- would tend to be more convinced by arguments on two fronts, which were tended to more likely than not make me treat this exposure as a hazardous air pollutant, a toxic air pollutant, per the criteria that have been delineated by statute.

So in particular to get to specifics, I think that the document does not adequately evaluate emerging data on the potential role for diesel particulate exposure in terms of airways diseases, including allergic airway diseases, upper and lower, the potential for its relationship to bronchospasm, the acute health effects that could be quantified for human control, human exposure studies in the laboratory, the animal data emerging in relation to immunologic effects related airways responsiveness. That's one area globally that I think has been unemphasized.

I think that in terms of the carcinogenesis issue, I couldn't agree more with what Stan said about the approach to the overall strength of the consistency of the reported associations and a series of data, and I think that a relative risk of 1.4 for an environmental exposure is by no means a weak association at all. It would be useful to have the document put into context with some of the other

well-accepted associations are, not just for ETS and lung cancer risk, but other environmental exposures and effects, be they carcinogenic or non-carcinogenic.

I think it would be useful to have the Cal EPA go back and try to clean up some of this morass about the Garshick study, but I by no mean feels that this study -- this report rests or falls on the analysis of those data.

And I think that for some reason, which is understandable based on the history of preparing these documents, too much emphasis has been put on the quantitative risk assessment of the carcinogenic risk, because that's what you typically do in these documents, rather than looking at to what extent you can quantify it, yes, but to what extent you would take the approach of looking at non-cancer end points.

And in particular what is -- do you still feel confident accepting the EPA point five -- no, five micron -- five microgram per cubic meter diesel levels as being your non-carcinogenic, no effect level, both in terms of what the contribution is to PM 2.5 or even PM 1, potentially. And also in terms of what these new data are suggesting in terms of non-carcinogenic influence.

That would be my guidance of the things I want to see.

CHAIRMAN FROINES: I think we're going to break

now. What should we do, 45 minutes? We'll be back here at 2:00 o'clock.

(Thereupon the lunch recess was taken.)

A F T E R N O O N S E S S I O N

CHAIRMAN FROINES: Okay. George, we have a quorum and we're set to go.

DR. ALEXEEFF: I'd just like to sum up briefly on No. 3.

As I indicated, there were three different exposure patterns that had been used in trying to analyze and reanalyze the Garshick data set.

As I started to discuss, there are criticisms that have been provided to us, or comments, let's say, provided to us that questions the validity of each one of these type analyses and each one of these approaches.

And the issues that are involved with each one vary, and that is what has in part created some of the confusion.

However, at the same time I'm not sure if ultimately a resolution will ultimately occur, although that would be what we would desire, but hopefully we can at least identify what are the major assumptions that are resulting in different analyses and then we may not be able to resolve which assumption is more appropriate.

CHAIRMAN FROINES: You can't do a Monte Carlo?

DR. ALEXEEFF: I had a similar slide. Here it is.

So we would like to propose to go back and revise this portion of the document regarding the cohort study.

We want to continue to look at these analyses, these difference exposure patterns.

First of all, I want to look at the reanalysis conducted by Dr. Garshick on the original cohort to determine whether or not a risk assessment based on the original cohort would still be valid.

Second of all, I wanted to clarify the differences between our analyses and the analyses of Dr. Crump to look at how looking at the individual data, whether or not that would be a useful approach to risk assessment.

And after we look at those various approaches we'd like to update the calculations, make whatever revisions to the document are necessary with regard to this specific comments, as well as these general comments, and then based on the results of one, two and three, reevaluate whatever risk calculations are made with this cohort.

That's basically our proposal.

CHAIRMAN FROINES: Leave it up there.

Stan is not here, but it seems to me that this is an issue which the panel can give you advice on, and it seems to me to make sense for us to say to go ahead with these four approaches.

DR. ALEXEEFF: What we are attempting to do is simply look at each assumption that's made. For the key assumption, those seven, and maybe a few others just to see

under which circumstances they influence the results and in which direction they may influence the results, to see what we can ascertain about that.

DR. FRIEDMAN: One thing I'm not clear on, I understand that after Dr. Crump did his analyses, Dr. Dawson did some additional analyses.

DR. ALEXEEFF: Yes.

DR. FRIEDMAN: Are those part of this picture and are -- how do those relate to what you're planning to do?

DR. ALEXEEFF: That is the case.

The actual comments we received, okay, were on our use of the original cohort data, okay. So that first exposure pattern, that was one set of analyses.

There was a set of second set of comments regarding the original 1991 submission that Crump did and the results of that.

And then there was a third set of comments or issues raised with regards to our reanalysis of the data and the issues resolving in those, the analyses.

And in particular the issue that again results is this is our reanalysis, although this is Dr. Crump's submission, and the issue results -- the issue of concern is this dropoff, particularly this dropoff point here, and the issue of whether or not a dose response can be realized from this analysis.

So we're trying to understand are the -- what factors result in this slightly different display of the data.

But so in our report are the analysis of the data is there, and the comments, we have comments on our reanalysis of the data as well. So those would be ones that we're looking through as well. It's almost like the three sets of analyses that we're trying to reevaluate, but it could be that only one of those approaches is the most valid or could be that they all have some validity or that they all are hopelessly not resolvable. I mean, there's a number of options.

DR. FRIEDMAN: We have heard the basic difference between the first two was that the adjustment for age was based on the age of entry.

DR. ALEXEEFF: Right.

DR. FRIEDMAN: And the second was based on the adjustment for attained age.

DR. ALEXEEFF: Correct.

DR. FRIEDMAN: Could you tell us just briefly that the third set of analyses, what's different about that?

DR. ALEXEEFF: For the first set, the age variable appears to be an important variable. And part of it probably has to be, although in the exposure pattern since it only goes from 59 age, age variable becomes very

important, when you have the ramped exposure or the roof exposure and you have a larger age distribution or the exposure age, that factor seems to be as important. Okay.

Now in the --

DR. FRIEDMAN: I'm sorry. I don't understand what you just said.

DR. ALEXEEFF: For the original Garshick study, the expression of age appears to be an important factor.

In the second study, or reanalysis by Dr. Crump, there were -- one of the major issues raised is that even with the ramp approach there is some instability in the results based upon how one classifies the exposure groups.

And then in the third approach, the roof approach, the comment is that even with the roof approach this is not a linear situation and therefore then a slope is not appropriate.

DR. FRIEDMAN: Was there any difference in the way age was categorized in the third approach?

DR. ALEXEEFF: Actually, in this third approach we only categorized it by attained age. Okay.

But was that correct? Maybe Dr. Dawson should clarify this.

We did attained age in the biologically-based one.

DR. DAWSON: This particular graph, which is in our report, is for using -- it's externally standardized to

start with by the U.S. lung cancer rates.

Then in addition to that it has a covariant for birth cohort, that is age in 1959.

So, you know, that is the basis for that.

But the thing that I'd like to point out is that in these roof-type approach, in our hands how you adjust for age is far less important than in using that lock, just from 1959 on, because, presumably because you have different starting ages, different starting exposure times, and so your collinearity becomes much less of a problem in that.

So if you -- in the report we adjust for age a whole bunch of different ways and the results in slope don't vary that much. That's right in the report.

And also not in the report is pictures of how this visual trend looks and they jump around a little bit, but not substantially.

DR. FRIEDMAN: Your trend looks pretty much like Crump's trend, right? Am I --

DR. DAWSON: That's a reproduction of his, and in some ways it is like his, yes.

DR. ALEXEEFF: No, what you meant was this looks a little like the original result that I showed you. Is that what you're saying?

DR. FRIEDMAN: You showed the original showing a nice dose response trend. Then Crump's, his high dose level

came back down to almost the base line.

DR. ALEXEEFF: You're saying this looks like that?

DR. FRIEDMAN: Yes. And this is the third one, right? Looks like that?

DR. ALEXEEFF: Yes.

DR. FRIEDMAN: I keep hearing about big differences between what you and Crump found and doesn't look that way.

DR. DAWSON: No, that's right. Except that when he does the analysis himself, he uses this business of keeping background in the calculations. He doesn't take background out. So he does get different results and it jumps around in different ways, I guess.

And it tends to give much less statistically significant slopes than this does.

Our results all gave statistically significant slopes. That is in the report. Whereas his do not.

DR. FRIEDMAN: I see. So even though it doesn't look like there's a trend, if you do some kind of regression analysis, you do get a significant --

DR. DAWSON: That's right.

In some ways this trend business, I'm beginning to think is a little bit misleading, but those are big clouds of points, they don't just represent a single point, but they're exposures over a wide category and the responses

over a wide category, so there's big clouds of points up there that we tried to represent by arrow bars, but maybe it's not clear enough.

DR. FRIEDMAN: I wonder if it would be useful to show the cloud.

DR. DAWSON: They begin to look really funny when you try to do that, at least all the ways I thought of.

If you get zeros and then spikes and a whole bunch of -- I've seen them plotted that way. It looks really weird, but maybe it would be worth it to do it that way.

DR. FRIEDMAN: You know, the scatter plots without lines between them, maybe you can see a trend in some of the uncertainty. I don't know. I'm just leaving it to you to decide the best way to present it, but I'm wondering if you feel that this is misleading to see it in this way, whether that it would be helpful. I don't know.

DR. KENNEDY: Excuse me. I'm pretty much a neophyte in all of this and this may be a really dumb question, but as I understand it, much of the importance of your slope and much of the thrust of the criticism is based upon your use of this information to develop not only a zero point, but to then to make recommendations about ambient exposure and risk.

What I'm seeing -- is that correct? Is that a totally wrong assumption?

DR. ALEXEEFF: I think the issue is applying this type -- first the analysis and then applying the results of the analysis to ambient exposure.

DR. KENNEDY: That's sort of what I'm getting at.

What comes up over and over and over again in these discussions is that pretty clearly something is going on here that isn't pleasant. This stuff is doing something bad.

I guess the question is at this point, based on the available information, can you really make that final recommendation and can you make that final assumption? Is it adequate to simply say the data -- the consistency of the data are not to show that too mics per meter squared per whatever it is represents toxic threshold, but to simply say that is it a question, the issue of diesel exhaust as a health risk in this case, specifically in terms of its carcinogenic risk, is clear. What is not clear is that upon that piece of information.

DR. ALEXEEFF: Well, I think that in the first couple of slides that I had information from the Health and Safety Code, when it asked us to evaluate the health effects, there is this statement in there that if there's a threshold, we're supposed to develop a level, essentially like a safe level.

And then at least to get -- apparently to give us

some flexibility it says, well, if we can't find the exact threshold, just kind of give a range of what the risks are, and that comes out to be a lot of work. I think it was written in a way to try to make the process move, but I think in the end we're really focusing on what's the top of the range, what's the bottom of the range.

Now, whether or not we can proceed without having a range as part of our analysis, I think I leave it to the Air Resources Board to let us know how the process might be affected on that.

DR. KENNEDY: I commend you on the incredible amount of work that you've done trying to find the truth in this. I think I'm sort of in awe of it.

But certainly from the animal data it's awfully hard for me to see, based on the mechanism that comes out of what is available, I can't make a comfortable jump to people because the difference and the whole issue of clearing mechanism. So you may be stuck.

DR. ALEXEEFF: Right. Well, there is, I think one thing I think we would like to do is there are in the document at least four pieces of evidence, four pieces of quantitative information. One is the non-cancer information I went through earlier today, which does provide us some quantitation.

And then there are three methods of calculating

risk. One is this animal data and there's actually sub-methods within that.

And then there's these two epidemiological cohorts.

So we're not required to calculate a risk for every data set we can find. So if when we -- when all is said and done and the dust settles, if there is a data set remaining that one could quantify the risk, then I think that would be sufficient to move us along.

Or in the past we've often identified what we felt was clearly the superior data set and decisions were made on that basis.

So I think what we feel compelled to do is to look at each one and to try to analyze it, look at the comments made and to see if the data set can stand up or not and if not move on to the next data set and then see what remains in the end.

CHAIRMAN FROINES: Let me move it ahead, because this actual discussion is a good one, but I think it's one of the discussions we're going to have to have when we actually review the document and make some final decisions and so we are -- this discussion will clearly come up again in a different context.

So I want to go --

DR. BYUS: Let me make one comment, John, one

sentence, and that is I -- most of this controversy seems to be on establishing the dose response relationship or the epidemiology data, not establishing the overall correlation. It's not surprising with a relative risk of 1.5 that it's going to be difficult to do, to establish the dose response relationship.

So when you do the analysis, just in the final document, really make it to -- it would help me if you made it clear all the discussion of Crump and everyone, their assumptions, how does that affect -- if you lumped all the data together, how does that affect the overall association and relative risk of 1.4 as opposed to teasing out a dose response relationship.

I think there are two different things, they are in my mind.

Clearly you want to try to get to the dose response relationship, but if you can't get it, you still have the original association and you don't really want to confuse the two things, because I think that's what's sort of happening. It's sort of happening in my mind.

DR. ALEXEEFF: I think that actually Dr. Kennedy was in some ways speaking to the same thing.

DR. BYUS: Same thing.

DR. ALEXEEFF: Can we have an occasion without a quantification to his response.

CHAIRMAN FROINES: Or what is -- I would like to avoid this discussion, because I think it for -- because we've been very successful about talking about science all day and we're now slightly bordering on policy-related questions, because it goes to what is the level of the evidence with respect to dose response that's required in terms of defining a substance as a toxic air contaminant. And those are issues yet to be defined.

We clearly have extremely strong evidence for the qualitative issue. I don't think there's much debate over whether diesel is a carcinogen.

The question has to do more with dose response and that there is also evidence for nonmalignant respiratory effects. There is increasing evidence, especially out of UCLA, on diesel exhaust and its relationship to asthma and allergic rhinitis.

So that there are a number of -- and Paul was talking earlier about acute effects.

So when we look at acute effects, asthma and allergic rhinitis, nonmalignant respiratory disease and cancer, there's certainly a body of evidence developing about toxicity associated with diesel exhaust.

The question though that we're clearly going to have to spend a lot of time on is what is the dose response within that context, and what is the level of evidence

required in terms of determining some of the substance of the toxic air contaminants.

And I don't frankly believe that George has to have the number down so he could put it into Grauman's Chinese Theater, you know, next to Frank Sinatra or something.

So those are things we are going to have to consider, because they mix policy and science.

DR. ALEXEEFF: So I think we're done --

CHAIRMAN FROINES: I think basically the panel is agreeing for you to proceed on that basis.

DR. ALEXEEFF: So the next issue is where should we go from here in terms of analysis. Did you want us to now go through the discussion of the meta-analysis or to the -- we're at No. 3.

Now which issues --

CHAIRMAN FROINES: Meta-analysis, and then we're going to go to Joe Mauderly.

For those that don't know, and are interested, Mauderly has a nice book out that came out from last year, called Particle Overload in the Rat Lung and Lung Cancer, and it discusses a lot of these issues, so if anybody wants to borrow it, I can ship it to you. If anybody wants to look at it with some care.

DR. GLANTZ: Can I just say one other thing?

CHAIRMAN FROINES: You mean you think that by walking in here late, you now get to have --

DR. GLANTZ: My students are like we're now a whole lecture behind in my course.

One other thing, I just wanted to -- not that I'm trying to open up another rat's nest or anything, but I think it would be worth at least adding some discussion if there's any data on it for cardiovascular end points. This is a kind of building onto what Paul said.

Because I realize that there's not a whole lot of data out there probably, but if you look at my beloved ETS literature, there's good evidence that -- good animal evidence that 1,3-butadiene facilitates arthrosclerosis, and I think there's a lot of 1,3-butadiene in diesel exhaust. And also benzopyrene.

And there's at least some evidence out there in the literature that particulate air pollution is related to cardiovascular mortality.

My guess is there isn't enough information out there to do anything very quantitative, but I think in the interest of completeness, and since you don't have anything else to do, it would be worth -- that was a joke, George.

I think it would be worth at least doing a literature search on it and putting in some discussion of that to --

CHAIRMAN FROINES: Why don't you assign that as a class project in your biostat class, since all your students are interested now.

DR. GLANTZ: That was like Biostatistics 1 and they came in and were totally snowed. Actually, they said that it was very interesting and they could follow it, until we got into the argument about the workshop, and then they said it was too sophisticated. Too esoteric at that point.

I'll shut up and start writing notes.

DR. SEIBER: Just one comment.

I was wondering about cardiovascular effects too and if there are any, wouldn't they be in the same epidemiological studies that we're looking at? Didn't they, when they looked at the death certificates and so forth, distill that out or maybe it just wasn't addressed. I don't know.

DR. ALEXEEFF: Well, I don't -- Michael, have you seen any information on cardiovascular effects?

DR. DAWSON: Yeah. The cohort study for which we have the data with the 55,000 people has the cause of death coded. And so all those cardiovascular deaths are right there. In fact, Dr. Crump, in one of his submissions, called attention to the fact that cardiovascular deaths were also increasing in this. And but, you know, just something that we haven't gotten to doing.

DR. ALEXEEFF: Actually, on a follow-up, I think that last week Dr. Crump made the presentation showing that the trend that he was finding in lung cancer was also a similar cardiovascular trend of going up and then going down.

But, anyway, there hasn't been much analysis, but there appears to be some data out there.

CHAIRMAN FROINES: I really want to push us along. I think we're going to run out of steam and it's been going very well so far.

So there's an action note that you'll look at cardiovascular to see what is there. It may be secondary to respiratory.

DR. GLANTZ: I think if you look in the ETS report, I think you'll find some mechanistic stuff that might be helpful for some of the shared PAHs and stuff.

CHAIRMAN FROINES: You said something that made me curious, and I know now that I'm out of turn, but if somebody does know the concentration of butadiene in diesel, I'd be very interested in learning that.

Let's go ahead.

DR. LIPSETT: All right. My name is Dr. Michael Lipsett. I haven't really been involved in this diesel process until a little bit more than a year ago when I was asked to undertake a meta-analysis of the relationship

between occupational exposure and lung cancer.

And so what I'm going to talk about now briefly is what -- I'm going to skip a few of the transparencies, but I'm going to talk about what we did in this meta-analysis after first giving you a little bit of background about what meta-analysis is useful for.

And then I'm going to talk about the substance of some of the comments that we received and how we plan to respond to those.

First, these were the commentators from whom we received comments, specifically on the meta-analysis.

Now, what is meta-analysis good for? What are they used for generally? It's two purposes.

One is to provide summary estimates of effect, summarizing a body of research.

But when you combine data from a number of different studies to provide such a summary estimate of effects, one of the underlying assumptions is that these are homogeneous with the respect to the effects being measured.

And when you deal with occupational studies, you don't necessarily think about homogeneity, you consider differences in exposure patterns, differences in the industries, differences in times people were followed, differences in study design, differences in the types of analyses that are done and whether or not different biases

are controlled for, confounders, this type of thing.

So in occupational epidemiology, you think actually that apriori you think about heterogeneity being kind of like the basis from which you're going to be starting.

So that brings us to what the other purpose of meta-analysis is. And that is when you do find that there's evidence of heterogeneity, that is wide variability of results of different studies, you can use meta-analysis to explore what are the reasons for this heterogeneity, what are the study characteristics that underlie these differences of results.

And that's the goal, not always successful, but that's what we tried to do here was to both degenerate summary estimates, at least for subsets that turned out to be relatively homogeneous, and also to explore what are the reasons underlying heterogeneity.

Now, there are a lot of limitations of meta-analysis. I'm not going to go into all these things here, but one of the principal ones you need to be aware of is that it can't be used to answer questions of causality, per se.

George briefly went through some of the other standard Bradford Hill criteria for examining causality, based on epidemiologic studies. That is covered in our

Chapter 6 as well.

So in this meta-analysis we started with a literature search, trying to identify as many studies as we could, published between 1975 and 1990 using meth line, tox line, and we supplemented the retrieval of these studies identified electronically with manual retrieval, additional studies that were cited in those.

And we had set up some, initially some inclusion and exclusion criteria related to what studies were going to be involved in meta-analysis.

At the outset we excluded studies that were minor, and the reason that we excluded minor studies was that there would be current -- likely to be current exposure to other known pulmonary carcinogens, silica, arsenic, radon, a couple of these which interact also with cigarette exposure or with tobacco smoke and felt that that would be too confusing to include those in this particular analysis.

So excluding those initially, we had the criteria. The first two were obvious, to lung cancer, the exposures needed to either refer to diesel exposure or occupational or potential diesel exposure.

We had to have in the study a presentation of the estimates of relative risk or standard errors for data that allowed us to calculate this information.

One of the things we were concerned about too was

inadequate latency. And we included a number of studies where there was clearly very adequate latency, that is allowing enough time to elapse between initial exposure and the follow-up to make sure that there would have been opportunity for lung cancer to develop and to be manifested then.

A number of studies were included also where it was not absolutely clear this was the case, but we were pretty confident that they were, because it covered a long time interval and they covered a period during which dieselization had been more or less effectuated in that particular industry.

We also excluded some studies that didn't follow people up past retirement age. And whereas this is the period in which a lot of lung cancers are manifested is after retirement age, we felt that this would produce distorted estimates of relative risk if we included those studies.

And finally the studies needed to be independent. And there are several cohorts or groups of workers for which multiple publications could be found and tried to include those that best met the other preceding criteria.

So having said what the inclusion-exclusion criteria are, we found 47 potentially eligible studies, 16 of which did not -- were excluded on the basis of those

criteria.

Of the remaining, from the remaining 31, we derived 40 risk estimates, and that may seem little bit puzzling, but a number of these studies didn't just look at truckers or dock workers, but had multiple occupational groups that didn't have overlapping personal experience.

And so, say, for six of the studies we were able to get estimates of relative risk for multiple occupational groups.

In terms of the data extraction, I think this is important to just indicate what we did here as well, was that we took the estimates of relative risk which included either odds ratios or standardized mortality ratios and persistence ratios, we extracted these, and we ended up calculating the standard errors principally from the confidence intervals. And either from confidence levels or in a couple of case from the stated P values.

And the specific estimates of relative risks were those that were taken from individuals in a cohort, say, that had the highest or longest level of exposure. Those are the most diesel-specific occupations or exposure groups, so in some instances some studies had, say, a category of general professional drivers and they also had truck drivers. We preferred to take the truck driving, long-haul truck driving industry over just drivers generally.

We used adjusted rather than unadjusted estimates when those were available, just for confounders.

And as I mentioned, we prefer -- several studies we had multiple estimates of effect in different occupations.

There are two general models that are used in that analysis. We used both in this particular one.

There's a fixed effects model. This assumes that each study is estimating the same relative risk. Okay. It assumes an underlying homogeneity.

As I indicated earlier, I think that this is probably unrealistic when you're dealing with occupational epidemiology studies.

And the alternative to doing this is using a random effects model, which doesn't assume a single comment underlying relative risk, but allows for this kind of heterogeneity and generation of risk estimates.

And in the random effects model, at least the one we used by DerSimonian and Laird, each one of the studies when you develop the pool estimates is weighted by the inverse, not only on it's own variance, but the interstudy variance.

Okay. In our initial analysis of taking all the studies together, there was significant heterogeneity and basically that pool of a lot of different studies that had

estimates that were very broad ranging. So statistically, and Dr. Glantz might want to weigh in on this here, too, is don't consider this appropriate to have this summary estimate of effect when you have that kind of heterogeneity.

But so we explored what were the potential sources of this kind of heterogeneity. And so we took subsets. We took different occupations, say truck drivers or dock workers and stevedores.

We took smoking-adjusted studies versus those that didn't adjust for smoking.

We just repeated this by doing the subsets over and over again and doing the basic kind of valuation of both what are the pooled risks and whether or not there was heterogeneity in those estimates.

And basically this was -- to do this we had created different indicator variables in order to do this sort of thing.

In addition we undertook a variety of sensitivity and influence analyses. These, for instance, a number of the studies that were excluded initially as being repetitive were redundant with the ones we had included, we switched places with those. There are number -- also there are a number of studies where we felt that even in the world of diesel exhaust exposure, that you couldn't really distinguish overall motor vehicle exposure from diesel

exposure generally, so we excludes those as one basis for sensitivity analysis.

We undertook influence analysis too, which is basically getting rid of a single study of time and seeing how that affected the risk.

Okay. And what we found, basically, was the pool estimates of a number of these different subsets that didn't have substantial heterogeneity or showed they were relatively homogeneous in the subsets, that they reflected the existence of a positive relationship between diesel exhaust exposure and lung cancer.

When we -- we were able to identify several important sources of heterogeneity among the studies as a whole, and one very important one is whether or not the studies had adjusted for smoking.

The one when we took smoking-adjusted studies, the pooled estimates we got showed no evidence of heterogeneity, and it showed a positive statistically significant risk estimate.

In the cohort studies, one of the characteristics that we had -- study characteristics that we had looked at was whether or there was a clear, healthy worker. For those of you who are not involved with occupational analogy, healthy worker effect is a manifestation and a way of selection bias, that people who are working are healthier

than the general population, at least at the time they are hired, and also they tend to stay healthier if they stay employed.

For all cause mortality, when you look at them compared to the general population, which is a number of these studies did, they appear to be healthier. They have lower, low cause mortality. And we found with this kind of selection bias that that is a substantial contributor to the heterogeneity of the cohort studies.

Okay. Within the smoking-adjusted studies too, we found a modest evidence of exposure response relationship, which is indicated in the tables in our Appendix D of the meta-analysis.

Okay. And generally when we undertook sensitivity and influence analyses, these didn't really change our results much, with the exception of exclusion of one of the railroad studies. And I'll show this graph momentarily.

It was a Finnish study published in 1994 that had substantially lower risk estimate than the other railroad studies which are all -- the other ones were all in North America.

This is one also that was compared where the rates of lung cancer in this population were compared to those of the general population of Finland.

Okay. So graphically, this is from, I think, one

of the tables in Chapter 6 of the book, we have -- is there a pointer here?

It's a laser. Thank you very much.

So this is the pooled estimate -- sorry this is on the log scale here, so this is a no effect type of line there.

This is the pooled estimate for all studies combined. As I mentioned, there was substantial heterogeneity in this one, so it's not by itself something we would consider to be -- not appropriate for drawing inferences from.

This is the cohort studies among which there was also substantial heterogeneity.

The case control studies and the smoking-adjusted studies, which tended to overlap substantially, there was not evidence of heterogenicity there. And these are ones for which we feel comfortable saying that this is a real -- what this corresponds to in terms of the relative risk is about -- a little bit more than 1.4 per each of these.

Studies not adjusted for smoking, substantial heterogeneity there. Truck drivers are relatively homogeneous. Railroad workers, at least with that Finnish study, included -- showed substantial heterogeneity, but when that one was excluded that was the homogeneous group.

And here are the number of other groups.

DR. FRIEDMAN: Michael, can I just interrupt?

DR. LIPSETT: Yes.

DR. FRIEDMAN: I feel much more comfortable with seeing the relative risks, rather than the logs of them, and I wonder why you put the logs up. I can't translate them immediately into some number that we all understand.

DR. LIPSETT: I'll --

DR. GLANTZ: The problem is their graphics program.

DR. LIPSETT: Stan knows the reason. That's exactly it. There's a problem with the program I was using. We can have someone else in our department who is better at graphics display it.

When I displayed it out on the untransformed scale, the confidence intervals on a number of the studies just went off the scales.

DR. FRIEDMAN: You need a log scale, but it's nice to have, instead of the logs on it, is the numbers, have a relative risk of one and then a .5 and 2 are equidistant from the one. And you can read off what the relative risk is which is --

DR. LIPSETT: That would be doable. Thank you.

DR. GLANTZ: You can't do logs in your head?

DR. FRIEDMAN: I'm pretty good at arithmetic, but not logs.

DR. LIPSETT: This is an example here also of the -- these are not pooled estimates, but these are the specific studies in the railroad industry again. And I'll -- I'm sorry, this is on a log scale as well.

This is the estimate for the Finnish study. And you can see why it was different from all the North American studies conducted on railroad workers.

Why, when this was excluded, and you pooled the estimates from the other railroad studies, it gave estimates that were comfortable -- were statistically homogeneous.

DR. KENNEDY: Wasn't that study very closely controlled for smoking, the Finnish study?

DR. LIPSETT: No.

DR. KENNEDY: No, it was not?

DR. LIPSETT: No.

And then George had showed this study earlier. These are all this -- this graphic, these are the smoking-adjusted studies. Again, on the log scale. And their confidence intervals.

And from which, we ended up with this pool, small pooled estimate, very very small on confidence interval there, from pooling these results. It was statistically significant, it didn't show any substantial evidence of heterogeneity.

So what were the comments we received? And I'll

hit --

DR. SEIBER: I don't quite understand that last one that you pointed out with the very small variance. That's a pool of --

DR. LIPSETT: That's a pool of all the smoking-adjusted studies.

DR. SEIBER: Which are all these others?

DR. LIPSETT: Right.

DR. SEIBER: I'm just trying to figure out how do you get a pool that has such a small variance when all the individuals have -- showing my ignorance of biostatistics here, obviously.

DR. LIPSETT: In any kind of study you're going to have -- this is not too much different from a standard study. You increase the precision of your estimate by increasing the number of observations and that's in effect what's happening there.

Stan, did you want to add to that?

DR. GLANTZ: Essentially, to grossly oversimplify it, I mean, basically you're treating it as if it was one gigantic study, so your sample size and number of events, when you put them all together, is a lot bigger, so your confidence intervals are smaller.

DR. LIPSETT: Okay.

DR. GLANTZ: I assure you that my ignorance of

atmospheric chemistry is at least as lean as your ignorance of biostatistics.

DR. LIPSETT: Okay. In terms of the principal thrusts of the comments that we received, one of them was that meta-analysis, undertaking a meta-analysis is not appropriate at all, because of the lack of really good exposure data.

And the next, there were a number of comments that were received from specific individuals about how certain of the calculations ought to be revised, we ought to pick a certain estimate of relative risk, rather than another one, because many of the studies presented five, six, ten estimates of relative risk.

The third, the comment that we received the most frequently was that the publication bias invalidates this analysis. What this refers to is, I'm sure you're all aware, but bear with me, is that with journal editorial policies in the past have tended to favor and publish the statistically significant results and individuals might have hesitated about submitting papers to journals that didn't show statistically significant results.

So in a meta-analysis where we're looking at a body of literature, what this will tend to do is favor finding a positive kind of relationship between your exposure and outcome, if there is a significant publication

bias.

And this is something we did address in the meta-analysis. I didn't want to go into it here, since my presentation is long enough as it is, but I think we probably could make the presentation somewhat more clearer, and in fact the way that we have addressed it in the publication is graphically. I've modified the graph and I think it makes it -- in the current version it shows case control and cohort studies separately, and I've modified that graphic to combine the case control and cohort studies, plotting the estimate of effect on the X axis and then the inverse of the standard error, which is in essence an indication of the variance of the study on the Y axis.

And when you do that sort of thing, if you have a lower density of points on the lower left-hand side of the graph, it's an indication that the small, statistically insignificant studies might not have been published.

Anyhow, this is something that we're going to be addressing in a little bit more detail.

In response --

DR. GLANTZ: What did you find?

DR. LIPSETT: In terms of publication bias?

DR. GLANTZ: Yeah.

DR. LIPSETT: With this second plot and with both the other plots too, it does appear that there is a modestly

sparser density of points representing the studies in the lower left part of the graph.

But so what that would indicate is that there's -- that it's possible that there might have been some smaller statistically insignificant studies that were not published. We don't know that. There are a lot of reasons why studies aren't published, certainly one big reason is they're underpowered and they shouldn't be published. I mean that's --

DR. GLANTZ: Yeah. I mean, when you listen to these arguments about publication bias, I mean one thing that the people who push it never argue is that the study was junky, it didn't deserve to be published.

You know, the fact is when you look at your charts, though, there were a lot of those individual studies which didn't reach statistical significance. So I think to argue that just because studies weren't reaching statistical significance in this area and they weren't published, you seem to have had several of them there.

DR. SEIBER: What happened to the -- excuse me, Gary -- the 16 studies that weren't included, were you able to look at those and distill any useful information out of the ones that weren't included in your meta-analysis, but they still were epidemiological studies.

DR. LIPSETT: Like there was, say, if it was

excluded for a presentation bias, that is if it didn't have information that allowed us to calculate a relative risk or standard error, we couldn't include it. If it was excluded because it was redundant, that is there were other studies in the same population, we actually did include it in one of the sensitivity analyses. We substituted all those for the ones that had been excluded.

So if I think that we did try in a number of ways to figure out if there were these exclusions if we ended up with biased results, and I don't think overall, my feeling is that we did not.

DR. FRIEDMAN: If so in this funnel plot there's a asymmetry on the left side and that there are more small studies with positive results than with negative, if you ignore the small studies and look at the larger ones, was it then more symmetrical and, if so, what would -- did you look as just the results of just using larger studies with smaller variances?

DR. LIPSETT: I'd have to look at the -- you mean in terms of the revised plot or the older ones?

DR. GLANTZ: He's talking about what you did.

DR. FRIEDMAN: Yes. If you have this plot which shows a deficiency of small negative studies, why not just eliminate all small studies and then look at the big studies where I assume there was a balance and there was no

deficiency or what did you get or is that the way you addressed publication bias or maybe you addressed it in some other way.

DR. LIPSETT: Well, I think that's actually that's not a bad suggestion. I mean, we didn't do it that way. I mean -- I don't think that there's really any satisfactory way of addressing publication bias from a quantitative perspective. I mean, it's not -- the way I've seen it done and what we did is basically to have this done in a graphical --

DR. GLANTZ: What page?

DR. LIPSETT: It's on Appendix page D 27 and D 28.

DR. FRIEDMAN: Is there any reason to feel that large, more reliable studies, negative studies, or studies with low relative risk were not published?

DR. LIPSETT: Looking at this, I would say no, but as you know patterns are somewhat in the eye of the beholder, but it would appear that most of the larger studies tend to center around the central estimate in each of these instances.

So that's a good suggestion, just to do a separate funnel looking at lower --

DR. GLANTZ: What I think Gary is suggesting is not to do a funnel separate plot, it's to add one more sensitivity analysis where you're simply excluding the small

studies entirely on the grounds that if what you're saying is it's a chance there's some small negative studies that you didn't include or that weren't published and as a result they're not there, so you're overestimating the risk.

What he's saying is just exclude the small studies, period, and see when you look at the large studies where you get a more symmetrical funnel plot, what do you get there. Since what you said is they seem to cluster around a central estimate anyway, you'll probably come out with about the same answer, and I think that's a good way to deal with criticism is to say -- because when you do the meta-analysis anyway, the small studies aren't going to be weighted very heavily anyway, because they're small.

So I think that's a very good suggestion. I agree with what Gary said. It shouldn't be hard to do.

DR. LIPSETT: No, it won't.

CHAIRMAN FROINES: In terms of the things that you want to address, the language that Moolgavkar used in his letter is a little different than what this language and so are you subsuming his comments into this proposal?

DR. LIPSETT: Okay. Well, Moolgavkar had several comments. He attended the workshop in July and he actually was pretty complimentary about the meta-analysis on a technical basis, although one of his comments that he said it's true is that the meta-analysis can't correct for any

deficiencies in the individual studies.

But what we're planning to do here is to address the other criticisms of Moolgavkar, which is the last one here, is to just explain more clearly why this meta-analysis is done and, too, we're updating the calculations. I'm going to redo a number of them based on some of the comments or suggestions and see if that makes a difference in the results.

We'll clarify this issue of publication bias and we'll do this as an additional sensitivity analysis as you suggested. And then one thing that was raised actually at the July workshop by one of the other individuals and also the Moolgavkar, I guess, is suggesting that not -- that one ought not do with this is to explore the range of risk that one might be able to identify quantitatively based on meta-analysis, that is based on the pool risk estimates and try to reconstruct historically who would have been the whole range of exposures to which people might have been -- whole range of exposures that people might have had in different occupations, and then use that as a basis for quantitative risk assessment.

We'd like to try to explore that if it's something the panel thinks would be an appropriate thing to do.

CHAIRMAN FROINES: I think that means that you have to come up with some estimates of risk that bracket

some range of exposures that occur.

DR. LIPSETT: Yes. For instance, when you are looking at several of the occupational groups, we get some of the pooled estimates that are homogeneous, and we could look at whatever industrial hygiene data exists that we historically can construct or estimate what might have been the whole range of exposures that people might have experienced, and from that to try and generate a potential range of risk.

CHAIRMAN FROINES: Doing that is not contradictory to this comment. That's not a question. That's a statement.

DR. LIPSETT: That's a statement.

DR. GLANTZ: It's not a question of what?

CHAIRMAN FROINES: To attempt to bracket range of exposures is not really contradictory to his basically correct notion that no dose information, meta-analysis therefore would be inappropriate. They are two different exercises that they're talking doing.

DR. GLANTZ: I think, Michael, if you can figure out a reasonable way to do what he's suggesting, I think it's a good suggestion.

DR. LIPSETT: That's it.

CHAIRMAN FROINES: So we basically will, unless I hear any opposition, agree with what they've proposed and

with the added sensitivity analysis.

I want to make sure that the panel -- that the staff comes away not just having given presentations and then silence from us, but comes away realizing, knowing what we think they should be doing. And I think we've been clear up to now. In fact, we've been so clear that this may take ten years.

DR. FRIEDMAN: I just want to mention that I have had some discussions with Michael, because of my concern about the possible inadequate controls for smoking in some of these studies, and I think I've been persuaded by various literature that I've seen that smoking has been controlled for pretty well.

However, I still think that the definitive way to look at an exposure with complete control for smoking is to just focus on people who have never smoked, and this has not been done in the literature and I would hope that somebody might do this, because I think that gets rid of the question of any potential confounding that still exists, so-called residual confounding. I hope that such an analysis could be done for those studies which have identified they were never smokers.

DR. ALEXEEFF: I believe the -- this is George Alexeeff again, for the record.

The next issue that we want to talk about is the

comments submitted that the rat lung tumor data --

CHAIRMAN FROINES: George, before you start on that, I want to -- I don't know what the proper procedure -- I have two papers here both from Dale Hattis to US EPA on the issue of the Mauderly data in which Dale has raised some, I think, significant questions about the analysis that Mauderly has done. And so these need to go into your record in some fashion.

DR. ALEXEEFF: Okay.

CHAIRMAN FROINES: I don't know how to do that.

DR. KENNEDY: Hand it to him.

CHAIRMAN FROINES: I think that these should then be circulated to the panel, because they represent important -- some people, some scientists besides Mauderly looking at that data set and coming to somewhat different conclusions.

DR. ALEXEEFF: Okay. I don't know if we've seen that. I don't recall seeing that information. I'll be happy to look at it.

Okay. And that leads us to our next slide here.

The primary key comment is that the rat lung tumor data should not be used to generate quantitative estimates of human lung cancer risk from environmental exposures.

And this is a list of the individuals that have made this comment. And I think it's an important comment,

and particularly since Dr. Mauderly himself, whose study they are using in this cancer risk assessment, is making this comment.

So what I'd like to do is I was thinking of actually skipping over the background of what we did in our document. We told you we did the risk assessment, and now we have our comments saying we shouldn't, so I'll just skip that and go to what are the issues that are being raised by the commentators that we see that relate to this.

And I will be -- most of these are issues that were specifically stated by Dr. Mauderly, because I think he has made the most carefully-stated points.

Okay. First of all, keep in mind that the mouse and the hamster do not respond to diesel exhaust with the hyperplasia and do not develop the alveolar tumors that have been found in the rat studies.

Second of all, that meaningful increases in lung tumors in diesel soot exposed rats only occur at exposure rates overwhelming particle clearance defenses in inducing a strong, prolonged and progressive inflammatory and cell proliferative response.

I might mention that 2.5 milligrams per cubic meter is kind of a cut point.

The next one is there appears to be a threshold exposure rate for triggering progressive lung disease in

rats.

Now here's a couple of figures submitted by Dr. Mauderly. The first one is his own, and I assume the lettering is his own. What he's showing in this graph here, these are from a couple different studies, diesel exhaust results and whether or not this is exposed control lung tumor incidents and here's a measure of concentration, weekly soot concentration times time, and you can see that over here there's an increase sort, there's one up here, in tumor response, but that over here there are exposures that occur but no increase in lung tumors.

Related to that is this body of information which is just summarized partially here by Dr. Heinrich, where here again we have rats with tumors, cumulative exposure, since this is measure, but cumulative exposure, and we have diesel soot plotted here, again with no response here, but that's a zero. That's the control. But then we have two non-genotoxic agents that seem to fit along this line here of dose response, even though they're not genotoxic, but they fit along the lines in terms of particulate cumulative exposure.

This provides the support, which I think I mentioned, is that an inert substance may be causing the effect by a particle-induced mechanism, and not a genotoxic mechanism in the rat.

DR. GLANTZ: George, can you put those up? That may be true, but if you look at those two graphs, has anybody actually fit the line through it and seen if the zero is excluded from the 95 percent confidence interval, the intercept, but I bet you it isn't. I mean --

DR. ALEXEEFF: Stan, are you able to answer that question?

We haven't done that.

DR. GLANTZ: I mean, just put your pointer over the line and just see where the line goes, just take those points and they're pretty linear. There's a very good chance that it goes right to zero zero. I mean there's some variance about the line, because they're sampling the same thing in both of them, so I mean I think basically what you're getting down to in the top one is just that one point. I think is it 3 or 8 or 5, I can't -- the first point, and basically in the second one the second point. So you're making pretty strong conclusions based on one data point, basically.

CHAIRMAN FROINES: How many animals were in the study in the Heinrich study?

DR. ALEXEEFF: Heinrich study, is there 100 or 200?

DR. BUDROE: I think it's roughly 50 per group for one of those experiments. Those are a number of different

experiments on that graph.

DR. GLANTZ: Yeah. But even so, if you just draw the line there's a real good chance it goes, both of them go through zero, if you put a little bit of random error into it, which every study has.

I mean, it would be easy enough to just compute and see if the 95 percent confidence intervals for the intercept includes zero or not.

CHAIRMAN FROINES: That's the same problem -- these are the same pictures they showed at the workshop.

DR. GLANTZ: Yeah. I had the same reaction at the workshop.

DR. ALEXEEFF: In the Heinrich study, okay, these are actually fairly large study groups, 100 in the high exposure, 200 in the next high and then 200, roughly 198 and 217, so it's about -- it's larger than the general usual --

DR. GLANTZ: Right. But what I'm saying is just draw a straight line through those points.

DR. ALEXEEFF: I understand your point. I'm just --

DR. GLANTZ: You can say it's suggestive, but I bet you if you went through and did the analysis it's equally likely to just be sampling variation, draw a line that goes through zero.

DR. ALEXEEFF: Let me continue on with what their

points were.

In fact these are the comments that are made at the workshop they've submitted in writing.

CHAIRMAN FROINES: That has significance. There are two possible mechanisms. When you draw it the way they've drawn it, you are, by definition, assuming the correctness of one mechanism, and by not addressing the second, what the second mechanism would appear in the low dose region, you've essentially argued your case with your own data.

DR. ALEXEEFF: I think, Dr. Dawson, Stan -- I think we tried to model this, didn't we, look at extrapolation, and we're not able to separate.

DR. DAWSON: I wasn't involved in that.

DR. ALEXEEFF: Okay. Well, somebody can check to see if we tried to do low dose modeling and see what the result is.

DR. GLANTZ: Maybe there is --

DR. ALEXEEFF: Identified thresholds statistically --

DR. GLANTZ: Maybe they're right, but I mean just using the eyeball technique, I don't find those graphs a compelling evidence for a threshold. Maybe there is a threshold.

CHAIRMAN FROINES: But it's like in these

discussions we have, we start out the discussion by saying all the chemicals that you find in diesel exhaust, and you say there's arsenic and there is butadiene and there's 4-amino biphenyl, there's nitro PAHs and there's regular PAHs and on and on and on, and so we've got a hundred chemicals that are all carcinogenic and then we say irrelevant, forget it, let's go on with the threshold model.

You know, you can't have it both ways. Somebody also has to argue why the existence of butadiene in somebody's lungs is irrelevant, when we know that it causes cancer in humans.

So that how one approaches this, I rather think there are multiple mechanisms going on, which isn't to suggest that Mauderly's work is wrong, but there are many more going on than we're -- it's more complicated than we're treating it, and all ravens aren't black.

DR. ALEXEEFF: Just I think to make Dr. Mauderly's point, I think he finds that histological observations in the alveolar air space in terms of hyperplasia and accumulation, are occurring at the area where we see those black squares, as opposed to the other areas. So that's just another piece of evidence.

The other point is that that's being made is that the apparent threshold which is alluded to in the previous graph is two orders of magnitude above the environmental

exposure rates, and that at the same time, though, although there may be this threshold or there is this proposed threshold in rats, it's important -- it has been shown that also that the soot associated with mutagens are not important in the rat lung tumor response. So that's the information of the non-mutagenic materials that are also shown in this tumor response in about the similar kind of rate.

But even so, this response seems to be particular to the rats, if it's occurring -- it appears to be particular to rats, so it doesn't eliminate the role of organics in other species, including humans.

Now, there's a little information on chronic exposure of nonhuman variety of primates, and this is a new paper that was actually presented to us at the workshop.

And what this paper is showing is that chronic exposure of nonhuman primates to diesel exhaust does not induce the self-proliferative response that's found in rats. That's not to say there isn't any response. It's not the same kind of response as found in rats, particularly in the data with cynomologous monkeys and rats who were exposed for two years at two milligrams a cubic meter, they showed differences in their interpulmonary retention patterns and tissue responses.

So with the monkeys, they may have retained

slightly more particulate in their lungs in total, but they retained it proportionately in the interstitium, in contrast to the rats, who retained it in the alveoli.

And as a result the monkeys exhibit less alveolar inflammation, less fibrosis and less hyperplasia, which seems to be the prerequisite in the continuity of the other mechanistic approach where you have inflammation, fibrosis, hyperplasia and then tumors in the rats. This doesn't seem to occur in the monkeys.

Another bit of evidence supplied is that in coal miner pneumonoconiosis it's not known to increase the risk of lung cancer for those persons.

DR. SEIBER: Are we to -- I'm assuming you're saying, or someone is saying, that the human would be more like the monkey than the rat, and the rat may be unique in some respect, because after all the hamster also showed no response.

DR. ALEXEEFF: That is the argument being made, and the mouse as well. The mouse didn't show it. So the rat is showing a different kind of response than either other rodents -- in fact the point that's made in the next slide is that in comparing rats to mice, you think rodents would be rather similar, the response to not just diesel soot, but a number of particulate matter types of carcinogens is inconsistent or not -- they're not in

concordance, so you can see that for asbestos, beryllium, cadmium, that you can have this lung tumor response in the rats where you can show it, but in the mouse where studies have been conducted you're unable to find a similar kind of response.

DR. KENNEDY: Excuse me. Once again, I may be a bit out of place, but anatomically and histologically the tumors that we see in man that correlate with what I've read in rat is bronchial, alveolar or an adenocarcinoma that occurs peripherally and usually occurs in an area of prior chronic inflammation, it's called a scar cancer, it is seen as the only type of cancer which is not strongly associated with smoking, at least in women, and may well develop from a different mechanism from the tobacco-related lung cancer that we've seen evidently.

DR. GLANTZ: Not being an oncologist, would you go the last step and explain how that relates to the points he's making here?

DR. KENNEDY: I can't do it with asbestos because asbestos raises some very different important issues. Specifically asbestos in the absence of smoking gives you mesotheliomas and not much else. In smokers it gives you cancer everywhere, including the lung.

Many of these other, berylliosis, is again chronic fibrotic process that can be associated with scar cancer.

Again, I think all of this suggests that the mechanism of the cancer in carcinogenesis in the rat in this model, which need not invoke the mutagenic capabilities of hydrocarbons and other components of the vapor phase and non-particulate aspects, may I think suggests at least the real possibility of two mechanisms, and also may be an indication of why you don't see lots of cancer in these patients.

And at the same time may suggest that the smaller particles ultimately may be more dangerous, as you suggested this morning. We may be just beginning to start to see the effect of these particles as a carcinogenic compound as we get better and better at making micro exhaust particles that get further out in the periphery of the lung.

CHAIRMAN FROINES: We've done work over the years in which we take a compound and it reacts to form DNA adducts and presumably would proceed on to produce mutations, but it doesn't do so unless there's cellular toxicity. In other words, you have to start killing cells in the liver before it causes cancer, which is I think a little bit somewhat similar to this.

The interesting thing, though, is what we're finding is that if you -- if you take other compounds that also form DNA adducts and you have these compounds with cellular toxicity, that they start producing cancers as

well. So the issue actually may be a lot more complicated than we're thinking about it.

DR. KENNEDY: I'm sure it is.

And I think if part of the problem of coming up with an animal model, I mean, we've all worked with animal models, it becomes -- by the time you've got something you can work with and control consistently, you know, wittingly or not you've eliminated umpty-ump variables that you may not even recognize as existing and this may be again a bias that of investigation that we simply don't recognize.

CHAIRMAN FROINES: I think there are complicated mechanisms going on here. I'm not trying to suggest there aren't. I think Mauderly's work is right to a degree, but I'm not sure it's a sufficient mechanistic explanation.

DR. SEIBER: I think I'm kind of afraid that I'm running out of gas, I don't know about the other panelists.

But on the rat studies I have kind of a fundamental question when I look at the data in the back of the reports, page 63 and so forth, where you summarized all the -- it appears there's inconsistency in the results or in the rat studies that are cited in the table. Some showed no association, others, like Mauderly's, showed at the very high dose levels.

DR. ALEXEEFF: Right.

DR. SEIBER: Can you comment on the lack of

consistency or is it simply because they're all looking at different levels and maybe some didn't dose high enough to get the term or whatever.

DR. ALEXEEFF: One of the things that probably led Dr. Mauderly to this whole series of investigations is that in the diesel study generally what -- let me go back.

The general cancer studies they would dose the animals and then the animals would be examined after two years. And this -- and that's 24 months, and that would be -- that's the generally-accepted process.

In this case if one does that kind of a study, you generally find no tumors.

So it's the fact that they hold the animals to 30 months, which is still within their life span, but not within previous protocol, where they find the tumors.

So one issue is that it does requires for these rats to develop lung tumors at very prolonged, as well as high level of exposure.

So inconsistency could be the length of the exposure or maybe if one looks at the cumulative dose in terms of hours per day, as well as total dose, that maybe it's not sufficient.

You notice the graph that I showed with Dr. Mauderly's thing was this cumulative dose total and basically weekly -- last weekly set by time, so there's some

accumulation over the week, but these were, I think, were restrained, probably restricted to the longer studies where he's finding these results. He's not -- he's looking at just the long studies. And the same time in our analysis we try to take that into account by looking at this accumulation of soot of the total.

CHAIRMAN FROINES: George, what's your -- I think I'm getting tired too. What is your intent at this point in terms of --

DR. ALEXEEFF: Well,

CHAIRMAN FROINES: How do you want to handle the draft data, or what is to be done or however want to phrase it?

DR. ALEXEEFF: I think we want to incorporate the new information that was submitted to us by Dr. Mauderly in our revisions.

And the options, there's basically three options.

And Dr. Mauderly is really adamant about not making calculations. I'd like to leave it as an option.

But the other possibility is to make calculations, but do not use them in the negative risks.

The third is do as we have done, which is basically leave the calculations in the range of risk, but provide a lot of discussion about the uncertainties.

Our preferred option is to do -- not use the

calculations in the range of risk if there are human calculations that we can use. So our -- and that's actually what we always prefer to use, the human information, if possible. There's always the extrapolation effect. I think Dr. Mauderly has shown that there's some additional considerations that make the extrapolation from the rat to man uncertain, in this case.

So if human information -- if one could come to a conclusion for human -- that there is some human information that's useful in the quantitation, I think that's preferred over the rat data.

CHAIRMAN FROINES: Well, I think you have to make a decision based on what makes mechanistic sense, rather than take -- the epi has to stand on its own, so does the animal somewhat.

DR. ALEXEEFF: Well --

DR. KENNEDY: I mean the exposure differences in the animals are -- it's irrefutable. You're absolutely out of the league of ambient exposure range when you're talking about these animal experiments.

And at least to me, again, and I may be as a neophyte I may be completely out of the ballpark, but those criticisms seem very hard to ignore.

And on the other hand, again, I don't want to get back to issues of policy, I think that the Z factor, the

other mechanism, if you will, whatever else is at work here, is what we don't have a handle on. Ultimately, hopefully, where the risk range and the calculation will come from. It seems really implausible to be able to do it with the animal information understanding what we do about carcinogenesis in most other lung tumors in the human system.

DR. ALEXEEFF: I think one point, it's easy for us to say we'll use some human study out there instead of the animal data, and then don't worry about it, but I think that the table slide actually is an important point that I think ultimately the handles we're going to have to deal with another substance, but because what Dr. Mauderly's work is suggesting is that the rat lung tumor model in general is inappropriate for human cancer risk assessment, not just for diesel exhaust, but for all chemicals.

DR. KENNEDY: Absolutely.

DR. ALEXEEFF: All chemicals, because it's a particular particle thing.

But first of all I don't think it's appropriate for us, on the basis of just looking at this data, to now all of a sudden exclude rat lung tumor data for all chemicals. But at the same time I think we need to look at this issue of across all chemicals, so that we can make a very careful decision to see if we agree that this has occurred.

I think his point, and I've asked him, and he actually said it is his point, that this issue of the rat lung tumor data is for all rat lung tumor carcinogens and not just diesel exhaust.

DR. BYUS: George, I have a comment related to what Dr. Glantz said this morning about challenging the overall assumptions, that we have to -- we can't go back to ground zero. I mean, John, Dr. Froines also mentioned, we don't lose track of the fact that these particles have carcinogens all over them that we know are very potent human carcinogens and it just doesn't have one, it's 40, 50, 60 of them.

In fact, based on both the chemical causing mutation in addition to this sort of, I think more of a promotional proliferation response caused by the presence of a particle, and they both could give you an additive or synergistic thing.

But at these low levels, if you were to take, just calculate -- we were talking about this briefly this morning, if you were to try and figure out how much carcinogen is really there, how many animals would you really need to see an effect? I mean, 100 animals is not an effect, not a large number. I mean, you can have a five percent increase in cancer incidents, five out of a hundred of those animals could be getting an excess cancer. You

wouldn't see in the animal model, but in the human situation it would be a huge cancer risk.

So really the power of the lower dose levels to detect small increases in cancer, even lung cancer, are very low. So, I mean, and that's why you have to go to the higher doses so that you can extrapolate back.

DR. SEIBER: That's why we're doing a thousand times higher.

DR. BYUS: That's right. But when you go up a thousandfold, what happens in this thing, when you go to thousandfold, you really have a different entity there. It's not just now the chemical, it's the chemical plus the particle response is what it seems like to me.

But just because you get the particle response, doesn't diminish the fact that the chemicals are there at the lower doses and in these animal experiments you just can't measure the effect, because there isn't enough there.

CHAIRMAN FROINES: Well, it seems to me that there are sort of two issues, one of which is to say that Joe Mauderly does very good work and appreciate that, and he's a thoughtful person, and his data is indicative of one mechanistic approach.

Then you have another reality which says there are these chemicals in diesel exhaust that we know by themselves cause cancers in humans. That's also true.

And so we have to be careful not to throw the baby out with the bathwater, so to speak. We need an explanation at some level why butadiene or arsenic or nitro PAHs don't cause cancer, as well as saying that there's a particle overload that does. Because if we don't deal with both of them, then in a sense we are -- we're not doing science, we're doing advocacy, we're taking the position that seems to be the most relevant, and I think you have to be careful about it.

DR. KENNEDY: I would propose that you can say it exactly the opposite. You can say that thank God for diesel particles, because they prevent these adducts from getting too far into the lung such that they are producing -- their exposure, your exposure rate gets too high.

I mean, I think that the truth is to where we're talking about the hydrocarbons and diesel and it's nasty stuff and they are terrible molecules, but it's extremely difficult to show, has to this point, been extremely difficult to show their role in carcinogenesis in this system, either whether it be animal or human.

You can't say that about the hydrocarbons in tobacco. They bite you on the nose.

CHAIRMAN FROINES: But I think that's why I asked George and his staff to go through the entire data, because there is evidence to indicate that these compounds are

bioavailable.

Once you know that, then you do have to address the question of their carcinogenicity, because if they were just -- if this was a plastic matrix and these particles were captured in that plastic and they went into a lung, and they went out the lymph system and they went out and were completely cleared, then I would agree with you. I think that happens, for example, in chromium spray paints.

DR. KENNEDY: I'm not saying -- I think the bioavailability data are critically important. They've been raised as part of the criticism of this.

In fact, they should -- you should find them in the secretions or you can find them in the lymphatic system, terrific, because that raises certainly my conviction that this is bad stuff to a higher level.

I haven't been able -- I haven't seen that.

CHAIRMAN FROINES: That's in the document.

DR. SEIBER: I agree with the commenter or what I understood of the comment, and that is we all suspect, we know there are chemicals in diesel, they're in a big table in the back of the reports, and really nasty ones, and therefore we think there's a problem.

But unfortunately the data that we're presented with, such as this rat study, doesn't address that.

And so you can suspect that's the case, and I tend

to share it, but you've got to have some data upon which to base that. And that's why we went back and asked about summing up individual chemicals. We know they're there. We need that data. We just don't have that.

DR. BYUS: What I'm saying --

DR. SEIBER: In the system --

DR. BYUS: The low doses, the reason you don't see -- there's a difference between there not being an effect and not being able to measure the effect. It's two entirely different things. We're not being able to measure the effect because you don't have enough animals to see it.

DR. KENNEDY: No dispute. It is not incumbent upon us to somehow find or help to have generated the data that will demonstrate --

DR. BYUS: In a sense that's true, but for dose extrapolation --

DR. KENNEDY: I'm not talking dose threshold at this point. I'm simply saying --

DR. BYUS: That's Mauderly's point. Mauderly's point is that -- I didn't go to the workshop -- but if you read the transcript, I mean, he says his data essentially is definitive, that there is a threshold. And that is not true. I would take total issue with that.

In order to make that statement, you would have to do probably an animal study of tens of thousands of animals

in order to make that statement. And that's been done, the mega-mouse study used hundreds of thousands of animals.

DR. KENNEDY: For the mechanism that he proposes.

DR. BYUS: That's right.

DR. KENNEDY: He's correct.

CHAIRMAN FROINES: Well, I think that the key question that was raised at the workshop by Paul Blanc was that the -- if one agrees that the rat toxicologic data is not useful for risk assessment purposes, if one buys Joe Mauderly's point of view, he is not saying that that applies to humans, nor should he.

DR. KENNEDY: Neither are we.

CHAIRMAN FROINES: He's saying -- I think it's an important point.

DR. KENNEDY: Absolutely right.

CHAIRMAN FROINES: That the rat is irrelevant to the human.

DR. KENNEDY: You bet.

CHAIRMAN FROINES: Therefore, you can't turn around and argue thresholds and whatever for on humans.

DR. KENNEDY: Without question.

CHAIRMAN FROINES: Let me just read something here that I think is sort of interesting. He says, this is a fellow from Boston University, he argues however a single carcinogen, particularly one as complex as diesel exhaust,

may very well exert multiple effects and operate via several mechanisms. The following hybrid formulation may be closer to the truth than either of the two competing models, that is the overload and the genotoxic. The induction of cancer by diesel exhaust is not rate limited by self-proliferation, but is a function of PAH metabolism, adduct formation, inflammation, and lung cell proliferation.

And, finally, human epidemiologic evidence indicates a much higher incidence of lung cancer among diesel exposed railroad workers than accounted for on the basis of particles alone.

So that I would argue that probably what we're dealing with here with the animals is a lot of uncertainty, but we're probably dealing with a more complex situation than either simple model really can address.

And what it means is that we have to do a lot more research in this area to clarify this, and it may mean that one can't use the animal data for risk assessment purposes.

DR. KENNEDY: I think that's the truth.

DR. GLANTZ: Well, if I can comment here.

I'd rather not get into whether you can or can't use the rat data for risk assessment as a general principle, but my reaction in reading the report was why bother. I mean, I agree with the position that George is recommending. I think that the rat data is interesting, because it tends

to -- it's supportive evidence for the carcinogenicity, but to me to go through all of these interspecies extrapolations and worrying about the particulate loading and all that other stuff, when you've got human epidemiology to base the number on, which is actually a higher number, based on the human epidemiology, why even include the risk assessment based on the rats? I think it just confuses matters, frankly.

DR. KENNEDY: Because the epidemiologic data gives you association, it doesn't give you causality.

DR. GLANTZ: Right. Right. But what I would do with the rat -- no, I'm not saying they should throw the rat data out of the report. I think you want to keep the discussion of the rat studies, because it supports causation.

What I would take out is the quantitative risk assessment based on the rat.

DR. KENNEDY: Absolutely. I agree.

DR. GLANTZ: Whether the rat is a good or bad model for human risk assessment is a whole other argument. I think in the case of this document, you simply don't need it because you've got direct human evidence, so why embroil yourself in that controversy?

But I think you should keep the rat information in there to go to the question of the causation.

I would just take it out of the chapter on risk assessment, because of all the reasons that are being discussed here. I mean, I think you're asking -- it's adding complexity and uncertainties that aren't necessary.

DR. ALEXEEFF: Can I ask a clarification?

DR. GLANTZ: Yes, sir.

DR. ALEXEEFF: So on this scale that I had here, does that mean do not do the calculations?

DR. KENNEDY: A, B, C or D.

DR. ALEXEEFF: Do not use them? I'm just -- I want to make sure I understand.

DR. GLANTZ: I don't think they add anything. I just think it confuses matters.

I would use the rat data. I would use the rat data as evidence of causation and leave it at that.

And I would have a good discussion of a lot of these issues that we've talked about, which in fact the document already has, and just take the stuff from the quantitative risk assessment about rats out. I don't think it adds anything and it confuses matter.

DR. KENNEDY: I would certainly support that.

I can't agree with everything that's been said, but I think your document is much stronger without the attempt to establish association, which is very obviously -- I mean, by your own admission is weak. Just demonstrate it

for what it is and go on with it. I think that it's a better paper and it's closer to the truth.

DR. GLANTZ: Yeah. So, see, George, everything else you've done today has made more work for you, but we just eliminated one thing.

DR. KENNEDY: Which you had already done.

CHAIRMAN FROINES: I just --

DR. BYUS: I sort of go --

CHAIRMAN FROINES: I sort of agree with doing the calculations, but not using them.

DR. BYUS: That's what I think.

There is the outside chance --

DR. ALEXEEFF: How does one decide that --

DR. SEIBER: There's no problem with doing the calculations, as long as you make it clear what they can and can't be used for. I think that's almost --

CHAIRMAN FROINES: Because if all of a sudden, you know, we go out and do the seminal experiment and find that Mauderly was wrong, which clearly is not going to happen so easily, but I mean the point being that it's worth having looked at the issue, but not use them. And give reasons why you're not using them.

DR. GLANTZ: Put in it the appendix in small type.

DR. ALEXEEFF: Okay.

CHAIRMAN FROINES: But I think the important thing

is not whether you do calculations or not. The important thing is the reasons you give for what you do. That's the key issue.

I mean, because other people are going to read this. And OSHA is going to read it, EPA is going to read it. So other people in other agencies are going to want to know what is the position of the State of California on this issue and so that means that you should have it done relatively completely and then address the uncertainties in the way that you think is, you and then we, think is most appropriate.

DR. SEIBER: I have to leave. If I stay a few more minutes I'm going to be here all night, because I have to get to Pleasanton.

CHAIRMAN FROINES: I'm hoping that your move will create a groundswell and that we can all leave.

And my question is, George, Genevieve, panel, does anybody want to pursue --

DR. GLANTZ: I have one other thing and that's the issue of the schedule.

CHAIRMAN FROINES: I think that is what Genevieve coming to do.

I want to say, though, I think this is one of the better -- one of the best discussions we've had on the science of these issues and even though we didn't cover all

the ground I think that we -- it was a very positive, open discussion and hopefully will help resolve these issues as we move along.

And the final thing I want to say, it's clear that the decision of the panel is for the staff of the ARB and OEHHA to move forward with this document and move forward towards producing a document that will be considered as -- will be considering diesel exhaust as a toxic air contaminant. That is the decision we're making.

MS. SHIROMA: Okay. Thank you.

In terms of the schedule, both George and we have discussed revisions that we need to make to the report and that will take a bit of time.

We also then need to provide for one more comment period on those changes, on the revisions that we would make in the report.

So in talking it over with George and Bill, this is mid October. We will likely need -- Stan, don't blanch -- a couple months to incorporate all these revisions and there's a whole list of Part A and Part B and also on the executive summary. And then to provide a comment period.

So essentially we would be coming back to you with a revised report formally submitted to you in the early 1998 time frame. That January-February time frame.

DR. GLANTZ: Now, when you say come back to us, does that mean we'd have the meeting in January, which means the report would go out for public comment in December sometime?

MS. SHIROMA: Yes. That would be the outlook.

DR. GLANTZ: I would hope that the report will come out, go out to public comment in time for us to meet in January with this as an action item, which means that you have to have -- Genevieve, wake up.

MS. SHIROMA: I'm sorry.

DR. GLANTZ: Which means that the report will probably go out for public comment sometime in the middle part of December or beginning, middle of December, to give people adequate time.

I think we want to have one last public comment period, but I don't think we don't want to give people two days. I think you should give them a reasonable length of time, but I'm hoping we can see the thing come to us as a action item in January.

DR. ALEXEEFF: I think --

DR. GLANTZ: There's not that much left to do.

DR. ALEXEEFF: In terms of the workload, I think in terms of the rat data I think that's fairly straightforward as to what we are trying -- we're winding down on that one.

But I think in terms of the cohort, there are still a number of issues resolved -- unresolved, and I don't know if what's more important to work towards their resolution. I mean, it may not be a resolution of some of those issues. It may just be various choices of assumptions.

But so one question is working towards that resolution could take longer or maybe at some point some decision has to be made that, well, these are the issues on both sides of the plain.

DR. GLANTZ: I think, George, that you should aim to have a document out for public comment the first part of December and it should be the best you can make it.

I think in terms of the issues about these epi studies what we have been talking about, that I think you're making good progress in either resolving the issues or outlining them.

And I think another -- you're almost to the saturation point where you're either going to come to a resolution on some of these things or you're just going to have to come forward and say here are the controversies, and the SRP, here's our recommendation, what the SRP should do about them, and we'll take them or not take them.

I think you should be able to get that done to a reasonably good level in time to get something out by

December.

CHAIRMAN FROINES: I think that the important thing, crucial thing, is for George and the ARB to determine what they think is the best range of risk within the limitations of the information, describe the uncertainties associated with that, and then we can move forward.

Again, we don't need to have -- we never have had, if you remember for perchloroethylene, we acknowledged that there were quite significant uncertainties in the risk assessments. And it went through and it went through just fine.

We were -- the law doesn't hold us to a standard of proof that says this is the gold standard and absolute truth. We understand that in this field of science there are uncertainties and the point is that George needs to come in with the best estimate of risk that they can, which is what is required by the law, and then we need to proceed.

DR. GLANTZ: I think we would hope that we be able to meet in January, which means that the report would be out in December, before Christmas, or Hanukkah.

CHAIRMAN FROINES: I think the key -- this is the most important chemical we have dealt with. If we did it in January, that would be good. If we do it in February, that would be fine. And much beyond that, I think we'd be

unhappy.

But I think we need to do the steps properly to hear people's points of view properly and to give George -- he's got quite a bit of work now because both Paul and I are interested in more discussion on the non-respiratory -- on the nonmalignant, non-cancer effects, so that there's another dimension.

MS. SHIROMA: Okay. Bill, do you want to add something to this?

Bill reminded me that by that January-February time frame we expect to be able to provide you with a briefing on the CE CERT data results also. Okay.

So we'll work on that schedule and get the report back out in that early December time frame, provide at least a 30-day comment period and come back to the panel.

DR. GLANTZ: I would say just -- you said at least a 30-day comment period. I think 30 days is okay. The typical comment period when the reports have reached this terminal stage in the past was ten days, if you remember back. So we're talking about three times what had been traditionally used. I think I would hate to see it go over 30 days, because that's reasonable -- it's not unreasonable in lieu of all the complexities, it's not unreasonable to do 30 days. In fact, that's what I had recommend.

CHAIRMAN FROINES: Let me make a point.

I may be wrong, though, the next three months we may see new science, because people are doing experiments around the world, so we may see new science.

But we may also see reevaluation of the existing science and that, I think, one could do within the 30-day period. I don't think that Kenny Crump is -- may have other things to do, but I think he's basically -- they're all using basically the same data sets at this point. Unless something new comes in. If something new comes in and Joe Smith in Japan has just finished a major diesel study, of course things have to change.

DR. GLANTZ: But the Nobel prizes were just given out, so it's unlikely. Next year.

I think that -- I mean, this has been going on almost ten years, and we're getting to the point where I think the marginal value of new information it seems we're -- the curve is saturated.

MS. SHIROMA: And I'd like to emphasize, we would ask for comments on the proposed revisions to the report, because we provided large opportunity to comment on the rest of the report.

DR. GLANTZ: Yes. Here it is.

So, yeah, I would also add -- I mean, people can comment with whatever they want to say. I mean it's --

MS. SHIROMA: Certainly.

DR. GLANTZ: But the -- but I would urge for the record the commenters to try to limit their comments to the new points, because as someone has to read all this stuff and digest it, the more focused on those issues, the more useful it will be in terms of getting a good document.

CHAIRMAN FROINES: But I want to add one other thing in terms of commenters, and that is that there are some people in the scientific community who are at this point relatively neutral on all the scientific issues in this thing.

And I think that we should consider getting -- seeking comments from some of them, on some of the sticky issues.

For example, I would very much like to have Duncan Thomas at USC look at the epi data, both with respect to Garshick and the meta-analysis. I think he would be good.

And I think we should -- we as a panel should be thinking of other people whose judgment, whose reputations are unquestionable, and whose neutrality, objectivity is unquestioned and to see if there's anybody who we could get to give us more comments.

MS. SHIROMA: OEHHA and we can follow up on that.

CHAIRMAN FROINES: Do we want -- and we'll need suggestions from people on this panel.

MS. SHIROMA: Would you like us --

DR. GLANTZ: I move we adjourn.

CHAIRMAN FROINES: We are trying to make a record for the next few months.

DR. GLANTZ: I'm sorry.

CHAIRMAN FROINES: When we're finished, we'll be really finished.

MS. SHIROMA: So other suggestions? We have Dr. Duncan Thomas from USC.

CHAIRMAN FROINES: People have to get names to you.

MS. SHIROMA: Okay. So in fact we'll probably --

CHAIRMAN FROINES: We can always ask Hal Morgenstern and Sandra Greenland at USC, UCLA, to look at this epi work.

DR. FRIEDMAN: Do you want us to do something with these now?

MS. SHIROMA: Bill, calendars?

MR. LOCKETT: Yeah. You can do that after we adjourn. We just need to know your schedule for January, February and March.

CHAIRMAN FROINES: Thank you. We're going to close the meeting.

I appreciate everybody sitting out there, their patience, because it's been a long day. But I think it's

been a very substantive day and I think in that sense we've hopefully accomplished something.

(Thereupon the meeting was adjourned at 3:58 p.m.)

CERTIFICATE OF SHORTHAND REPORTER

I, JANET H. NICOL, a Certified Shorthand Reporter of the State of California, do hereby certify that I am a disinterested person herein; that I reported the foregoing meeting in shorthand writing; that I thereafter caused my shorthand writing to be transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting, or in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 25th day of October 1997.

Janet H. Nicol
Certified Shorthand Reporter
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