SYMPOSIUM:

ESTIMATING PREMATURE DEATHS FROM LONG-TERM EXPOSURE TO PM2.5

STATE OF CALIFORNIA

AIR RESOURCES BOARD

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PROCEEDINGS

AIR RESOURCES BOARD CHAIRPERSON NICHOLS: Good morning, everybody. We've got a great attendance here today and a terrific panel.

My name is Mary Nichols. I'm the Chairman of the California Air Resources Board. We invited you all here today for this symposium, and we're delighted that so many people accepted our invitation.

The purpose of the symposium from the Board's perspective is to have a frank and robust conversation about the science underlying regulatory efforts to deal with long-term exposures to PM2.5. And because this is a topic which has been so extensively covered and written about, we're focusing on the issue of premature death, although we recognize there were many other health effects associated with PM2.5 as well.

I'm going to turn the podium over in a second to our Research Division staff to talk about the logistics of the day. But I did want to let you know that I and several other Board members are here in person and other Board members are going to be here by video or watching the recorded version of this later, because there is great interest on the part of all of my Board members in the outcome of today's discussion.

So with that, once again, thanks. Welcome to

Sacramento, especially those of you who had to struggle through snow storms and other adversities to get here. We really appreciate your willingness to spend this day with us. Thank you.

HEALTH AND EXPOSURE ASSESSMENT BRANCH CHIEF SMITH: Good morning. I'm Linda Smith. I'm going to go over a few of the logistics of the meeting.

First of all, thank you all for attending. We're just very, very happy to see you all here and looking forward to your discussion.

And I'll read the statement. Please look around you now and identify two exits closest to you. In some cases, the exit may be behind you. In the event of a fire alarm, we are required to evacuate the room. Please take your valuables with you. Do not use the elevators. While staff will endeavor to assist you to the nearest exit, you should also know that you may find an exit door by following the ceiling-mounted exit signs. This also goes for our overflow room, by the way, if any of you are in the Byron Sher auditorium.

Evacuees will exit down the stairways possibly to a relocation site across the street. If you cannot use the stairs, you will be directed to a protective vestibule inside the stairwell.

The rest rooms are in the hallway on either side.

And in the Byron Sher, they're outside and to the left and around the corner.

We do have lunch forms for our panel members. And we'd like you to fill them out and enclose payment in the envelope by 10:00. And staff will be coming around to collect the payment.

And one final note, we do encourage the audience to ask questions. We have question cards. And staff will be picking up those question cards around the break period and the lunchtime as well.

It is being webcast. We ask when you speak that your mike is on. On is red, which means it is a hot mike, so it can be turned on and off. And we do have a clock up there, so we'll try to keep to our schedule as best we can.

And with that, I thank you very much and turn it over to the participants. Thank you.

DR. SAMET: Good morning. I'm John Samet from the University of Southern California. And I guess my official title this morning and this afternoon is facilitator. I'm going to try and keep us on track and on schedule and make sure that we have time to engage in a discussion and to answer everyone's questions.

Just as a reminder, I think particularly to those of us sitting around the table, this is a meeting for the

public. And while many of us are used to discussing the matters amongst us in highly technical terms, I think it would be important for us all to remember that we want to be communicating about this issue in a way that will be understood by all. So as you use technical terms, if they're important concepts and they need explanation, do take a moment to make that explanation.

We have a tight timetable, and I think we'll just turn to our first speaker, Dan Greenbaum from the Health Effects Institute who's going to provide a historical perspective on the topic. Dan.

PANEL MEMBER GREENBAUM: Thanks, John. And I see my slide will be there, and I can just move this around. Will I have the cursor as well?

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER GREENBAUM: Well, thank you very much. I'm really glad to be here. I'm looking forward to a set of very interesting discussions among all of us and hopefully providing for the broader audience both here in the room and elsewhere a better understanding of what we do and obviously what we don't know because science by design should be somewhat messy. We always know some things and still need to know more.

I'm going to give you a brief historical

perspective.

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PANEL MEMBER GREENBAUM: So we've known for some time that high levels of exposure to particulate matter and the larger mixture -- we're talking greater than 500 micrograms per cubic meter -- are known to cause premature death. What started a lot of the current debate is in the 1990s some new short-term studies and a couple of long-term studies came forward that were suggesting associations of premature mortality with exposure at much lower levels, lower than 50 micrograms per cubic meter. And my institution, HEI, and others have done a substantial amount of work since then to try and test and extend these short-term and long-term results.

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PANEL MEMBER GREENBAUM: This is not a new problem on one level, although we should be lucky we're not living in 18th century London when this quote was made --

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PANEL MEMBER GREENBAUM: -- or in mid 20th century settings where we had very, very serious high levels of pollution and fairly well determined increases in mortality in the 1930s in the Meuse Valley and 1948 in Pennsylvania and probably best known in 1952 in the

so-called Fog of London.

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PANEL MEMBER GREENBAUM: Those events set off a series of research activities over the last 50 -- really almost 60 years now of varying levels of sophistication, improving levels of monitoring of air pollution, improving statistical analyses, and leading us to the kinds of studies we're going to talk about a lot today.

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PANEL MEMBER GREENBAUM: In the 1990s, we saw first a series of new studies of individual cities tracking daily changes in air pollution with daily changes in health, mortality or other markers of health, like hospitalization. These are so-called time-series studies, and you're going to hear that term a lot during the day.

There was some 40 studies in Europe and the U.S. They showed a relatively consistent small increase in mortality and hospitalizations, something like .5 percent increase to one percent increase for 10 micrograms per cubic meter.

And for those of you that are less familiar with these kinds of graphs, I wanted to spend a second in the first one to illustrate because you're going to see a lot of these during the day. And some of them are going to be vertical and some are going to be horizontal. But the

concept is -- sorry. My mouse is not working.

But the concept is that in this case the vertical line would represent no effect in the particular city being studied. The small dot to the right or left of that line would indicate -- if it's to the right, it would indicate an estimate of an increased association of mortality. And the two lines that back each dot are the 95 percent confidence intervals. So statistically there's a reasonable certainty that these results are within 95 percent of the true result, although that certainly will have questions and issues about that. So this -- we are going to see a lot of these kinds of slides and that's roughly what each one of them will show.

There were significant questions about these studies -- significant questions about the studies. Most notably how were these cities selected and were there some where analyses were done but no results -- no effect was seen, so they didn't get their way into the published literature, so-called publication bias?

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PANEL MEMBER GREENBAUM: One response to that was a set of systemic multi-city studies that were done. The first one was in Europe funded by the European Union called the APHEA study. HEI funded investigators at John Hopkins to conduct the National Morbidity, Mortality, and

Air Pollution Study, or NMMAPS. And then most recently, we actually with joint funding between HEI and the European Union brought together investigators from both of the earlier sets as well as Canadian investigators to conduct what we called the APHENA study. And those results were published late last year.

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PANEL MEMBER GREENBAUM: So NMMAPS, which covered 90 cities in the United States, was originally reported in 2000 about a .4 percent increase per ten micrograms of PM10. These were smaller results than the previous studies suggesting that perhaps there are studies now being included that had been left out of earlier analyses, although overall our Review Committee, intensive peer Review Committee, found enhanced confidence in the results as a result of this.

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PANEL MEMBER GREENBAUM: In 2002, investigators at Hopkins as well as at Health Canada realized that the statistics used in these studies had some serious problems, and that caused a revised set of analyses for over 36 studies that EPA identified and which were suggested to a separate review by an expert panel of the Health Effects Institute. Most of the estimates of effects for these studies actually went down, although our

review panel felt bottom line that the effects were still positive, even when controlling for other pollutants. But revised analyses -- these revised analyses also raised some new questions. And there was a need for continuous improvement. And quickly, to point out --

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PANEL MEMBER GREENBAUM: -- .4 percent was the result in the original NMMAPS. .2 percent vary, but still relatively significant was the result in the new revised one.

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PANEL MEMBER GREENBAUM: One of the things that NMMAPS investigators always did was present the full set, all the 90 cities. What you'll see here is a large number here. Remember that line is now horizontal, but the same kind of concept. A large number of cities -- and those cities are for the most part showing positive estimates of effect. But the 95 percent confidence intervals do in most cases extend below that line, because of the small number of days that were available for each of those days. The most consistent results were actually in southern California and in the northeast, with the northeast having somewhat higher results.

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PANEL MEMBER GREENBAUM: And part of the analysis

showed there were statistically significant pooled results in the industrial midwest.

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PANEL MEMBER GREENBAUM: The other kind of study and what started my role in 1990s was the so-called cohort study. We're going to spend most of our time today on that.

The American Cancer Society study was published first by Dr. Arden Pope and colleagues in 1995. Prior to that, an analysis of the Harvard Six Cities was published in 1993. These are from that. It suggests that risk of premature mortality in Steubenville, Ohio, the most polluted city, were higher -- substantially higher in Portage, Wisconsin, the least polluted city by about 26 percent higher.

These became the basis of every major estimate of benefits during the '95, '96, '97 time frame from supposed potential reductions in particles. These showed higher risks, four to six percent increase in mortality, for ten micrograms than the time-series studies.

In 1996, there was a lot of controversy about these studies, about access to the data. Given there are only two of them, could others get access in order to conduct reanalyses of these.

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PANEL MEMBER GREENBAUM: And HEI was asked by all parties, Congress, EPA, industry, and the original investigators to conduct such a reanalysis. We were given access to the data by the American Cancer Society and Harvard. And there was a lot of key questions.

Were the studies accurately conducted?

Could the studies be replicated?

Would different models, statistical models, and analytic approaches produce different results?

How do different studies control for the individual information we had about each person in the study? Smoking, for example, which we know is an important risk factor.

Were there other systemic city differences between the most and the least polluted city which could result in effects that were independent of whatever air pollution effect there was?

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PANEL MEMBER GREENBAUM: We had an extensive detailed process to deal with this. Our Board appointed an independent expert oversight panel who was charged with competitively selecting a new team. That was a team lead by Dr. Daniel Krewski of the University of Ottawa to identify the relevant questions and to oversee the work.

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PANEL MEMBER GREENBAUM: We then -- and this is true of every HEI study -- had an independent peer review panel, all the same subject matter experts who had had nothing to do with the reanalysis. They basically take apart the results of the first study, see a comprehensive report, and put it back together and prepare a commentary.

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PANEL MEMBER GREENBAUM: And given a wide interest in this, we had an advisory committee made up of key stakeholders, prominent critics, and scientists with relevant skills. I noticed a number of names on this list who are in the room here today. And their job was really to help us make sure that the expert panel make sure they had as much as possible the right questions being asked and thrown at the original studies.

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PANEL MEMBER GREENBAUM: So the audit did extensive random testing of individual data files. The team did detailed duplicate analyses. There were over a dozen different statistical models tried. Nearly 30 individual variables from the original databases were now applied. And there were a number of efforts to try and assess differences between cities, income levels, and a number of other factors that might have influenced the results.

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PANEL MEMBER GREENBAUM: And overall, the reanalysis was able to replicate the original results and to assure the quality of the data. It then tested those results against alternate explanations. And this is just quoting from our review, "without substantially altering the original findings of an association between indicators of particles and mortality."

The reanalyses also identified new interesting areas of education as a modifier of these effects, the potential effects "of SO2 because our Review Committee didn't think SO2 itself was having these effects, but fundamentally found that the studies were reasonably sound."

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PANEL MEMBER GREENBAUM: Subsequent to that -- and we'll hear more about this today -- both Dr. Pope and Dr. Krewski and others did continuing analyses. They extended the follow-up of the mortality in that cohort to more years, 16 years for studies published in 2002 and 2004 and then to 18 years in the most recent HEI follow-up which was published last year and which I know Dan Krewski will go into in some substantial detail. That study was also subjected to detailed review by the HEI Committee.

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PANEL MEMBER GREENBAUM: And very briefly, that study found about a four to six percent increase in nationwide premature mortality for all-cause mortality for ten micrograms per cubic meter, found substantially larger estimates of effect for ischemic heart disease, a form of heart disease that can lead to ischemic cardio or heart attacks.

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PANEL MEMBER GREENBAUM: They did inter-urban analyses in Los Angeles and New York with much, much more refined exposure analyses. Of great interest to us, found substantially higher risk than the national levels in Los Angeles but not of substantially higher risk of ischemic heart disease in New York, causing our panel to suggest that you need to be cautious. Yes, you might find something in Los Angeles as they did, but you shouldn't extrapolate that necessarily to other parts of the country.

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PANEL MEMBER GREENBAUM: So just to briefly wrap up, we've had 20 years of investigation, analysis, reanalysis, and have built confidence in the basic finding of a relationship between PM exposure and premature mortality. Even at these relatively low concentrations have been some additional national cohorts analyzed, the

Medicare cohort, the Veteran's cohort Dr. Lipfert has been working with, the Women's Health Initiative.

Science, of course, has further questions to answer. It always does even as decisions are made. And looking forward, we still need to think of continuous improvement in the epidemiology in the models used, in dealing with the regional variability, in looking for more and younger cohorts, because these cohorts are getting older. And it gets harder and harder to make conclusions as that happens. And we have better mechanistic understanding than we have and we need to improve that further, and we need to systematically look as HEI and others are doing at the toxicity across PM components and sources to better understand that.

Thank you very much.

DR. SAMET: Thank you, Dan.

For those of you that have looked at the agenda, you recognize we're already behind. But I think we have -- I don't want to chew too much into our discussion time, so just ask the next set of speakers, all of whom have too many slides, to remember to try and stick to the time.

So next we're going to move on. Mary Ross from the U.S. EPA who will tell us about the integrated science assessment for particulate matter. Mary.

(Thereupon an overhead presentation was presented as follows.)

MS. ROSS: Thank you. I don't think I have too many slides, but I'll try to be real quick.

The title of mine is Integrated Science Assessment, what I was asked to talk about was EPA's review of the particulate matter science, the U.S. EPA, and the conclusions we've drawn over the past decades.

And so I'll just briefly highlight -- okay. And this is supposed to -- but just briefly highlight what our conclusions most recently and go into a little -- just for the audience, the next slide is the NAAQS process.

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MS. ROSS: And National Ambient Air Quality Standards are set under the Clean Air Act. There is a few slides added to the end -- for people who aren't already familiar with this, there is a few slides added at the end as supplementary material.

But the Clean Air Act requires us to identify common -- many sources ubiquitous to pollutants, and there are six of those. Particulate matter is one of them. We set standards for them. And the Clean Air Act recognizes the science is constantly building and evolving so it requires us to review the standards every five years. As part of that process, we plan.

The Integrated Science Assessment is highlighted in yellow. So that's the part the Office of Research and Development does. And that then supports policy assessments, risk and exposure assessments. Zack Pekar is going to talk more about that later this afternoon.

And then all of this builds to support regulatory decisions about whether the standards are adequately protecting health and the environment. This is an ongoing process. We finish one set of standards as we did for PM in 2006 and we start all over again.

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MS. ROSS: The next slide just briefly highlights what an integrated science assessment is and it began its life as an air quality criteria document. We've changed the name. We've changed the process a little bit in the last few years. The basic pieces of the review of the standards remains the same, the review of the science and the policy and risk assessments, but the integrated science assessment is intended to provide the scientific basis for the review of the standards. It evaluates and integrates evidence from scientific disciplines across the health effects side, toxicology, controlled human exposure, epidemiology, and also ecological and environmental effects.

The integrated science assessment we've recently

completed has conclusions and causal judgments for both health and ecological effects. It includes fine particles, coarse particles, ultra fine particles to the extent possible.

For this one, I note at the bottom for this particular symposium, I'm focusing on the effects of fine particles, but we have conclusions about other types of particles and other types of effects in the integrated science assessment.

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MS. ROSS: Briefly, the next slide shows the causal framework that we have developed in the past few years. We've always drawn causal conclusions, but actually Dr. Samet has been at the front end of driving us to use more consistence, terminology, more of a standard approach to how we draw these conclusions so that we don't use scattershot language, which happens in many cases.

So for all of our reviews now, we determine whether or not we believe there is causal relationship between the pollutant and the health outcome or ecological outcome, and these five categories with causal of course being the highest and not causal at the lowest.

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MS. ROSS: The next slide I won't even read over. It shows an example -- we won't spend any time on it. It

just shows an example of the language that's used for this. So we have some sort of standard language so as we're drawing these, we look to our language to make sure we're building on these and let's not spend any more time on that slide.

Let's move to the next one.

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MS. ROSS: But that's just an example. And all of our integrated science assessments include that table and all of our decisions are drawn in that framework.

This shows just a highlight that this is not new to this review. We've drawn conclusions in previous reviews, including the last two reviews. In 1997 -- stepping back for a minute. There is a slide at the back of the presentation that shows the history of the reviews. We established PM standards in 1971 based on total suspended particulate matter. And we've continued to review those standards as we've gone through.

In 1997, we added a standard for fine particles for PM2.5. At that point, based on the evidence that Mr. Greenbaum just went through, there were quite a few new epidemiological studies. And we usually don't count studies. But in this case, I remember there were only nine studies that measured particles. There was a lot of evidence from toxicological studies of components of fine

particles; little experimental evidence on the mechanisms for particles as to the mixture.

But the basic conclusion at that time was likely causal. So the second down, causal determination of ambient PM, in this case, the determination was made on particles as a whole. The studies range from fine particles to TSP.

In the next review that we just completed a couple years ago, there were hundreds of epidemiological studies. So the body has grown, quite a few using PM2.5 directly, and a greatly expanded body on experimental evidence that shows mode of action of the particles themselves. At that point, we drew a conclusion that was likely causal relationship between PM2.5 and a broad range of effects. Mortality and morbidity sort of grouped together.

So we've drawn these conclusions of essentially likely causal over the last couple of reviews. We haven't actually used our structured nice language, so it's not always consistent in how we characterize it. But we've drawn conclusions that particulate matter is associated with health effects for the past few reviews.

In the current review that we're underway -- if you move to the next one.

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MS. ROSS: We just completed an integrated science assessment last year. The review of the standards is underway and is anticipated we'll have a final decision on whether to retain the current standard or change them in 2011. The integrated science assessment now, the evidence is continuing to build.

Now there are hundreds of ecologic studies, many including PM2.5 and the coarse fraction particles. There is a greatly expanded body of evidence, experimental evidence that indicate mode of action, specifically for cardiovascular effects. And there is a growing body of evidence on the constituents of particles, which is something that is of great interest, the different sources of particles.

And the next two slides summarize the first one is our causal determinations for PM2.5. And in this case, we determined that the relationships were causal for cardiovascular effects and mortality, likely causal for respiratory effects, and it was difficult to determine for central nervous system effects.

So this growing body of evidence has now drawn a conclusion of causal. When I say cardiovascular effects, that includes cardiovascular mortality. There are a lot of studies that look at mortality. Many of them look at mortality all together. But cardiovascular mortality, of

course, is at the most severe end of the spectrum of effects for cardiovascular effects.

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MS. ROSS: So the next slide shows our association for long-term exposures. That was short-term exposures, such as Dan Greenbaum was talking about the studies that look at acute changes. These are long-term exposures. Means exposures over years of your life what kinds of effects does that have. And we again have drawn conclusions that PM2.5 relationship between long-term exposure to PM2.5 and cardiovascular effects, including mortality. And mortality is the broader category. Again is causal, likely causal for respiratory effects and less evidence for reproductive and cancer relationships.

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MS. ROSS: So if you move on to the next slide, a real brief overview of the long-term exposure studies for PM2.5 that are going to be discussed in a lot more detail by Dr. Pope, Dr. Krewski, a whole range of speakers.

But looking over it all, we concluded causal relationships -- there were consistent associations with the mortality in a broad range of studies now. And I highlight the Harvard Six Cities, American Cancer Society, the Women's Health Initiative, the really large cohorts. There are quite a few other cohorts for which associations

have been reported. There's epidemiological association with cardiovascular morbidity, cardiovascular health effects in the Women's Health Study.

There are new animal studies that we didn't have annual studies looking at long-term exposure to fine particles and cardiovascular effects in the previous review, but there are new studies using animals showing things like arthrosclerosis development, changes in vascular-related effects that give plausibility to the relationships you see in the epidemiological studies.

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MS. ROSS: The next slide is one of those figures that Dan Greenbaum explained briefly. This is the associations from long-term exposures, and this broad range of effects includes mortality and cardiovascular effects. You can see the cardiovascular effects on the whole. What we're seeing here is positive associations. That means they're on the right-hand side of the line, not including a null effect. Many of them are statistically significant, meaning they don't cross that central line. So there is a general pattern of positive associations. These are ordered in terms of the air quality. So they're ranging from lower concentrations. So the mean there is presented at 10.7 for the very lowest concentration area and up. So you see a pattern of associations, even in

some of the lowest concentration areas there.

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MS. ROSS: And the next slide briefly recaps the short-term exposures to PM2.5. Again, we determined causal relationships. Here this is based on a pattern of consistent associations and epidemiological studies for a broad range of cardiovascular effects, hospital admissions, and more subtle effects, like heart attacks and also cardiovascular mortality.

Looking across epidemiology, toxicology, and human studies, human experimental studies, you saw myocardial ischemia, which is like heart attacks. Evidence for that in all different types of studies.

There was evidence in the experimental studies for changes in basal motor function, which is consistent with the effects you see in epidemiological studies. I won't belabor these points, because they get into technical details that probably isn't needed. The body of evidence all together in this 2,000-page document that we produced really came together to suggest causal relationships and the Clean Air Scientific Advisory Committee supported that.

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MS. ROSS: I threw in this slide. These often show an example of the types of relationships and the

subtle effects you can see that lead up to those. And the more subtle effects of the oxidated type stress and inflammation are things you can often see in animal studies. This shows the pattern of coherence and plausibility of the underlying potential mechanisms that lead to things like hospital emissions or mortality that you measure in the epidemiological studies.

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MS. ROSS: And the last couple slides focus -- this is on particle constituents. This is something we've been paying more and more attention to. In this document, we focused on studies that looked at source relationships and ambient particulate matter. There's different types of approaches of source apportionment or comparing effects across studies. It was different components and ambient particles.

Overall, the conclusion was many components are linked with various health outcomes. But it's not sufficient to be able to differentiate effects of different constituents on different health effects. It is logical to believe that different constituents could have different effects. Some could be due to irritants effect. Some can be due to inflammation so that you could have different types of particles being more associated with different types of outcomes.

At the bottom I put a couple examples of some hints of the evidence, like cardiovascular effects. And some of the apportionment studies seem to be more related with motor vehicle emissions, and even also road dust related sources. The mortality associations seemed also to be related to combustion sources and sort of a transport source. But these were just real hints. We couldn't draw main conclusions. I think there is something that there's growing attention. There's more and more studies looking into this and this will be a focus of our next review.

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MS. ROSS: Moving almost to the end, another thing we've looked at is the relationship, the shape of the relationship. How does it change? How does the risk change over the concentrations? And there have been quite a number of studies.

I picked this one out of the Women's Health Initiatives that shows the patterns of relationship. Overall, we haven't been able to identify a threshold or place at which health effects stop. It seems like a linear kind of relationship that runs across the distribution of air quality data. This is just one study. I think you're going to see many more of these kinds of slides.

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MS. ROSS: I'll just draw conclusions on the last slide. There is a tremendous body of research. EPA itself is spending billions of dollars funding grants and some intramural research into the effects of fine particles and that's really building and coming to fruition now. There's increasing coherence between the disciplines, between the epidemiological and the animal studies on the types of effects that you see.

We conclude causal relationships now especially for cardiovascular types of effects for fine particles for both long-term and short-term exposures. And there is a growing body of effects that you can see with the different constituents. At the moment, it's really we can't rule any constituent in or out. It seems like all of them seem to have some effect. And we still don't identify a bright line at which health effects begin to occur.

And that concludes it.

DR. SAMET: Thanks, Mary.

I would just point out these documents are available on the EPA website if you want them. This is a very quick tour of a very large document, as Mary suggested.

We're going to move on to our next set of

speakers. Leading off, Arden Pope from Brigham Young University. Arden.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER POPE: Well, thank you. I appreciate the invite to come and share some of this research. Basically what I've been asked to do is give an overview of the PM related mortality studies in 15 minutes. So that's all right.

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PANEL MEMBER POPE: The reality is it's impossible to do. Mary has already discussed this a bit. She showed a little figure. But the reality is that we now know from a huge amount of research, most of which has been reviewed by the EPA -- but others, myself and others, we know that inhaling fine particulate pollution into the lungs results in all sorts of impacts on the lungs outlined by many, many studies.

We also are now beginning to learn that there is a systemic effect. The whole body is affected really by what originated sometimes in the lungs, but essentially as a result of this inhalation of particle pollution. And as a result, we have numerous studies that have looked at the effects of exposure to air pollution on the blood, on the vasculature, on the heart, and even on the brain.

Naturally, we cannot speak about all of this today.

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PANEL MEMBER POPE: But it's already been mentioned, for example, there have been a huge number of daily time-series studies. Dan mentioned this. I won't go through these studies, except for to say that here's another forest plot that Dan has described what we mean.

You can see essentially the percent increase risk in mortality associated with exposure or short-term exposure to particulate pollution is fairly consistent across either meta analyses of many, many studies for these multi-city studies that have been conducted. And now the daily time-series studies really includes studies of over 200 cities, and many of these cities have been studied multiple times. The results are we have small but remarkably consistent associations across the meta analyses.

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PANEL MEMBER POPE: At any rate, I'm trying to make a point. The overall literature is now far too massive to review in any short presentation. So the objective of this presentation is to focus on the most relevant studies to estimate overall mortalities effects. These are the cohort studies of long-term exposure that

have already been mentioned.

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PANEL MEMBER POPE: Now, it's hard to review these studies, even this narrow focused set of studies, these perspective cohort studies in any one slide. But here you can see again as a forest plot you have the various estimate of the studies. You have the 95 percent confidence intervals. What we have here is the percent increase in mortality per ten micrograms per cubic meter of PM2.5 across a whole host of studies. And I've got the results broken out in all-cause mortality, cardiopulmonary, cardiovascular mortalities, and ischemic heart disease mortality. Now, some of these studies are going to be covered in more detail throughout the day, but I want to give a brief overview of what's going on.

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PANEL MEMBER POPE: So first, let's start with the -- would you back up, please?

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PANEL MEMBER POPE: Let's start looking at the Harvard Six Cities Study briefly. It's the maroon colors. We get estimates here, here, here for all-cause cardiopulmonary and cardiovascular disease mortality. The Harvard Six Cities Study --

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PANEL MEMBER POPE: -- was published originally in 1993 in the New England Journal of Medicine. At the time, it was a 14- to 16-year prospective follow-up of just over 8,000 adults living in six U.S. cities. There was monitoring of various pollutants, including PM2.5. The data were analyzed using the most sort of relevant and sophisticated statistical models over the time. These have been proved over the years, but have not changed the results much. We can control for individual difference in age, sex, smoking, body mass index, education, occupational exposure, et cetera.

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PANEL MEMBER POPE: The bottom line is the Six Cities included two relatively clean cities, two relatively dirty cities, two cities sort of in the middle. And over the years as you followed up the cohort, we saw that individuals living in the more polluted cities tended to die more rapidly than those in the cleaner cities. And even after controlling for age, sex, race, cigarette smoking, and various other factors, we continued to see --

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PANEL MEMBER POPE: -- an increased adjusted relative risk associated -- for mortality associated with air pollution. Now, of course the biggest risk factor in this was cigarette smoking. Substantially bigger than for

air pollution. But in the Six City study, we observed there was a statistically significant increase in the risk of mortality associated with fine particulate air pollution as sulfates.

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PANEL MEMBER POPE: As Mary already mentioned, these results tended to suggest a near linear exposure-response relationship.

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PANEL MEMBER POPE: There was a lot of controversy with regards to this study and its sister study, the ACS Study, we'll talk about in just a minute.

As Dan has already mentioned, the Health Effects Institute oversaw a very large reanalyses of the Harvard Six Cities Study and the ACS Study. Dan Krewski who's here, Rick Bernette, Mark Goldberg, and 28 others over a period of about three years reanalyzed these data and, as Dan mentioned, got essentially the same results. There have been now two publications doing extended analyses of the Harvard Six Cities Study.

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PANEL MEMBER POPE: So now if you look at that forest plot I showed at the beginning, you can see the Harvard Six Cities Study gets these results. Basically, about a 15 percent increase in all-cause mortality

associated with ten micrograms per cubic meter, and bigger increases if you focus in on cardiopulmonary inventory or cardiovascular disease. This was a well-designed study that's undergone extensive peer review and reanalysis, and the results are robust and reproducible.

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PANEL MEMBER POPE: Motivated by the Harvard Six Cities Study, we conducted analyses using data from the Cancer Society Cancer Prevention II Cohort. This was data using air pollution data for up to 151 cities and risk factor data for over half a million adults enrolled in this cohort.

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PANEL MEMBER POPE: Again, the results were similar to what we saw in the Harvard Six Cities Study. The biggest risk factor was cigarette smoking. But there was a significant effect of both fine particles and/or sulfur oxide pollution.

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PANEL MEMBER POPE: This study, along with the Harvard Six Cities Study, was reanalyzed as part of the HEI analysis project.

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PANEL MEMBER POPE: We did an extended analyses published in 2002 in the Journal of the American Medical

Association. Again, a number of the people. George is here. Dan is here. I'm here. A number of us that were involved in this study.

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PANEL MEMBER POPE: Bottom line is again we observed this near linear exposure/response relationship between exposure to fine particles and all-cause mortality. But the biggest effect still was with cardiopulmonary mortality.

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PANEL MEMBER POPE: Another reanalysis focusing on the general physiologic pathway of disease or at least trying to get a feel of what's going on. Again, we observed that most of the results were actually being driven by ischemic heart disease and related cardiovascular disease.

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PANEL MEMBER POPE: This study -- I'm sure that Dr. Jerrett is here. He was very involved in this reanalyses at the L.A. area. Interesting for those of you in California. Again, we use the ACS data to look more specifically at --

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PANEL MEMBER POPE: -- metro area, differences in exposure in L.A.

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PANEL MEMBER POPE: And it's already been mentioned, but this more recently HEI funded analyses that was conducted was the most extended follow-up in spacial analysis of the ACS Study.

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PANEL MEMBER POPE: Now the point, of course, here is when you look at the Harvard Six Cities Study and the ACS Study, we're talking decades and decades of work and reanalysis and refining the results. But in the end, these studies -- that Harvard Six Cities and the ACS studies provide robust and reproducible results. You can see the ACS results are somewhat smaller, except for the L.A. area, than the Six Cities study, but qualitatively similar with bigger effects for cardiovascular disease.

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PANEL MEMBER POPE: There is this interesting study or actually a couple of studies done recently I'll refer to as the U.S. Medicare Cohort studies. John Samet is here. He was one of the principals in that -- investigators in that study or both of these studies. Basically what they did is established cohorts of Medicare participants for Six Cities, the same Six Cities as the Harvard Six Cities Study, cities of the ACS Study. And they also had analyses of the entire U.S. stratified by

east, central, and west regions and by age. And they actually got somewhat similar or somewhat larger excess risk estimates for the Six Cities and ACS cities and for the entire U.S. The significant excess risk was not observed for the west region or for the oldest age group.

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PANEL MEMBER POPE: There is a series of studies of California Seventh Day Adventist, often referred to as the AHGMOG studies, again showing the effect estimates here, somewhat larger for cardiopulmonary disease.

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PANEL MEMBER POPE: Fred Lipfert, Dr. Lipfert is here. He's been involved with this Veterans' Administration hypertensive male study. Basically excess risks were most strongly associated with traffic source pollution, primarily traffic density. In single pollutant models, PM2.5 was associated with mortality risk. It was significant for the first follow-up, '89 to '96, but it was not statistically significant. Still positive, but not statistically significant for the second follow-up.

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PANEL MEMBER POPE: James Enstrom is here. I'm sure he'll talk more about this study. This is the eleven California county elderly study, a cohort that was enrolled in 1959. These are just the California part of

the cohort of the American Cancer Society Cancer Prevention I Cohort. They were recontacted in '72. There was an initial follow-up from '73 to '82 and a subsequent follow-up from '83 to '02. And basically what they found is for the initial follow-up there was a significant PM2.5 association right here, but it was not significant for the subsequent follow-up.

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PANEL MEMBER POPE: The Women's Health Initiative Study has been mentioned already. Basically, they focused on cardiovascular events, fatal and non-fatal. And they got large pollution effects on both fatal and non-fatal events as illustrated in the figure.

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PANEL MEMBER POPE: There's a Nurses' Health Study that's recently been reported. Again, they got stronger associations with cardiovascular disease than all-cause.

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PANEL MEMBER POPE: Oslo, Norway, this Intra-Metro Study published. They gave estimates for men and women for two different age groups and found significant excess risk, but they were smaller for the older age group than for the younger age group.

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PANEL MEMBER POPE: A number of other studies have been conducted in Europe and the Netherlands and France and Germany. These have been reviewed by Burt Bruacrev (phonetic) and others. Again, you can see these effects. We just don't have time to talk about them in detail.

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PANEL MEMBER POPE: And then one study that is of particular interest here in California, the California Teachers' Study, Art Ostro. It's not in print yet, but it's published online. It's a cohort of about 45,000 former public -- all female public school professionals followed up from 2003 to '07. And they get exceptionally large associations. And again, they're larger for cardiovascular disease than all others.

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PANEL MEMBER POPE: So that's a quick run through.

How do we decide what's the right answer? Well, first off, it's hard to do that. There's been one attempt, this expert judgment of mortality of the impact of changes. You can see that there are multiple things here, but there are 12 experts as a matter of full disclosure. "J" is me. I know I'm not supposed to tell you that, but now you know.

So bottom line is my view is sort of in the middle of the 12 experts that we had at the time. That was in 2006.

Just so you know where I stand, I actually think based on the California Teachers' Study I probably have a little larger uncertainty on the upper end because these results were so high. I don't know if it pulled my mean up much or not. But here imposed on this sort of summary of all the studies, this is sort of the central estimate of the experts, the low and the high. You can see they kind of pretty well fit the data.

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PANEL MEMBER POPE: So what do we know? Well, the predominant statistical inference from all these studies is that long-term exposure to elevated levels of PM2.5 is associated with elevated risk of mortality. And we're all kind of coming to the same conclusions: The EPA, numerous reviewers, myself included.

Reasonable central estimates of the effect is somewhere between five and 15 percent. But it could be higher, maybe a little bit lower. In general, PM2.5 exposure is more strongly associated with cardiovascular-related mortality. And there is evidence that PM-related excess risks are smaller for older populations and design as cohorts age with longer

follow-up.

Thank you.

DR. SAMET: Thank you, Arden, for that more than fast tour of a lot of information. Nicely summarized.

Next we're going to move on to Dan Krewski from the University of Ottawa. Dan.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER KREWSKI: Thanks very much, John.

It's a pleasure to be here this morning and talk about work that we've done on the American Cancer Society's CPS II cohort extending back to 1998, 2008. That's 12 years we've been following this cohort.

Next slide.

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PANEL MEMBER KREWSKI: Do I do the slides?

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PANEL MEMBER KREWSKI: The objectives of the study were three-fold. Dan Greenbaum has given a very brief overview. But the detailed objectives were to look at an assessment of confounding and modifying effects, ecologic covariate, spacial auto coloration and how they might affect risk estimates. Look at more refined measures of air pollution exposure getting down to the intra-urban scale ZIP codes in particular, and to see if

we can find a critical period of exposure that was most strongly related to mortality or attributable to air pollution.

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PANEL MEMBER KREWSKI: We did have updated air pollution data for fine particles, PM2.5. Our previous analysis had focused on particulate exposure in 1980. So those data correspond to about 20 years later, circa 2000.

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PANEL MEMBER KREWSKI: More cities were included. The main results are shown in this slide.

If you could just touch the button once.

You can see here that PM2.5 is related to all-cause mortality, cardiopulmonary mortality, ischemic heart disease, and lung cancer in this study but not in the previous study, because we had a smaller number of lung cancer cases and not a significantly elevated result. But this was found in this particular study. These are for 1998.

1980 data, if I go one more --

DR. SAMET: Dan, can you take a moment and just explain what a couple of the numbers are for those who may not be -- they're small. And I'm not sure everyone maybe knows what an HR is.

PANEL MEMBER KREWSKI: Let's take a look at the

hazard ratio for all-cause mortality. The first point I was going to make if we look at the data circa 1980, we have about a three percent increase in all-cause mortality for every ten microgram per cubic meter increase in particle loadings. So if you had a 20 microgram per cubic meter linear response, that would give you a six percent increase and so forth.

If we go to the year 2000 where we have more cities, 116 compared to 58, more subjects, almost half a million as compared to 350,000 with the enhanced coverage of cities, the risk estimate is almost the same. And that's pretty much comparable regardless of which cause of death we looked at, that the use of air pollution data in 1980 or 2000 didn't make a huge difference on the estimates of risk. The explanation for that is air pollution is probably declining at somewhat comparable levels, proportionate levels across the country. And this would lead to a relative risk, which is pretty much constant in terms of unit increase in exposure.

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PANEL MEMBER KREWSKI: Some of the results for sulfate particles, you see about a four percent increase in all-cause mortality for five micrograms per cubic meter sulfate particle leading. Similar effect for cardiopulmonary, ischemic heart disease, lung cancer. If

we go to the more contemporaneous exposure data, risk estimates are again comparable.

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PANEL MEMBER KREWSKI: I'll just point out on this slide that ozone did show -- summertime ozone did show an association with all-cause cardiopulmonary and ischemic heart disease mortality. Not quite significant here. So it's mainly cardiopulmonary and all-cause we picked up in this analysis.

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PANEL MEMBER KREWSKI: In this analysis, we wanted to do a careful assessment of the potential for impacts by other variables confounding. And we looked at a whole series of ecologic covariates, the percentage of households that had air conditioning, educational attainment. There is a strong correlation between socioeconomic status as indexed by education and population health -- we wanted to adjust for that -- ethnicity, employment, and/or variables. We had information on these variables right down to the ZIP code level and also at the metropolitan area level. We adjusted for both.

And to make a long story short, these are literally hundreds and hundreds of analyses. We basically found relatively little impact of the ecologic covariates,

if there was any impact tended to increase the risk estimate slightly.

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PANEL MEMBER KREWSKI: We also looked at the possibility that spacial auto correlation could impact upon the results. If we look at two individuals in close proximity in space, they might be impacted by their common environment more than two individuals much further separated. So we actually had a model which looked at spacial auto correlation at the metropolitan area level looking at different metropolitan areas around the country at the ZIP code level and using a random effects Cox model, which is one of the things that our group pioneered in the original reanalyses. We found some evidence of spacial clustering which the effect of increasing the uncertainty in the data as expressed by other increased variants or effects or widened confidence limits on the PM2.5 risk estimates. Widened slightly, not enormously.

Next slide.

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PANEL MEMBER KREWSKI: This was one part of the reanalysis that I was particularly fond of. I thought with detailed information over a 20-year period year by year exposure data, people moving around the country, we'd have lots of variation in individual exposure patterns.

Your temporal exposure pattern going back 10, 20, 30 years and being able to tease it out in the last five years, the last ten years to 25 years ago that is responsible for air pollution related mortality.

When all is said and done, we actually had insufficient inner-individual temporal variation to really identify a clear critical period of exposure. This is still an open question. How long ago in the past is exposure most relevant for mortality related to air pollution?

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PANEL MEMBER KREWSKI: The intra-urban analysis beginning with results in Los Angeles that Mike Jerrett will talk about in more detail with a more accurate measure of exposure by focusing on smaller local areas right down to the ZIP code level as opposed to an entire metropolitan area. You would expect to get more accurate measures of risk, more accurate the exposure measure, the more accurate the risk estimates you'll get.

And in fact, this analysis -- this first analysis shows risk estimates for L.A. that were about three times greater than previous analyses that focused on intra-urban analyses of the type I just described. We replicated these results in New York and found -- did not find

increases in most causes of death, all-cause pulmonary lung cancer. We did find significant effects in increased ischemic heart disease.

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PANEL MEMBER KREWSKI: Looking at the entire ACS cohort versus the cohort members in Los Angeles and New York City, there didn't seem to be any meaningful differences in the attributes of those cohort members. So we can't contribute it to the differences in socioeconomic status vis-a-vis the national study. But the topography and geography between L.A. and New York are quite different. And our thinking is that's probably responsible for the differences in risk that we see between these two large cities.

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PANEL MEMBER KREWSKI: Well, having worked on this for -- I think I calculated 12 years previously, it's kind of nice to sit back and reflect on what have we learned over that decade of research.

I read a paper in the New England Journal of Medicine last year which said, well, when we followed the cohort through to 1989 as part of a reanalysis that Arden Pope had mentioned, we ended up with the following risk estimates for these different causes of death.

So the way to read this is for I think an increase of -- I've cut off the footnote here -- 10 micrograms per cubic meter, we get a 10.8 percent increase in all-cause mortality. Confidence limit going from 2.2 to 7.6 percent. We get a ten percent increase in cardiopulmonary mortality, 12 percent increase in ischemic heart disease, 5 percent increase in lung cancer, not significant in the original analysis because the number of lung cancer deaths was modest. No impact on other causes of mortality.

If we look at Arden Pope's reanalysis, which extended the follow-up period from 1989 through to 1998 and used two different exposure metrics, circa 1980 and circa 2000, we get similar risk estimates regardless of which exposure data set we used. I showed that earlier today. But we also find that original analysis of follow-up through to 1989 roughly comparable to what we got with the extended follow-up through the 1998.

If we look at the most recent results in the report that I was describing in detail, we see again significant findings/risk estimates which are more or also in the same ballpark as we go from follow-up through to 1989, right through to the year 2000. So consistency and reproducibility over a series of analyses with more and more follow up with the cohort as indicated in this slide.

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PANEL MEMBER KREWSKI: The last thing I want to mention -- this is my second to last slide, John -- is a paper that's just come out which a number of us were involved in, which was looking at greenhouse gases. I could want to show in the next slide just one result --

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PANEL MEMBER KREWSKI: -- where we were able to look at elemental carbon as a risk factor for the general population. George Thurston is doing work on a whole series of individual constituents of air pollution that may spread further light on this question.

But of the constituents we looked at, elemental carbon was the most potent in terms of resulting in the greatest increase in risk in all-cause and cardiopulmonary mortality, although there was some sensitivity to the inclusion of other pollutants in the risk model. But if we look at the actual levels of air pollution across the U.S., not just sort of a fixed increase, but the increase in the fifth to 95th percentile, because sulfate is much more prevalent, it actually results in a much larger population health impact in terms of attributable risk due to that exposure. And it's also much more robust with respect to multi-pollutant adjustment.

I think that is my last slide. Thank you.

DR. SAMET: Okay. Thank you, Dan. I assume you're going back to the Olympic curling team.

Just again for those of you who may want to find out more about the analyses, on the Health Effects Institute website, the original analysis, reanalysis report, and then an extended report, the more recent analysis, the Health Institute reports are available. They summarize much of this.

And now move on to Aaron Cohen from the Health Effects Institute.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER COHEN: Hello. Good morning. I want to talk to you this morning about an effort that I've been engaged in now for almost ten years to estimate the Global Burden of Disease attributable to air pollution.

Next slide, please.

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PANEL MEMBER COHEN: This is an ongoing effort. Well, actually, let me step back a second.

The reason I think I'm here is that we have evaluated as part of this effort much of the same evidence that is of interest to the Air Resources Board in their work. And there was some interest in seeing how we had

done it and what we had concluded and made of it.

This Global Burden of Disease comparative risk assessment has been done periodically since the early 1990s under the World Health Organization. The project is now based at a Gates-funded institute at the University of Washington called the Institute for Health Metrics and Evaluation.

The purpose of the Global Burden of Disease project is -- and I go to the last bullet here -- to produce disease, injury, and risk burden estimates for 1990 and 2005. This is the current update I'm going to tell you about, using comparable methods for 21 regions of the world which collectively span the global population. Air pollution is just a small part of this. Air pollution is one of more than 35 risk factors that will be -- whose attributable burdens will be estimated in this project. And the goal is for each of those risk factors to estimate their attributable burdens using comparable methods so at the end of the day the estimates can be roughly compared in terms of their magnitude.

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PANEL MEMBER COHEN: The last time this was done under the egests of WHO was in 2002. It was in the WHO's world health report and the methods for the comparative

risk assessment, including the methods we used for outdoor air pollution, in a separate two-volume collection. The most important message in this slide you have in your packet are the web sites. I would urge you to, if you want to learn more about this, the methodology and the results, please go there. I think you'll find it interesting.

Next slide.

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PANEL MEMBER COHEN: The last time we made these estimates for the year 2000, these are the results. These are the results. And what I'm showing you here on the X axis is mortality -- estimated attributable mortality in thousands. And this is within a total mortality envelope for the world of 55.86 million deaths estimated by the project for the year 2000. And these are the 20 major risk factors and the numbers of deaths that were attributed to them in the year 2000.

And the project that -- you can see that they are a very diverse group and they include at the top end here tobacco, high cholesterol. We have low food and vegetable intake. And then we have among these four I think people would probably agree on environmental factors: Unsafe water, sanitation, hygiene, indoor smoke from solid fuels, urban air pollution, which is the estimate that our group

was charged with making, and lead exposure at the bottom.

And I want to draw your attention for a second to what we estimated for urban air pollution for the year 2000. And this was done using the results of the American Cancer Society Study as reported in the 2002 paper that Arden Pope described to you earlier. We estimated roughly 800,000 deaths on a global scale in the year 2000 attributable to urban outdoor air pollution. This was in estimates made for cities over 100,000.

And the color codes on the bars of interest, most of those deaths were occurring in lower mortality developing countries. That's like China and India. And we can contrast that with some of the results for some of the other environmental factors, unsafe water and indoor smoke, which had much larger attributable mortality burdens assigned to them in this effort. And most of those deaths were taking place in very poor countries.

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PANEL MEMBER COHEN: Now we're now redoing those estimates. I'm going to tell you what we're going to do and how we're planning to use the evidence. We're going to include a lot more people, people in cities less than 100,000 and rural areas. And importantly, we're beginning to be using now what is a much more extensive evidence

base from cohort studies which has been very nicely described by Arden Pope earlier. We're beginning to use a much more extensive evidence base to estimate burden of disease attributable to outdoor air pollution.

Next slide.

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PANEL MEMBER COHEN: A little bit on the GBD process. It begins in the sort of light colored box on the left with a systematic review of the evidence on the health effects of each risk factor. In our case, air pollution. By systematic review, this means essentially applying established methods of meta analysis to ascertain what work has been done and to use that information to decide first whether there is evidence to support a causal association with a particular risk factor and exposure -- in our case, air pollution -- and then to try and use that information to derive a concentration-response function for estimating burden of disease.

And the key thing here is that all the risk factors do it the same. So all of the 35 risk factors, air pollution included, follow a methodology for doing this. And this ensures, we hope at the end, that we can make the kinds of comparisons that I talked about on a couple of slides, a couple of slides ago. And it's designed to try to eliminate special pleading on behalf of

your favorite risk factor. And I think in my experience it's been fairly successful in doing that.

The next step which I put a red box around is very important. This is actually where we are in the process now. And it involves extensive external peer review organized by the project over all of our reviews or systematic reviews and of our proposals for concentration-response functions. And there is a feedback loop from that process.

So the work I'm going to describe to you today is going to be subject to external peer review and may change. I don't think it will change much, but it may change. But that's part of the process and an important part of the process.

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PANEL MEMBER COHEN: This is the outdoor air pollution expert group that is responsible for our work. I co-chair it with Ross Anderson. Quite a number of people involved, in part because there is a whole sub-project involved in estimating what the annual average concentrations are of fine particles around the world, which is very tricky business because in many places there aren't many measurements. I'm not going to talk at length about how we're doing that, but I would be glad to talk

after the meeting with people if they're interested.

Want to site particularly in the work -- I'm going to talk about in the next slide or two of the work of Rick Bernett at Health Canada who's been responsible for developing our approach to concentration-response function estimates for mortality.

Next.

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PANEL MEMBER COHEN: Just a couple of points about what we're doing and in some ways contrasts with what's been done in other impact assessments of air pollution. We're focusing on cause-specific, not all-cause mortality. The reason for that is that the contribution of different causes of death to all natural cause mortality is different around the world. In Africa, for instance, there's high rates of maternal mortality which we don't think is associated with air pollution. So we don't -- and HIV, and we don't want to use an all natural cause mortality result in that setting. So we focus on cause-specific, not all-cause mortality.

We estimate attributable numbers of deaths. We also estimate an entity called disability adjusted life years, which actually takes into account both effects on incidences and effects on mortality. It is the sum of the years that you live with disability due to the disease and

the years of life that you lose due to the disease. And the sum of that is a disability adjusted life year for any particular cause. So we have two metrics of impact of air pollution that we're going to quantify, and one is death which is fairly commonly done and the other is disability adjusted life years.

As I said, I'm not going to talk in detail about how we're estimating exposure. It's a combination of methods based on remote sensing, satellite data, and chemical transport models.

One of the challenges that we face that fortunately you don't is that annual average exposures, level of exposure, and levels of PM around the world are much, much higher than they are unfortunately in the United States. So we have to develop a concentration-response function that deals with annual average concentrations that can be as high as 100 micrograms per cubic meter PM2.5. I won't talk about that, but you should know that's consumed a lot of our effort.

And then finally, we are going to estimate -- we're going to provide our estimates of the overall uncertainty in attributable burden of air pollution. And these will not only include and quantify our uncertainty in the epidemiology we're using, it will also include the

uncertainty in our estimates of exposure as to the best of our ability to quantify that and our uncertainty in the baseline mortality rates to which we are applying them. So this is an important feature of our work.

Next, please.

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PANEL MEMBER COHEN: Well, this graph is very similar to ones that you've seen all morning. On the X axis are the different cohort studies that have been done. These are all natural cause mortality and relative risks for ten microgram per cubic meter PM2.5. That's on the Y axis. And we have beginning at the left the American Cancer Society Study and ending on the right with Dr. Enstrom's work. This is indicative of the studies that we reviewed as part of our systematic review. And we looked at these studies and we looked at other people's reviews as well, reviews that have been conducted by WHO, by Konep (phonetic) in the UK. We reviewed all cohorts of studies of long-term exposure through 2009. And we focused for reasons I told you before on nine cohort studies that looked at the association between long-term PM exposure and mortality.

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DR. SAMET: Roger, hold questions. We're really

tight on time. Go ahead.

PANEL MEMBER COHEN: Now, the first bullet here gives the bottom line of the review that we did. And in view of our expert group, the evidence is most consistent with the causal association or causal effect of long-term exposure on cardiovascular disease and lung cancer.

And specifically how we came to that conclusion is by considering whether the competing explanations that might account for the evidence presented to you today, what are the competing explanations for that other than causality in terms of confounding, the influence of other uncontrolled risk factors or other biases that are endemic in epidemiological research, broad consistency with other related exposures, particularly combustion source air pollution exposures in other than general population settings and evidence for biologic mechanisms. And Mary went through some of that evidence with you earlier.

And in light of that, we concluded that the most reasonable explanation for this evidence is a causal relationship. We concluded that the shape of the concentration-response function at least up to 30 are linear or best treated as linear. And as you can see from this slide, which presents the results for ischemic heart disease mortality, which would be important in our estimates, the relative risk estimates both in terms of

the percent increase in mortality and in terms of the uncertainty around them as reflected in the confidence intervals do vary.

Next, please.

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PANEL MEMBER COHEN: We focused on six out of nine studies that reported risk by selected causes of death that we're most interested in for reasons that I said earlier, and particularly on five studies that used actually measured PM2.5 concentrations as opposed to estimates converted from other PM metrics.

And what this slide is showing is the relationship between the risk estimates, the relative risk estimates for cardiovascular disease, ischemic heart disease, cerebral heart disease, respiratory disease, and mortality and lung cancer mortality from the ACS Study, the most recent follow-up of the ACS Study, and the other studies that provided estimates for the cause-specific outcomes. And we saw a broad consistency here, although the estimates for the American Cancer Society study appear higher for ischemic heart disease.

Next.

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PANEL MEMBER COHEN: So bottom line here: What are we going to do and how are we going to use this in our

burden of disease assessment? We are going to use the results from the most recent follow-up, Krewski 2009 and the American Cancer Society Study, to provide a concentration-response function between about five and 30 for ischemic heart disease, cerebral heart disease, respiratory and lung cancer mortality using the exposures from 1999 through 2000. We looked at several model forms to sort of the exponential model that's given you the Cox proportional hazards regression. This slide shows a comparison between that and linear risk model for ischemic heart disease. They aren't very different. We looked at a few others as well. So our central estimate is going to be from the American Cancer Society study.

Next, please.

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PANEL MEMBER COHEN: We are going to estimate as well uncertainty intervals around that concentration-response function that I gave you. And the uncertainty intervals are not going to be based just on the American Cancer Society; they're going to be based on all the cohort studies that gave estimates for a particular cause of death.

This again is ischemic heart disease. Statistically, this is going to be modeled as a gamut distribution. What that means basically is that in the

opinion of our expert group, we thought that air -- there's no evidence that long-term exposure to particular air pollution reduces your risk of mortality for any specific cause that we're interested in at least, but that there might be no association at all between it. So our uncertainty intervals is going to reflect -- those are going to reflect those assumptions.

And then as I said before, they'll also reflect and try to quantify the uncertainty that comes from our methods of estimating exposure and the uncertainty from the project-wide methods that are going to be used to estimate mortality rates.

Next, please.

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PANEL MEMBER COHEN: So three summary points. In our view, the literature supports a causal interpretation of results of the study of long-term exposure. These studies and specifically the ACS Study that Dan Krewski provided to you we think provides a basis for estimating Global Burden of Disease attributable to outdoor air pollution in combination with the other evidence as I've discussed.

And finally, I'll stress again the fact that our estimates of uncertainty are not going to simply reflect the uncertainty in a concentration-response function from

a particular study, but rather all important sources that we can quantify. So thank you very much.

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PANEL MEMBER COHEN: If you want more information, you can go to this website to learn about the Global Burden of Disease project. And I'd be happy to answer any questions in detail people have.

DR. SAMET: Thank you, Aaron.

Maybe a few quick summary remarks. Just remember, of course, everyone dies. Our chance of dying is 100 percent. What these studies are about is does particulate air pollution lead to some people dying earlier than they would have otherwise?

And the discussion about causation has to do overall with can a conclusion be reached that particles and inhaling particles in the air increase risk of dying? And we heard from EPA about their methods. We heard from Aaron about a set of methods that are being used by this Global Burden of Disease group.

The second question is: If you say, yes, particles are leading to premature death, then how much is that increment? And what you heard about is studies that are used -- Arden provided a review. Dan touched on a number of. And you heard from the speakers about different studies and how they have tried to say, well,

how much is that increase and how much is that increase in relationship to some increment, some increase in the concentration of particles in the air? And conveniently, most people do this for an increment of ten micrograms per cubic meter.

So you saw this question, well, how much is that increment? And what Aaron described, which I think gets to this question of quantifying overall how much extra there is, when the global burden does this, they're saying around the world, how many deaths are accelerated by this? And these are not people who would be immortal if air pollution didn't exist or cigarette smoking didn't exist. It's some advancement and that's what these estimates are about. And you saw some of the statistical machinery that's used to make these calculations sort of laid out in a lot of technical words. But that's what is being done to say how much is this increment.

So we're about 20 minutes behind. If we can try to get back around quarter of, no later than ten of to get started again. Thanks.

(Thereupon a recess was taken.)

DR. SAMET: The next presentation is James Enstrom from UCLA.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER ENSTROM: First of all, I'd like to thank Dr. John G. Tellis for the incredible integrity and courage he showed in the November 19th, 2009, statement that he made to the Board that's led to this symposium.

And I'd like to present a somewhat different approach on this. And my talk is on a broader subject on CARB diesel science from 1998 to 2010. And because I've never personally met most of the scientists in this room, I thought it would be appropriate to give a little background on myself.

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PANEL MEMBER ENSTROM: I received a Ph.D. in elementary particle physics at Stanford University in 1970 --

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PANEL MEMBER ENSTROM: -- from Nobel Laureate Mel Schwartz. It was from Mel I got the great enthusiasm I have for science that's lasted now for 40 years. And in addition, when I changed careers and became an epidemiologist --

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PANEL MEMBER ENSTROM: -- I got incredible training at UCLA from probably the two most renowned epidemiologists at UCLA, Roger Detels and Lester Breslow. And proud of the almost 40-year relationship I've had with

Lester Breslow, who's widely known in California as Mr. Public Health.

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PANEL MEMBER ENSTROM: Because of the research I did in the 1970s, I became a Fellow of the American College of Epidemiology the first year the college was organized. And I have a cert here signed by Abraham Lilienfeld from 1981.

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PANEL MEMBER ENSTROM: I've tried to examine the qualifications of people associated with CARB because of my involvement with the report that has led to this symposium. And unfortunately, I can't find any employees of this organization that really belong to the American College of Epidemiology, the Society for Epidemiological Research, or the American Statistical Association. And I think it's appropriate they should have some epidemiologists and statisticians. I'm not sure if they have a single Ph.D. epidemiologist employed in 1300 employees. I think it's really important that this be kept in mind when evaluating some of the reports that come from the organization.

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PANEL MEMBER ENSTROM: Because of my background in two areas of science, I've sort of ranked the what I

consider levels of science. Physics is a rigorous experimental science with fortunately verifiable results. And since 1901, it's resulted in an annual Nobel Price, most of them for experimental physics, some for theoretical. But that can't be said for chronic disease epidemiology. It's an observational public health science often involves weak and inconsistent relationships that rarely withstand independent verification.

And another level down in my estimation is air pollution epidemiology which suffers from the ecological fallacy which means you're not actually measuring air pollution levels on individual subjects. They're imputed from levels that are generally obtained from monitoring stations that are not necessarily representative of the actual exposure of the individual subject. Also, there is geographic variation in air pollution epidemiology and lack of access to the underlying data.

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PANEL MEMBER ENSTROM: Because of my training, I've become extremely sensitized and always had an extreme interest in ethical conduct and scientific integrity. And I would like to go over three documents that are relevant I believe to the situation at hand.

First of all --

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PANEL MEMBER ENSTROM: -- because I've been at the University of California since 1971, I'd like to point out University of California standards of ethical conduct. And just the middle quote there is, "Members of the University community engaged in research are not to knowingly omit data or results to misrepresent results in the research record." This is also known as a process called falsification.

Next.

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PANEL MEMBER ENSTROM: I was looking for a perfect quote to describe my concerns today. And lo and behold, three weeks ago in a lead editorial in Science Magazine appeared this quote from the president of the U.S. National Academy of Science Ralph Cicerone. "Public opinion has moved toward the view that scientists often try to so present alternative hypotheses and ideas that scientists will withhold data and try to manipulate some aspects of peer review to prevent dissent."

I think this is a very, very troubling statement, and it shows the level at which this concern has gone. When it goes to the president of the National Academy of Sciences, it's pretty much reached the highest levels of science in the United States of America. And I think people have to keep this editorial -- you should read the

entire editorial. And all the statements that are in it are very, very important.

Next.

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PANEL MEMBER ENSTROM: Another aspect directly relevant today is a policy by the Health Effects Institute which applies to studies that we've published, a number of which have been mentioned today. It says, "Access to data underlying studies of the health effects of air pollution is an important element of ensuring credibility, especially when the studies are used in controversial public policy debates. It is the policy of the Health Effects Institute to provide access expeditiously to data for studies that it has funded and to provide that data in a manner that facilitates review and validation of the work."

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PANEL MEMBER ENSTROM: Now, my primary concern today is not the air pollution epidemiology that's been discussed, but how this has been turned into regulations that effect diesel trucks and other diesel engines in the state of California. And so in my research going back on this entire process, I believe it started with something that's known as the Scientific Review Panel on Toxic Air Contaminants.

Next slide.

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PANEL MEMBER ENSTROM: This started with a Legislative Bill AB 1807. It was the Tanner Act of 1983. It set up a nine-member scientific review panel, and the members were to be highly qualified and appointed for a term of three years. And the members were to be nominated by the president of the University of California, and the pool is to include three nominees for each discipline.

Now, it turns out this process has not been followed as I interpret the code sections.

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PANEL MEMBER ENSTROM: The panel has been dominated by three individuals for the entire 26 years that it's existed. And they're toxicologist John Froines of UCLA, statistician Stanton Glantz of U.C. San Francisco, and epidemiologist Gary Friedman of Stanford and Kaiser. And these men have received reappointments, but apparently not with additional nominations by the president of the University of California.

And most troubling to me as an epidemiologist is the fact that Gary Friedman has served on the panel now for 16 years without a formal appointment. It includes the period in 1998 when diesel exhaust was declared a

toxic air contaminant. In doing so, he's prohibited any other epidemiologist, such as myself, from serving on this panel. I don't think this is appropriate. So in my mind, this next document --

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PANEL MEMBER ENSTROM: -- is a very key element of why we're in the situation we are. This is the last appointment letter of Gary Friedman showing his term expired January 1st, 1994. And how this has happened I would really like an explanation, because that's in my mind totally inappropriate. And it is a sign that there really are some things in this agency that really need to be addressed.

Next.

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PANEL MEMBER ENSTROM: The decision to declare diesel exhaust a toxic air contaminant was made April 22nd, 1998. And going back and reviewing the transcript for that meeting reveals that 38 percent of the transcript lines were by John Froines, 19 percent by Stanton Glantz, and only 3 percent by Friedman. And this was mainly a discussion of Epidemiologic discussions on railroad workers and truck drivers. And it's in my mind very unfortunate he wasn't discussing issues like the actual exposure levels of these subjects to diesel. It wasn't

determining the relevance to the California population and wasn't really addressing the criteria for causal relationships as he should have been. And so this is also disturbing to me.

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PANEL MEMBER ENSTROM: What I'd like to do now is to go over evidence. This is switching back to the subject of the symposium today. And it's evidence specific to California that I don't think has been properly addressed. And it's evidence I believe that shows no current relationship between PM2.5 and premature deaths in California.

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PANEL MEMBER ENSTROM: This is a map that's published in the 2000 Krewski HEI report showing PM2.5 concentration levels from the 1980s. Shows the highest concentrations were back east. California's actually at the low end for most of the state, sort of middle range for the L.A. area.

Next.

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PANEL MEMBER ENSTROM: Now, turning this into risk, there's a map, Figure 21 in that publication showing the relationship between PM2.5 and mortality across the nation during the period 1982 to 1989. And this is the

reanalysis of the Pope 1995 study again showing the risk is predominantly in the east. And there's no real excess at least according to the legend in the figure. The risk was actually listed as being below 1.0. So to me it looks like there is a clear geographic variation here.

Next.

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PANEL MEMBER ENSTROM: Now, this geographic variation was presented at an EPA meeting in 2001. This was a public comment sent in by John Heuss, July 11th, 2008, showing the map broken up into four regions of the United States.

In the west region, there is a -9 percent excess risk for PM2.5. And mortality again supporting the notion there's no current effect in California as of -- this would be as of 1982.

Next.

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PANEL MEMBER ENSTROM: My study came out at the end of 2005 using the original CPS I cohort for California subjects. And I found a small effect from '73 to '82, but no risk at all, 1.00, from 1983 to 2002. And so this again is showing no effect in California.

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PANEL MEMBER ENSTROM: Next is a paper published

at the end of 2008 -- actually one online August 12th of 2008 by Professor Zeger and Samet from Johns Hopkins. And it again found no effect in the western part of the United States.

In that study, the western part of the United States was defined as California, Oregon, and Washington state. And this is an extremely large cohort of Medicare enrollees. And shows that there again is geographic variation because they found a substantial effect east of the western United States.

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PANEL MEMBER ENSTROM: The next piece of evidence is the 2009 HEI report by Krewski and others that are in this room, particularly Michael Jerrett and Arden Pope. And what I did here was divide their results into time periods. And it looks to me, if I'm interpreting this correctly, that the major effect is in the 1980s, '82 to '89. And not in the 1990s. If you break it down by decade, and then if you break it down by the last two years that are available, 1999 to 2000 down to an effect of 1.014, and that's not statistically significant.

Now, there are a lot of numbers in that table. These numbers came out of Table 33. But again, I believe the effect is diminished from the 80s to 90s. And since we're now in the 21st century, we need to look at data as

recently as possible, because of these declines.

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PANEL MEMBER ENSTROM: Next bit of evidence comes from my own letter that I submitted to the New England Journal after a paper came out by Professor Pope in January of 2009 showing there's some relationship between declines in PM2.5 and increases in life expectancy in the state of California. And this letter was not published, but it is published as a comment on the CARB website.

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PANEL MEMBER ENSTROM: This leads me to another aspect of this that I think is troubling, and that is points that are not really represented well -- go ahead.

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PANEL MEMBER ENSTROM: The report I don't believe from the 2009 HEI report properly addressed my paper or the Zeger/Samet paper. The risk map is actually missing in this paper. Instead of clarifying the request that I made for geographic variation, there's no map in the 2009 report. And there's no discussion of California-specific results.

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PANEL MEMBER ENSTROM: This is a Table 4 from Pope's paper showing life expectancy increases with declines in PM2.5. Just a week ago, there was a

presentation made by Dr. Stan Young showing if you divide this into the east and the west, you get the eastern portion supports the findings in the Pope paper but the west portion shows the line goes in the other direction. And again, this is something that I think needs to be addressed in fully presenting evidence.

I've got a number of other slides which are part of my presentation. I really don't have time to go through them right now. But I'd like to make some concluding points. I'd like people to look over these points, because they're all critical to assessing the Tran report and so forth. But skip forward several --

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PANEL MEMBER ENSTROM: Keep going.

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PANEL MEMBER ENSTROM: This is about California's actually a very healthy state. If you look at the data from the CDC, you find that it ranks fourth from lowest in total age-adjusted death rate as of 2005. And it's sixth in life expectancy at birth. And this is I think an incredible indication that California is really a very healthy state. And you have to put priorities on all of this. And I think we're doing quite well in terms of our overall health.

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PANEL MEMBER ENSTROM: I'd like to conclude by making recommendations based on my findings.

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PANEL MEMBER ENSTROM: First of all, I think there needs to be an objective reassessment of the relationship between PM2.5 and premature deaths in California with independent reviewers not connected to CARB. They need to assess the relationship of PM2.5 to diesel PM in California and the need for diesel regulations that CARB has implemented, because I'm not seeing the connection.

And then agencies like CARB and HEI need to fund all legitimate researchers, including critics, in order to show a commitment to objective air pollution epidemiology.

And I still believe, as many others have requested, that there be an independent investigation of the reasons why all Board members weren't informed of the fraud regarding the Ph.D. by Dr. Tran.

And thank you very much for allowing me to speak.

DR. SAMET: Thank you.

As a reminder -- so two announcements.

One is for those watching the webcast who cannot view the slides, go to the ARB website on the symposium and you can download the slides.

And questions for the afternoon panel, if you can

leave them at the desk when we take the lunch break, just leave your written questions.

And move on now to Fred Lipfert.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER LIPFERT: Good morning. And thank you. And I wanted to thank CARB for the opportunity to be here and Jim for providing me a slot to deal with the overflow in my afternoon presentation.

Let's have the first slide, please.

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PANEL MEMBER LIPFERT: Let me just say while that's coming up, for those of us from the outside who are essentially without portfolio as I am -- I'm waiting for that slide to come -- not that one.

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PANEL MEMBER LIPFERT: Jim showed you his credentials which are very impressive. Mine, not so much.

I would just have to say I've been doing this stuff for 40 years. I'm probably the oldest guy in the room and maybe the baldest. So why don't we let it go at that. If you really want to know, I can tell you at the break.

Next, please.

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PANEL MEMBER LIPFERT: This slide echoes what Jim had showed. There was no collusion. We did this independently.

But I really want to focus on this end, because this is typical of these age-specific mortalities graphs. They all come together at some point where we're all going to die. What's important for this discussion is that half of all deaths in this age group includes a few of us and has not been studied very much. So when we find things down in here, they may not apply up in there.

Next, please.

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PANEL MEMBER LIPFERT: Now I have some bad news for those of you who are building a career around PM2.5 mass. It's not really a pollutant. It's a collection of substances that really relate to the method in which they were collected. I'm probably one of the few people in this room who's ever held one of these filters in his hand, but they collect all kinds of things. And the problem with that is that you don't know what to control based on what you have found on that filter. There are no sources that emit PM2.5. They only emit constituents. So if we don't study the constituents, you don't know what to control. That's a fact of life, but it hasn't been realized.

Indicators are part of the regulatory process. It was mentioned this morning. The first thing you do is select an indicator. That's all well and good for regulation, and I certainly don't have any problem with the fact they are regulating. The problem is that you can't do epidemiology on indicators because they're all surrogate measures.

And what you learn in the Statistics 102 is when you have a surrogate measure as your independent variable, you can't find the threshold because it's obscured by the air involved between the real stuff and the collection of mass. So it's high time that -- sorry, Aaron, if this affects your global project, but PM2.5 in India is certainly not the same as it is in California. So I'm just not at all sure it makes any sense to keep on using this measure.

Next slide, please.

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PANEL MEMBER LIPFERT: There are essentially three statewide studies of long-term PM2.5 and mortality in California. Now, Michael Jerrett's very interesting study is not included because it's just L.A.

I'm not going to say whose cohort is better than somebody else's cohort. That's not the point. The point is the size. That if you're going to try to make sense

out of all three of these studies, you have to weight by the number of deaths. And the slides that show Six Cities, the Women's Health Study don't take into account of that. So if when one wanted to come up with an overall estimate, you really have to have this number.

The Ostro study was mentioned earlier. I'll have more on that this afternoon. I'm trying to whet your appetite to stay tuned.

Let's go on, please, to slide number 18.

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PANEL MEMBER LIPFERT: And no fair reading ahead. That's it.

Now, the other problem with the kinds of air pollution epidemiology we've all done is that we have to rely on the locations that EPA chooses to take data. And this slide, which is from our 2006 paper on traffic, shows counties that happen to have NO2 measurements on this line. The ones that don't are over here. That's a factor of ten difference in terms of traffic density and in terms of many other pollutants. So we have gone to great pains to try and make studies that do involve all counties. And I'm going to talk about that this afternoon. And I think that's it.

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PANEL MEMBER LIPFERT: The last slide has to do

with whether we really know what the emissions are. There are people, including here in California, who are making on-road measurements of vehicle pollution. And what's being found over and over again is that in 2000 here in Los Angeles almost 70 percent of the total fleet emissions are coming from ten percent of the vehicles.

Now that's a huge problem, and it has to do with smog checking. And I'm not going to go there. I don't know anything about the California regulatory system. But it tells us two things. It tells us we have some low-hanging fruit to pick which are the high emitters and there was some fruit picking going on earlier today on some of the slides. I'm talking about a different kind of fruit picking here.

And furthermore, we don't know what the emissions are. If 70 percent are not from the regulated vehicles from which all the models are based on, we don't know what's out there. We've done studies as if we did, but I'm pointing this out as a major problem in trying to get to the root of the matter.

That's it for now. Stay tuned, and I'll talk to you again this afternoon. Thank you.

DR. SAMET: Thanks. And next to present is Rob Phalen from the University of California Irvine.

(Thereupon an overhead presentation was

presented as follows.)

PANEL MEMBER PHALEN: Thank you. Thank you to the Air Resources Board. I've lived in California a long time, and you all have done a fabulous job in cleaning up the air. And I just want to say thanks. And thanks for holding this meeting.

I was once introduced at a meeting by, "We invited him to cause trouble." I'll try to live up to that.

I do think causing trouble is a good thing. Because without that, we make simple -- we make conclusions that are too simple and not warranted.

So I'd like to comment on seven items.

Where we are in terms of the toxicology understanding of air pollution is what chemistry was before the periodic table. That's pretty bad. We're using, for example, mass as an indicator of hazard. And it would make as much sense to use mass as an indicator of hazard in the air as it would to evaporate water samples and residue and use that as an indicator of hazard for the water samples.

There are probably 30 other properties other than mass proposed as to what's driving the health effects. High on the list are metals such as vanadium. So it might be wise to establish whether or not that's what's driving

health effects or some other properties and then control that, because it will upset the economy a lot less.

The second comment that I have, we're stuck with an antiquated system. The U.S. EPA is a phenomenal organization, really a lot of talented people. But they're stuck with having to use indicators such as mass that are not chemically specific and also to set national standards that have to apply to absolutely everywhere in the United States.

And there's a real problem, especially for us in California, where a lot of PM2.5 is related to our dry climate and dust. Now, we can't control the dust. So if we have to meet an EPA standard for PM2.5, we have to go after things like diesel trucks, because we can't control natural dust. And that does significant economic harm, I believe. And if you really want to hurt people's health, you could put them below the poverty level. That's one of the highest risk categories you can be in the United States.

The next comment is that I'm concerned about the philosophy that we need to go ever lower, lower, lower in terms of our standards or ever more stringent in terms of our standards. I think the microbiologists have taught us if we sterilize everything in the environment, we'll lose our ability to handle microbes in the environment.

And in fact, another way if I wanted to harm all of your respiratory health that I would consider would be putting you in a clean room for about two weeks, because your respiratory tract is not going to maintain its defense for the lifetime of its cells. And some of those are a matter of a few days. So when you would come out of this clean room, you wouldn't be able to handle being near other people, because we shed seven million skin scales per minute into the air.

Another comment -- and I've only got about three more -- is the way we address risks. We address them one at a time. And I think Dr. McClellan has said there is a magnifying glass effect. So when you are looking at one risk and one potential cause, that's the whole world to you. And we don't consider offsetting risks. For example, if you drive up the cost of electricity -- one and a half minutes, John, thank you for the reminder -- people are going to die because they don't have air conditioning. They don't have adequate heat. If you drive up the cost of goods, they're going to die because they don't have adequate nutrition, et cetera.

The National Academy of Sciences was asked by EPA in 2006 to evaluate risk assessment and how it's done today. And among the recommendations, they said you have to look at all the alternatives of a decision, not just

one decision and one end point. You have to look at all of the alternatives and balance them. And most importantly, you have to let the public know what all the alternatives are. You can make a standard tighter. You can make a standard more lax. You cannot change a standard. What are the consequences of those three decisions in terms of also the indirect health effects, the effects caused by the cost of goods and services.

Lastly, I think we've let the public down in terms of public information. And I think us toxicologists have been guilty of that as well. It benefits us personally to have the public be afraid even if these risks are trivial. If I wanted to see heart disease reduced, I'd ask everybody to lose one pound of weight rather than tighten a PM2.5 standard. I think it would do more good and it would upset the economy less. You would also get some benefits in terms of cancer risks.

So we haven't really implemented the National Academy of Sciences philosophy yet, partially because it requires expertise that we don't really have incorporated into our agencies.

So in sum, I believe that from the point of view of a toxicologist for 35 years, who started trying to integrate things over the last ten years, that the science isn't strong enough to do significant regulation of PM2.5.

Thanks very much.

DR. SAMET: Thanks, Bob.

Now moving on to Michael Jerrett from the University of California Berkeley. Mike.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER JERRETT: Thanks very much.

Can I have the next slide, please?

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PANEL MEMBER JERRETT: I'd like to cover three important studies that are California specific. Give you a little bit more flavor for the detail and the rigor that goes into these studies to give you some idea of how much you can trust the results.

The first is the American Cancer Society Study which we heard a number of speakers discuss already. The next is the California Teachers' Cohort, and then finally is the Seventh Day Adventist so-called ASMMOG study from Loma Linda University.

Next, please.

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PANEL MEMBER JERRETT: So for the American Cancer Society Studies, we have two studies I'll present. Both have long-term exposure estimates for California wide and Los Angeles studies. They're both based on the American

Cancer Society Cohort Cancer Prevention II Survey. And one of the real strengths of this study is we have the capacity to control for an extensive array of confounders. So we have 20 individual confounders as well as seven indicators of neighborhood poverty and income. And other things have been widely associated with health outcomes and mortality in the United States.

Next slide.

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PANEL MEMBER JERRETT: This just gives you a list of our smoking variables, 13 in every single model.

Next, please.

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PANEL MEMBER JERRETT: We include educational variable, marital status, body mass index, alcohol consumption which have all been associated with health outcomes.

Next.

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PANEL MEMBER JERRETT: Occupational exposures were extensively assessed by Mark Goldberg and Jack Siemiatycki, two leading occupational epidemiologists, with a dirtiness index based on over 150 options. So we have an indicator variable that measures occupational exposures to particulate matter and carcinogenic risk

potential.

We also have indicators of diet. So fat, fiber, citrus, many of the major food groups that are known to affect health are included in every one of our models.

Next, please.

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PANEL MEMBER JERRETT: The exposure for the Los Angeles study are based on the monitoring of 23 sites. And we developed a land use regression model which essentially uses these sites as a dependant variable and used adjacent land use and traffic and industrial output as predictors.

What we see is a large gradation in air pollution across Los Angeles that follows patterns as to what we might expect: Higher along highway corridors, higher along the ports of Los Angeles and Long Beach, and higher in the inland areas.

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PANEL MEMBER JERRETT: The exposures that we'll be using for the statewide studies are based on a Kriged model, and those are based on a best estimate of our monitoring sites because they're based on two of them available in California. But we want to assign this to many more people. So we need a way to statistically assess the best values between those sites.

I can say from spending months developing this model that it fits the data very well and can reproduce predictions at sites that have a high degree of accuracy. We see a pattern in California that's important for interpretation and while known higher levels in Los Angeles and in the central valley and to some lesser extent in the San Diego region and in the lower levels of central California.

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PANEL MEMBER JERRETT: The L.A. study used ZIP code level data which is what we were permitted to use at that time for nearly 23,000 subjects. For the statewide analysis for the first time, we've actually gone back and bio-coded their home address. So we have a much greater level of precision about where they live. And in both cohorts, we followed them up from 1982 to 2000. And in the statewide we have about 22,000 deaths. So fairly substantial number of deaths to deal with for statistical analysis.

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PANEL MEMBER JERRETT: We used a Cox survival model with allowance for clustering at the ZIP code area. One of the key things about statistics is we're assuming our observations are independent. If they're not independent, they can't trust our significance test. So

we've gone to great lengths to make sure the data are collected for any non-independence by proximity of where people live or different regions of the state.

We conducted analyses to look at clustering at different geographic scales beyond the ZIP code, so we looked at air basins and counties. And we've also included a latitudinal term that measures a north/south gradient to see whether or not there is any residual confounding due to this broader trend of north/south difference in culture and economy.

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PANEL MEMBER JERRETT: We also tested a number of other pollutants in the models and tested them as co-pollutants.

So this is a crowded slide, but I wanted to include it just to show the modeling process we generally go through. We start off with just the PM variable. This is for all causes of mortality. It's a relative risk over ten microgram incremented exposure. And we can see there is about a 20 percent increase that's highly elevated above one statistically significant PM model for all-cause and about a 41 percent increase for ischemic heart disease.

As we start to put in individual level covariates, those are the variables that I talked about

earlier, it takes down the factors we might expect. We put smoking in. Smoking is a determinant of health that may also be associated with air pollution exposure because people of lower socioeconomic status tend to have higher exposures and they smoke more. So we see that goes down.

And then we put in this array of many, many other variables at the neighborhood scale, and we get a fairly stable estimate which comes down to probably our best estimate, which is including six of these variables. And we can see that we've got a 12, nearly 13 percent increase in all-cause mortality and about a 26 percent increase in ischemic heart disease. It's robust to inclusion of different measures of other pollutants as well as the proximity of freeways to the subject's home. So convincing evidence it's not confounded by a wide array of variables that we know can predict death and could associate with air pollution.

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PANEL MEMBER JERRETT: This is from the statewide study and this is against the inner-quartile range of about 8.5 micrograms per cubic meter. These are percent increases in mortality. And we don't see in the statewide assessment an elevation in all-cause mortality in regulation to particulate matter. But we see this pattern that's been observed in numerous other studies that Arden

Pope brought up that cardiopulmonary mortality, cardiovascular, and ischemic heart disease, they all occur.

So as we move from -- also to more plausible biological end points, we see larger effects. And we see an elevated effect for respiratory mortality. But we don't see a lot of examples here, so it's not significantly elevated.

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PANEL MEMBER JERRETT: So we've tested for latitude, county clustering, and ozone as a co-pollutant. And these results stand up. So they are slightly lowered when we include ozone, but significantly elevated. We started wondering why would we see such high elevations in cardiovascular disease but not high elevations in all-cause mortality. Well, if we look at our 22,000 deaths, close to 10,000 of them are coming from cardiovascular disease. But there is another 9,000 from other causes. And the dominant cause in that other grouping is cancer. And what we see is when we take cancer out of the all-cause, we see a risk estimate that's very sum to what Dr. Enstrom got, about four percent increase. And we have to ask what does cancer have to do with it.

Next slide.

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PANEL MEMBER JERRETT: And this is a map. You can think of this as the mortality that we weren't able to predict with our individual level variables like smoking and alcohol consumption. What we see is that after we apply all those individual variables, there isn't much residual variation left in the cancer outcome where we have the most pollution. So our model is predicting these outcomes very well where we have a lot of pollution.

We haven't honed our statistical models to look at cancer outcomes because we've been focused on cardiovascular mortality. I think we probably need -- these are preliminary results. We need to go back and to include things like family history of cancer and other variables to get a better assessment of why we're seeing this negative association with cancer. But we do understand why we're getting a null result for all-cause now, and it's because we see this negative association with all cancers.

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PANEL MEMBER JERRETT: So the next study I'd like to discuss is the California Teachers' Cohort.

I'd like to thank Bart Ostro for sharing his slides with me on this.

It's a statewide cohort -- very impressive

slide -- 133,000 women that were part of the State Teachers' Retirement System. It was established by Leslie Bernstein and others and Peggy Reynolds to look at breast cancer risk factors. But it's been used for many other health outcomes. There's annual re-contact since 1995. There's follow-up to 2005. And there's linkage to hospitalization as well as mortality through statistical databases.

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PANEL MEMBER JERRETT: There is a monthly residential history that is a great strength, so we can see when people are moving and whether that has an impact on their exposure.

There is low active smoking prevalence, highly educated group of women, only five percent at baseline. It's an aging cohort that is experiencing some mortality. And there's little likelihood of significant occupational exposures. There are socioeconomic differences, because they're all teachers.

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PANEL MEMBER JERRETT: This author's examined all-cause cardiopulmonary, ischemic heart disease, and pulmonary mortality.

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PANEL MEMBER JERRETT: And they were particularly

interested in this initial study looking at different species of particles. And we've heard some criticism we shouldn't just look at particles in their aggregate. So they took eight counties where there was speciated data, so data on different types of particulate matter available. And they measure the PM mass but also elemental carbon, sulfates, nitrates, and a variety of other elements that Dr. Ostro found in time-series studies were associated with mortality.

Next, please.

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PANEL MEMBER JERRETT: So the monthly residential histories were bio-coded, and they summed up the long-term exposure by their person months at the pollution sites so they had monthly estimates of pollution. And then they looked at two sizes of rings or buffers around the monitoring sites, eight kilometers and 30 kilometers. Those were designed to simulate the Harvard Six Cities counties, the smaller rings, or the ACS Study to show the average metropolitan area size covers a wide swath of California and a wide variety of exposures.

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PANEL MEMBER JERRETT: In Los Angeles, this is what it would look like. There is the inner ring and the central area of the city, and the larger buffer would

cover most of the Los Angeles County.

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PANEL MEMBER JERRETT: So all of the models were fit with the same type of modeling structure we've been using in all of our studies, Cox proportionate hazards. So we're looking at time of how long someone survives compared to others at the same time and comparing their pollution levels. And what we have included here is basically the same grouping of variables plus some that are particular to women to control for confounding.

Next, please.

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PANEL MEMBER JERRETT: The study -- I'll show you the results. The slide seems to have been omitted. I'm not sure if it didn't come up. There is a summary slide.

Suffice to say they found very large risks in the range of 1.8 hazard ratio for the teachers' cohort for all-cause mortality and going up to about 2.8 for ischemic heart disease. So much larger risks than what we've observed in other studies. And perhaps we can discuss some of the reasons for that later.

Let me go on to the Adventist Study, and I'll focus on the Chen paper, the most recent work.

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PANEL MEMBER JERRETT: And this study had a

smaller sample, but it was non-smoking, non-Hispanic Seventh Day Adventist, so people that would not have the major confounders for smoking in their lifestyles. They had to have lived in the same location for ten years or longer, within five miles of their residence at the time of enrollment. Most came from San Francisco, the South Coast, and the San Diego air basin where there is a 13 percent statewide random sample.

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PANEL MEMBER JERRETT: And PM2.5 in this study was imputed, because it wasn't available historically for eleven air sheds based on the visibility that was available at airports. So there is a long history of trying to impute air pollution exposures from other indicators.

The authors were able to show fairly convincingly they could replicate PM 2.5 values at later time periods by using airport data.

By the time they had followed up to 1998, they had something like 3200 subjects available. So it's a much smaller study. But because it's a non-smokers, I think it's an important study. And they had the vital status for coronary heart disease assessed by death certificates and verified by social contacts through family. They included roughly the same list of

confounders, minus the smoking variables we might have seen in other studies.

Next.

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PANEL MEMBER JERRETT: And what we see is, for women, significantly elevated risk of about 40 percent. So the hazard ratio is a 40 percent increase, significantly elevated, and a negative hazard ratio for males that is statistically insignificant.

Next, please.

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PANEL MEMBER JERRETT: Now sometimes you need a picture to tell many words, and I think this picture summarizes things nicely.

I have the National American Cancer Risk Society Study for risks estimates that are in the so-called Krewski report. So this shows for all causes cardiovascular disease, ischemic heart disease, from my Los Angeles study. Bigger error bars, because we have a smaller sample, but comparable risk estimates. This is the California-wide study. There's slightly smaller overall than what we're seeing in some of the other studies, but significantly elevated for cardiovascular ischemic heart disease and cardiopulmonary not shown here and all-cause, minus cancer.

The event to study, we see this large increase for women but not for men. And then the California Teachers' Study we see a very large increase, nearly tripling of ischemic heart disease death and a near doubling of deaths for all causes.

So if we go back and we think about leading epidemiologists like Rothstein will say, they'll say don't worry about single studies. Don't worry about particular confidence intervals. Look at the pattern and the risks. And the pattern we see here is that for every California-wide study, there is a significantly elevated risk of dying in relation to air pollution.

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PANEL MEMBER JERRETT: So the California-specific study shows association between mortality and PM2.5 that are quite consistent. There's some heterogeneity in the effect sizes, the groups affected, and the causes of death associated with PM2.5, and that's why we need to continue to study this problem, to better understand how we can improve public health.

And, finally, I would say the overall California studies are very consistent with the broader body of evidence presented by Dr. Cohen indicating there are associations between PM2.5 and mortality.

So it's I think comforting to see these

California-specific studies are producing results that are very similar to what we see in the broader body of literature. But I think when we're looking at those responses, we would never want to rely on a small group of studies. We want to rely on the other studies, the national studies, some studies that are coming out of other countries as well.

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PANEL MEMBER JERRETT: I'd like to acknowledge my funders, the Air Resources Board, the Health Effects Institute, and the National Institute of Environment Health Science.

I'd like to thank you for your time today.

DR. SAMET: Well, we're not doing too badly. What I'm going to suggest is that we consider going up to 12:30, which would still leave an hour before lunch for discussion.

Let me just first get a sense from the panel how many of you have comments that you'd like to make? I just want to make sure we get everything fitted in. And looking this way -- okay.

So what I would suggest is that we start at the top and work our way down. I think if there is a particular point that needs follow-up as we move from speaker to speaker, so we can maintain the thread, maybe

we can try to do that, rather than go one by one. So we have some coherence if there's particular things that need follow-up.

So Jim, go ahead and lead off.

PANEL MEMBER ENSTROM: I think that presentation by Professor Jerrett was quite interesting.

I'm a little confused by the way it was summarized because in terms of total deaths, which are what are used to calculate premature deaths by the Air Resources Board, if I didn't misinterpret what he said, there was no effect. Very consistent with my findings. So that would make my study and his study by far the two largest studies in California. And so I'm confused as to why he could say that's consistent with the national result.

Can I get a response to that?

PANEL MEMBER JERRETT: I think we find very significant an elevated risk for cardiopulmonary, cardiovascular, and ischemic heart disease which account for over half the deaths.

So I think what this is suggesting is that there are a number of causes of death which, expectedly so, are not necessarily associated with air pollution. And we have in our previous studies included all causes, all causes of death. So when we look at that, it's even

including traffic accidents and outcomes that we know are not related to air pollution.

Once we go to these more specific indicators from the toxicological evidence, from animal experiments and from human chamber studies, it's highly suggestive of the effects of the cardiorespiratory system, we begin to see highly significant results.

So I would suggest in summary that we see significant effects in California. I think the Los Angeles study as well demonstrates there might be heterogeneities by region in the state, and we see very large effects there for all-cause mortality. And that probably accounts for roughly half the population of the state. So there is ample evidence to suggest consistency between the studies at the national level and the studies in California.

And then if we look at the Teachers' cohort, the risks there are very large and elevated. And although there can always be the chance finding from one study, the strength of that association is one indication of a potentially real effect that's at work between air pollution and mortality.

DR. SAMET: I think just to interject, two comments on this thread.

One is that it is unusual to have an elevation in

cardiovascular disease mortality and not to see that carry through. And it sounds like you're exploring what within the data set may be leading to this overall null finding for total mortality. But I think it does need further exploration and understanding. So it sounds like you're on that track.

PANEL MEMBER JERRETT: We're working very hard on that and have not finished that analysis. And I want to emphasize these are preliminary findings, but I felt we wanted to give the most recent science possible to inform the Air Resources Board.

DR. SAMET: To the same point then --

PANEL MEMBER ENSTROM: If I could just follow-up.

If you include the Zeger and Samet study and you limit it to California, which hasn't been specifically presented, but if that data was presented, then I'd think you'd have the three by far largest studies showing no effect on total mortality in California. So I think that should be addressed fairly quickly, because it's important in terms of the relationship to premature deaths overall.

I'm not questioning any variation in specific causes that you found. But in terms of total mortality which has been used to estimate premature deaths, I think you've got three very large studies now indicating no effect in California.

PANEL MEMBER JERRETT: I think that Dr. Cohen's presentation, which is based on a large group of experts, shows that they have decided not to use total mortality in the burden of illness estimates.

DR. SAMET: I think there's two issues --

PANEL MEMBER JERRETT: I think the focus is on cause-specific mortality, and I think that's something that we need to do when we look at these burden estimates.

But Dr. Samet is right that we need to investigate further why we're seeing these results. I don't think we can generalize anything from the Zeger study at this point until the estimates are made specifically.

DR. SAMET: Well, I think two points we ought to take away for the discussion.

One is total versus cause-specific mortality and what is more important.

And second, and I think this is a point for the Air Resources Board, is whether there should be explicit reliance on evidence generated within the state or how evidence generated within the state is interpreted in the broader context, which is what I think you were alluding to, Mike. And I think those are important points for discussion.

Aaron, to this point?

PANEL MEMBER COHEN: To this point on total versus cause-specific mortality, I'm not sure what is the most appropriate thing for California to take in this regard. But I am sure that for the Global Burden of Disease comparative risk assessment we have to focus on cause-specific mortality for the reasons I gave, which is the aggregate of all natural cause mortality means different things in different places of the world and relates differently to the evidence on the health effects of air pollution in different places. And in general, in the Global Burden of Disease project, for that reason, what's called highly aggregated health end points, like all-natural cause mortality, is to be avoided.

DR. SAMET: Good. I think, Tom, did you have comments?

PANEL MEMBER HESTERBERG: I'm Tom Hesterberg, toxicologist with Navistar, Inc.

The question I had -- I'm a toxicologist. I'm not an epidemiologist. But I have read and there is a publication by Boffetta Paolo, who's the head of epidemiology at the International Agency for Research on Cancer. In that publication, he indicated in these types of ecological studies that it's plausible -- very plausible with all the uncertainties and potential confounders that if you have a relative risk less than 1.5

to this range that could be very well be residual confounding or unknown confounding.

And kind of a follow-up on that and along those lines, I know that the studies that have been presented today have addressed other copollutants. But those are only the copollutants that are measured at the monitoring sites. There are many other copollutants that go up and down with PM that are known toxics and known carcinogens that have not been taken into account. How would you take those into account if they're not being measured?

DR. SAMET: Let me ask, because you raise a number of issues that I know many people around the room have been thinking about. EPA has certainly considered these as well in their document. So would someone like to respond?

Dan, are you shifting forward?

PANEL MEMBER KREWSKI: That's a really important point. And Palo's results do indicate that if you have ecologic variables -- it's a really important point that you're raising about the potential for confounding by the different variables that may be related to air pollution. And if you have ecologic indicators of those variables, which means not at the individual level but for a group of individuals in a common area, the problem becomes even more important.

I think the results that Palo was describing are probably more for when the variables are primarily ecologic. But in the ACS cohort, we have several hundred individual variables: Smoking, diet, BMI, occupation. Those are all for each individual. And the only ecologic covariates are largely the pollution measures and also some of the socioeconomic and demographic variables that we include as extra assurances for avoiding confounding.

In our first reanalysis, we went to great pains. We looked at hundreds of variables. We looked at I think it was 20-plus ecologic covariates. We looked at every pollutant we could get our hands on. We constructed occupational exposure indices, put together whole suites of individual compounds that could be lung carcinogens, respiratory irritants adjusted for everything under the sun.

And by and large, after -- I hate to use the phrase torturing the data that way -- you know, we found that most of those adjustments didn't have a big impact largely because the original data are with our baseline model adjusted for over 40 individual covariates.

So a good point. But because we have a semi-ecologic study with many of the variables being individualized, we can do a much better job for adjusting for residual confounding.

Hope that helps.

DR. SAMET: Suresh.

PANEL MEMBER MOOLGAVKAR: On the same point, I think that's a very good point you made.

And I would point out to you, Dan, that when you looked at your 2000 study that the strongest association was found not with fine PM, not with sulfate, but with sulfur dioxide. And that when you did a joint pollutant analyses, the PM2.5 and the sulfate signal became statistically insignificant and the sulfur dioxide signal remained robust and strong.

And the repeated analysis of the ACS II data both by you and by Arden simply did not acknowledge that fact and did not do any more joint pollutant analyses. And I heard various explanation given for this, namely that sulfur dioxide is a precursor to sulfate and so on. But I don't understand why it would be a better marker for sulfate exposure than sulfate itself.

And so that finding is an embarrassment to the PM mortality hypothesis, but it needs to be explained and has not been explained. And your 2009 HEI report was also criticized I think. One of the critical comments was you didn't try any multi-pollutant analyses in that report. So I think that point really needs to be addressed.

PANEL MEMBER KREWSKI: We haven't yet published

the results yet, Suresh. But one of my graduate students, Roxanne Lewis, did her thesis where what I challenged her to do was take the six criteria air pollutants and say to herself, well, suppose PM2.5 is the primary pollutant. And let's adjust PM2.5 for each of the other five criteria pollutants and go through an exhaustive model building process to bring in all of the other individuals and ecologic covariates. And then I said, let's put that aside. That's chapter one.

And write chapter two, assuming that ozone is the primary pollutant. And then bring in one at a time and then multiply the other copollutants and other variables and sequentially work her way through carbon monoxide and SO2, SOX. And she's done that. And actually I think that's exactly what you're wondering. If you'd like to see those results, they are available in her thesis. We have a draft paper. It's quite an exhaustive analysis. And it's a little too complex for me to summarize here, and I don't have the paper in front of me.

PANEL MEMBER MOOLGAVKAR: Yeah, well, I trust your analyses, Dan.

But by and large, I don't like this trust me science. This is one of the reasons that data on which published peer reviewed publications are based. And specifically those peer reviewed publications are then

used for regulation. Those data should be freely available to all stakeholders. And these data sets have not been made available. That I think is an important consideration.

PANEL MEMBER JERRETT: Could I go back to the sulfur dioxide issue, if I may?

DR. SAMET: Go quickly. I sort of promised Roger the next here.

PANEL MEMBER JERRETT: Basically, we did explain in the reanalysis report that the robustness of the sulfur dioxide effect is probably because it's an indicator of near-source industrial emissions, many of which would be particles with a high sulfur content and that I think when people are in closer proximity has a much tighter range of variation. And it's a much better marker of individual industrial emissions. So it doesn't necessarily discredit the PM hypothesis. It strengthens it and shows a different type of exposure metrics is giving us more robust results.

DR. SAMET: And maybe just as a road map for the public, the discussion here is really about how do we know which of the different pollutants that people are breathing in is the important one. And we use these statistical tools, are they helping us and to what extent helping sort this out.

Roger.

PANEL MEMBER MC CLELLAN: I have some specific comments and I have more general ones.

I want to do the specific, because they relate to the ACS, which let me say I marvel at the richness of the data set, but I find it deplorable, despicable that the ACS limits its use.

Having said that, I no longer make contributions to the ACS because I do not find that acceptable.

I think, Dan, going to your comments about -- I don't know when it becomes ecologic, semi-ecologic.

But I'd like for you to say more about what you said were some of the individual level variables which I think are available only in a portion of the population and are pretty skimpy.

I'd ask people here do you remember how much lettuce you ate in 1980? How about 1990? You take any other variable like that -- do you, in fact, even recall your income in 1980 or 1970? Do you recall your parents' income? All of those are important factors.

But Dan, could you say more about the ACS cohort, which it was assembled not for this purpose at all but fortuitous for us it was assembled for our purposes and carry it forward. Because I think there's a key information in there that sometimes we overstate in terms

of just how strong that data is in terms of smoking, income, place of residence, so on.

So with that as an opening, maybe you can respond.

PANEL MEMBER KREWSKI: Thanks, Roger.

It's probably a good idea to characterize what the ACS cohort was originally set out to do and what types of information was included in the original design. The cohort was enrolled just around 1980, I think between 1979 and 1982 to be precise, over a period of several years. There are over 1.1 million people in the cohort.

The questionnaire for the ACS cohort -- if you were a cohort member, Roger, we could invite you to an interview and ask you all kinds of questions about how much lettuce you ate and those sorts of things that you're imagining.

PANEL MEMBER MC CLELLAN: But it was self enrolled; right?

PANEL MEMBER KREWSKI: Yeah, self selected.

So let me come to the representativeness as a separate issue.

So if you look in the first report we did for HEI in 2000, you'll see the entire questionnaire right there. That's all of the data you have on each of the individuals.

Now, there are some limitations. Smoking data is largely at baseline. There is some data that is gained by follow-up, particularly residents' histories on a sub-cohort of approximately 200,000 individuals where we know the residence in 1980. Follow up in 1990, a decade later, where you lived and every few years through the present time. We have a house that you may have moved into. That's good for getting residents' histories and getting retrospective profiles that might be time-dependent. So that's one strength of that sub-cohort.

PANEL MEMBER MC CLELLAN: There's about 20 percent of the total?

PANEL MEMBER KREWSKI: It's about 200,000 people in round figures out of a total of 1.1 million. So that's roughly what the cohort is designed to do.

There are at least 140 individual covariates that we've been working with. So it's fairly rich in terms of individual data.

Is that enough, just to get the discussion going?

DR. SAMET: Roger, back to the general comment level.

Fred, did you have comments you wanted to make?

PANEL MEMBER LIPFERT: Yeah, Dan, very quick question. Is your student working at the SMSA level?

PANEL MEMBER KREWSKI: I think Roxanne's thesis was based on the SMSA level analysis as opposed to the ZIP code level.

PANEL MEMBER LIPFERT: I strongly urge you to look at the local level. SO2 and CO2 pollutants looking at them or multi counties is doomed to failure right from the beginning. It's a waste of time.

It's amazing given that that SO2 showed as strongly as it did, as Suresh pointed out. In one of my slides this afternoon, I will show you how we have determined that SO2 is highly correlated with elemental carbon when you look at the whole country, and it's likely coming from traffic or perhaps from heating sources. So maybe it's not so strange. The scale is important, number one.

On torturing the data, you haven't Water Boarded it yet. There are two variables I can tell you about, that we have a veterans' study, both of which are highly significant. One is latitude which we represent by degree days. You probably read in the paper about vitamin B being important. That's a latitude phenomenon. So specifically in California with respect to Michael Jerrett's study when you're contrasting northern California with southern California, you need that variable. It's highly important in the veterans.

And the other one I'm not so sure is important, but we threw it in because we had it, is individual height which as you know is a predictor of lung function. That is very important. So we have more torturing to do.

There were two instances today of a veterans' study appearing on a slide, which I'm grateful for. That doesn't happen very often. But it's not appearing correctly. The quote is correct. There is a paper that looked at two periods, 1989 and later, but there are three or four papers that look at the whole period from 1976 to 2001 in which PM2.5 is strongly negative. It's significantly negative in some cases and depends on which data you use.

But in our first paper, we use the same data that Art did, because he got it from me. And so that was a nice comparison. The reason it's negative is because sulfate is negative. And we have been asking ourselves why do our veterans thrive in high sulfate communities in the northeast? Well, they do and I don't know why. But to characterize the veterans' study as supporting PM2.5 as a cause of mortality is incorrect.

Finally, on the question of all causes -- and Michael, I appreciate what you've done. You've shown the ways to a lot of us on many of these analyses.

But I have to disagree with what I perceived as

not being blind to the source of funding. What I heard you say -- and I hope you'll tell me it's wrong -- that when you got a negative result, you said, well, we have to find out what's wrong with this. You didn't say that about the positive result. And that's something that I find inappropriate.

Why would you think finding something negative is more out of line than finding some large positive result? You have to look at everything as carefully as you can.

And when I see results as in the Oster study, which I don't know much about which seems to imply -- and some of yours do, too -- that air pollution is just as harmful as smoking, I have a lot of problems with that.

So those of us that are working with industrial money are acutely aware of this problem. When we find that sulfate result or SO2 result for nickel, we report it, even though some of our funding is coming from people who emit those pollutants.

So I think people who take government money have an equal opportunity and equal responsibility to look at the high spots as well as the low spots.

End of sermon. Thank you.

PANEL MEMBER JERRETT: Well, we look equally hard at negative and positive findings. I didn't mean to infer that because this was negative we weren't going to -- we

were going to give it some extra level of scrutiny.

But it was puzzling to us why when we were seeing causes of death that account for about half of the total deaths having such significantly elevated rates why we would not see that reflected in all-cause mortality. So it had nothing to do with it being a negative result.

I think the fact I've shown it here today even in a preliminary form has suggested I'm going to always present the results I have as honestly as possible. And you're going to get the negative and positive ones as well, regardless of funding source.

PANEL MEMBER LIPFERT: I'm very happy to hear that. But yours is not the only one that's done that. In the literature, there are other examples where all cause is essentially nil and some cause is high, what you hear about is the high cause and what you don't hear about is the negative that's lurking out there somewhere that has to be there to make the all cause come out as low as it does. So we all know that cause of death data is not very good, especially in older people. And I think this is a philosophical point that we all need to wrestle with.

DR. SAMET: Couple of points. Just to put a name on what Fred is talking about, we're well aware of the phenomenon of publication bias, which is the greater likelihood that what is in the literature is both

statistically significant and positive.

I just want to make a comment to maybe Dan who's going to talk at the end. I think one other issue that has surfaced in this suggestion and probably merits some thought by the group is time periods. I mean, we talk about studies that go back into the 70s and 80s. It is 2010, as was pointed out, and we know the air pollution source mixture in the United States and presumably in California has changed.

So I think we've talked about spacial differences and their relevance to interpreting findings elsewhere for California. I think we should talk about time as well and think about to what extent these studies can provide more recent looks at what the risks may be. I think Arden got to that a little bit in some of his studies.

Michael.

PANEL MEMBER LIPSETT: My name is Michael Lipsett. I'm with the California Department of Public Health.

I'm a co-author with Bart Ostro on the California Teachers' Study. And I want to say a little more about this because Bart's analysis in that was a really small sort of sub-analysis just trying to look at which of the components of PM2.5 might be associated with higher estimates of risk. And it was I think from that

standpoint it was meant to be sort of a semi-qualitative look at, well, if you see organic carbon and sulfates showing up more strongly associated with outcomes than, say, some of the other elements, that was the main purpose of that. The larger study is actually under review and journal right now. But I'll tell you about it and what some of the results are.

As Mike Jerrett said, the California Teachers' Study was initiated in 1995. It was a consortium of university and what was at that time part of the California Department of Health Services. The main data center is at USC where Dr. Samet is the chair of the department. And the cohort was established initially to look at breast cancer incidents.

And a number of years ago, Dr. Ostro and I made a proposal to the Steering Committee of this group to try and construct long-term air pollution exposure estimates at the teachers' residences, which have been geocoded. And we developed monthly estimates using pollutant surfaces for the state of California that were generated by staff here at the Air Resources Board I think using inverse distance weighting. So what we had in this is estimates going back really to 1995, except for PM2.5. PM2.5 throughout California was not measured really on a statewide basis until 1999.

Okay. So we have these monthly pollutant estimates, and we have a lot of those individual covariates as they have in the ACS studies. And we've also included neighborhood variables or contextual variables like in the neighborhoods that these teachers live, looking at income, unemployment, this sort of thing. And overall, what we end up with -- and I'm not going to give the detailed results, because I didn't come here intending to make a presentation about this.

But the overall PM2.5 results are very close to those of the Women's Health Initiative. And they're not as high as in the sub-analysis that Bart had published, but they're very consistent with those.

And also wanted to mention the Chen study, too, which is only looking at effects in women. The Women's Health Initiative for our study, which is only women, and the Chen study, which is only women, do tend to be higher.

And to get back to John's point -- I'm sorry to go on so long about this, John -- was that these data that we have for PM2.5 in this analysis go from -- we started the exposure estimates in 1999 going through 2005 and the event follow-up starting in 2000 to 2005. And we ended up with -- but these are monthly estimates. They're not like a lot of these other studies, the Harvard Six Cities Study, the American Cancer Society Study. You're looking

at SMSA, the monitor. You're looking at California's entire monitoring network to develop these estimates.

And the people were limited as to whether they could be included in the analysis depending on the scale designation of the monitor. So say for things like NO2 and CO, they were really narrow areas. They were not included if they lived beyond five kilometers. For PM2.5, it was like 20 kilometers.

DR. SAMET: We'll look forward to the paper. Let's continue with general comments I think.

Roger, we're back to you, I think.

PANEL MEMBER MC CLELLAN: Well, just one bit on that.

In terms of this time period on it, I appreciate the precision and the efforts that are going into that current study. But I think we -- at least my personal view is the disease burden we're talking about has now manifested in terms of -- as one of the individuals noted very late in life. That is a disease burden associated with a lifetime of experience. And so I think it's very important when we look at these indicators as in the ACS Study of exposure for a particular time period we recognize that perhaps we're not even looking at the most significant time period there, that that occurred before they even enrolled in the study, recognizing as I recall

the age of that.

I want to just make a couple of general points. And John's already noted life is risky. And the probability of death for all of us is one for population. The question is not if people die, it's when they die and what they die of or what is associated with death. And I think we need to recognize that that's a pretty soft statistic. When they die is not. But the associated indices in terms of the death are very soft.

In general, individuals and societies value life span. The value then becomes a relative role of the multiple factors that impact life span for individuals and populations. Those that have a negative impact -- and I'm always pleased to see Arden Pope's presentation and see where cigarette smoke fits into that. That gives a benchmark to somebody looking at that data and especially to members of the public. But we also know others in terms of alcohol, being poor. We know those that have positive impacts: Education, income. And then also a host of factors. And quite frankly, I'll say most of the time they're in the noise level. And that's what we're talking about here.

But we as a group tend to put a magnifying glass on and focus on not just air pollution, we're now talking about PM2.5, one constituent within it. I think we do a

disservice to society with that. And the problem we have is, you know, we're talking at a discussion today that's the interface of science and public policy. That's a very uncomfortable piece of turf. Uncomfortable for scientists. They don't want to get too far over into the policy side. It's very uncomfortable for policy makers and politicians. But we need to recognize that's the turf we're talking about. And quite frankly, we need to have a more robust discussion there in terms of my view of emphasizing that science needs to inform these policy and political decisions.

At the end of the day, they are judgments that end up being made by policy makers and politicians. If they're going to make judgments to the public good, they need to see the total landscape, not just looking with the magnification lens on the issue.

So I urge CARB to take a harder look at what it is we're talking about and all the studies in terms of what were the covariates that were examined, whether we want to call them confounders or other risk factors, what were the magnitude of those, both on the positive and on the negative.

I find it interesting when I see a data set analyzed and ozone is way up at the top, but in fact when I see the data set examined later another pollutant is

there. But most importantly, I think we have to start looking at these in a broader context if politicians and policy makers are going to make decisions and going to have a positive impact on the public good.

And I'll admit my views are somewhat emotional and shaded. But quite frankly, today, the most important thing that I see for people is having a job and income.

DR. SAMET: So what office are you running for?

(Laughter)

PANEL MEMBER MC CLELLAN: I recognize that curve in terms of survival, so I've elected to not run for long-term office.

DR. SAMET: There was an appeal that we all turn off cell phones. The mikes are periodically beeping. If you could do that, I just set the example.

Bob, do you have comments?

PANEL MEMBER PHALEN: Probably if I was smart, I'd just yield to Aaron Cohen, but I'd like to just share another piece of information.

If we take the current PM standard and we have a person breathing it at that standard 24 hours a day for 80 years, an autopsy, you would probably find somewhere between two-tenths and two-and-a-half grams of material in the lung. The lung has a surface area of about the same as this room we're in, the floor we're in.

So as a toxicologist, I'm just confounded by some of these positive associations. And you see them over and over in hundreds of studies.

That was the comment I wanted to make.

DR. SAMET: Thanks. I'm just going to keep going around to see for general comments.

PANEL MEMBER MOOLGAVKAR: I see we're almost about to break for lunch, and I do have one general comment. And that is about the use of the Cox proportionate hazards model and the statistical analysis. This has become ubiquitous. Most epidemiologists or all epidemiologists use this model, but I believe that when looking at long-term epidemiological studies, the kind of studies that we are looking at in air pollution studies, basic assumptions of the model often do not hold. They essentially do not hold for potentially strong confounders such as cigarette smoking and possibly for other confounders or potential confounders like BMI.

So I think we need to look for other methods for analysis of data. I don't care whether it's random effect in Cox modeling or whatever. The basic assumptions of the Cox model do not hold.

DR. SAMET: Just going back for a minute to Melanie.

PANEL MEMBER MARTY: Just in response to the

comment about what you see in the lung is not what you've received over your entire lifetime. It's a constant exposure. Not everything is going to sit there and stay there for the rest of your life. So we've heard the same argument about asbestos as well. We don't see that as well. Actually, you see quite a bit. But it's not -- the particles, particle load you see at autopsy is not representative of everything that's gone into your lung, because there's clearance mechanisms.

DR. SAMET: Otherwise, our lungs would fill up. How's that -- to this point?

PANEL MEMBER LIPFERT: I agree with that, and I just wanted to point out that I alluded to earlier that we looked at four separate sub-periods within the Veterans' study, about eight years each. You can't slice it much thinner than that.

And to support what you're saying, if we calculate enough of air pollution deaths in each period and sum them, we get numbers that are different to what you get when you run all 26 years at once, which supports exactly what you're saying.

Now, we also find there are substantial differences by age and that the biggest long-term impacts are in the middle ages.

PANEL MEMBER MOOLGAVKAR: Well, Arden also points

out the difference with age that the risks go down.

PANEL MEMBER LIPSETT: And there are also differences by race. Caucasians are sensitive to different pollutants than African Americans.

And we are finding that -- I had one other point which just left me. I'll let it go at that.

PANEL MEMBER MOOLGAVKAR: Jim Enstrom's findings also support that point of view, because he finds different relative risks in the different periods. But I'm not talking just about the pollution effect. I'm talking also about how you control strong confounders. Just because you put in 25 tons for a confounder doesn't mean that you controlled it adequately.

PANEL MEMBER LIPSETT: There's right. And our original model in the Veterans' study had 206 interactions in it. We had age interactions, body mass, blood pressure, and a few other things. And those terms are significant. So we think we've addressed that concern.

I also have to say that because we were running so many analyses, we ran some short ones and took the interactions out and it didn't make a whole lot of difference. But the time factors do. And the reason they do in my opinion is because all of these variables were measured in entry to the study. And 20 years later, they are different.

The amazing thing that we find if we use AIC as a measure of model, it improves over time. So when we get down to the survivors in 1997, those guys fit the model much better than the earlier ones did. But then they're survivors. So perhaps there's less variation in their personal characteristics. But we have considered that and I wish others had as well.

DR. SAMET: Jim.

PANEL MEMBER ENSTROM: I'd like to amplify on the point that Roger McClellan made and that I pointed out in one of my slides regarding HEI policy, that I really think the time has come for HEI to force the American Cancer Society to produce some type of a redacted data set that is sort of the same model the National Center for Health Statistics uses so this data set can be independently analyzed by as many people that legitimately should be able to analyze it.

And until that day comes, I think people should stop supporting the American Cancer Society. I completely agree with Roger on that point. This is a travesty in my mind, given the importance and the economic consequences that are associated with this database.

Thank you.

DR. SAMET: Could you please address this, Dr. Greenbaum?

PANEL MEMBER GREENBAUM: Sure.

You put up a part of our long-standing policy of providing access to underlying data which actually predates the Shelby amendment which was passed by Congress in the wake of the 1997 air quality decisions.

Two things.

One, it may surprise everybody in the room, but despite that long-standing policy, we have only in the last month received the first request ever for us to provide access to that data, to any data for an HI study. I'd like to think that's partly because our studies are reported in a very comprehensive fashion. But we had not been asked to provide this kind of access for some extended period of time.

Having said that, we treat the issue of data access extremely seriously. We have already replied to the people requesting that data that we intended to pursue whatever means we can to do that. We do not own the data and we don't have statutory power over the American Cancer Society.

And there are -- I would definitely agree with you there are different levels of aggregation of the data that might or might not satisfy different people and might allow for different levels, but might or might not be allowed permission by the Cancer Society. But I don't

disagree that it would be valuable to try to make access to data available, and we're going to be making our best efforts to do that. And we haven't done that before because we had never been asked for the data.

I do have another general comment, but I don't know if you --

DR. SAMET: Just to amplify on one point. Actually, HEI did support distribution of the NMMAPS data through a website. Last time I looked, I think over 20 peer-reviewed publications had resulted from people accessing those data. And even before we did that, we had made data available -- albeit these are national data sets that we had done the work of reducing them -- Dan, continue with your other.

PANEL MEMBER GREENBAUM: That's a good point.

The IHAPS database, which many people have used, obviously has -- did provide the opportunity to do this. And we've actually made data sets available on exposure and other things on the web. So we're very committed to trying to do that.

I will say even that data set, however, has now hit a wall in terms of how it can be updated for mortality, because the National Center for Health Statistics can no longer make that data available without the specific approval of each individual state that

provides the data. And so even investigators who want to get the data from what was a central public source are having more difficulty doing it. We've been working actually with EPA and investigators to gain/regain access to that data for newer years, because it is very affordable to have that.

I wanted to make a broader point following up on a couple of things that were said earlier. And it has to do with the good news and the bad news of whether people in the ACS cohort ate lettuce in 1980. The good news is that actually -- and I don't think you intended this Roger, but it may have been interpreted by those who are less familiar with this -- nobody has been asking now of those people whether they were eating lettuce in 1980, because nobody would suggest that they could remember that. But those questions were asked in 1982. So theoretically people knew what they were eating in 1982 at that time.

The bad news and the challenge for all of us and -- it's a broad challenge -- is 1982 was a long time ago. And you made this point. I think it falls into the category that as these cohorts that we're dealing with age, their utility for doing these kinds of analysis declines. And we've made some of those points in the Medicare analysis, which Scott Zeger and others at

Hopkins, including John Samet, reported. There was no evidence -- an association in the over 85 group. You could interpret some of the further follow-up in the CPS I data that Jim Enstrom did as suggesting that. And it's because we all do die of something eventually.

And even in the most recent ACS analysis, interesting enough, education which seemed to play a very important modifying role in the early reanalysis with six years of follow-up no longer played that kind of role. And that may be also a function of this.

So I think the one point interpretation I wanted to say is we need to be a little careful if we try to say, gee, the most recent follow-up in these cohorts is not showing an effect. So there is no longer an effect. It may be true there is no longer an effect in that population in that cohort, but it's not quite the same thing as saying there's no longer effect in the general population. We can argue over whether there is an effect.

But I think it's important for us -- and I made that point that what it needs going forward is to figure out how to get a younger cohort, because this kind of data can only be tortured, Water Boarded, or whatever for so long before it's not cohesive.

DR. SAMET: Let me just check. How many commenters -- we've heard a lot from the left and on the

right, I just --

(Laughter)

DR. SAMET: On the right, I think Mike and Arden.

So Arden, go ahead.

PANEL MEMBER POPE: Mine's quick. I just want to amplify what Dan said there.

This is critically important. And one of the reasons when I presented the results is try to show what I could where they looked at longer follow-ups and older aged individuals. It's important we understand that as individuals age and as you follow-up the cohort, for a number of reasons -- one is because of susceptibility.

The other is because the baseline risk is right, so the relative risk will be going down or could be.

The other is the reason that Dan has discussed briefly is now we're having more and more exposure measurement as we move away from the time when we actually enrolled them. So this is critically important.

And with regards to cigarette smoking, you see precisely the same thing happening. In fact, the relative risks drop fairly substantially after about 40 or 50 years of age for cigarette smokers. And many of you know this. I know John knows this very well. Suresh knows this very well. The relative risk of smoking drops as you age.

So I just want to make that point, and it's

important to understand that just following the ACS cohort isn't going to be good enough. In fact, we maybe followed them maybe even too much.

The other point I want to make quickly, and that is there have been no hiding of results in these studies. There's no embarrassment about SO2, for example, from the ACS Study. The reason that that is pointed out is because it's very well reported in the reports. In the 2002 JAMA paper, the figures show SO2, SO4. I'll just read very briefly that the results section -- I'll just read the first line of results. "Fine particulate and sulfur oxide related pollution are associated with all-cause lung cancer and cardiopulmonary." There's no question that there's correlation between sulfur oxide pollution and PM2.5. We know that. We report that. And we'll continue to do so.

I will admit right up front I don't fully understand which constituents of these combustion-related pollutants -- which constituents are most responsible for the health effects. We just don't know that yet. But we do know over and over and over again if you analyze cardiopulmonary or cardiovascular disease mortality with these indices of disease-related pollution, you see the effects.

Thanks.

PANEL MEMBER MC CLELLAN: I want to address one point Arden just made, and that is you said relative risk. I think we've implied this -- Suresh implied this, but we've become married to risk. My God, don't we have any other ways to look at this data and present it? I think we've really become so wrapped up in the model that it becomes the message. And we need to be taking a broader view of it.

DR. SAMET: Hold that as a general point. I think Mike and then George and then lunch.

PANEL MEMBER JERRETT: I'll try to be as quick as I can.

I guess first a response to Roger on the issue of why air pollution is important compared to other risks. Air pollution effects everyone in our society. Smoking does not. So very large relative risk on smoking. If the prevalence in California is 13 or 14 percent, may have a lower burden of illness across the population than a smaller risk that effects the entire population.

PANEL MEMBER MC CLELLAN: I fully understand that. One of my parents died of COPD. One died of lung cancer. You probably have no more ardent anti-smoking spokesperson than I am.

You're missing the big picture, Michael. The big picture. I'm not talking about smoking. I'm talking

about all these other risk factors that fit in. And most importantly, income.

PANEL MEMBER JERRETT: With all due respect, Roger, I think nobody has been more comprehensive in looking at relative contribution of all those risk factors in all those air pollution studies than I have. So --

PANEL MEMBER MC CLELLAN: Unfortunately, you don't always report them in your paper. You said, "I analyze for them." Put them out in front so people can see them and understand them.

PANEL MEMBER JERRETT: They're there but --

PANEL MEMBER MC CLELLAN: Talk about how important they are.

PANEL MEMBER JERRETT: I have an important statement that was sent to me by the American Cancer Society. And that is that the American Cancer Society appreciates and fully supports the value and independent analysis, particularly when it comes to issues of public health for which there are political and commercial interests. This is why such examination was undertaken regarding the American Cancer Society's CPS II analysis of air pollution, the most influential study of small particular air pollution, particularly the Pope study.

Because the geographical location is a key component of the analysis, there is no way to de-identify

the data. The geographic address is the key to the analysis. Releasing the data publicly would expose the American Cancer Society to charges of unethical practice. It's hard to imagine an institutional review board that would sanction the release of data in which names and addresses are included.

Instead, in order to remove potential bias from those with special interest, the Health Effects Institute in Boston, an independent nonprofit organization that deals with scientific research on air pollution, was chosen to oversee an independent analysis. The group's solicited applications to reanalyze the Pope, et al, study as well as the Harvard Six Cities Study. The university of Ottawa led by Dan Krewski was selected. The replication project closely examined the data quality and independently replicated the analysis really to the third decimal place in almost every single analysis. It was amazing to be part of that to see the incredible job that was done by Harvard University and by Dr. Pope of Brigham Young.

So there have been a number of publications based on these reanalyses. And I think if we look at federal data standards for the release of micro data, the last time I looked it's in aggregation of 60,000 or more per geographic unit. Many of the metropolitan areas in the

ACS have far less than 1500 people represented. So you would redact probably somewhere on the order of half the data before you even could get access to it.

So my major point is that these are very delicate data that could affect the lives of over a million people. They cannot be released publicly without a great deal of scrutiny and through the proper review processes. And that's for the ACS to decide I think, because they're the ones that have gone to the trouble of collecting the data.

DR. SAMET: So let me just comment that there's certainly many people in the world worrying about sharing of data, access to data, privacy, confidentiality. And I think we'll have to see what happens, where ACS moves.

They're starting a third study that may be very important. And I think these are big broad issues.

George.

PANEL MEMBER THURSTON: Just a quick comment.

Dr. Moolgavkar raised the issue of the Cox proportional hazards model and its fit of smoking as a concern in these analysis. But the biggest effects and the most significant effects we see are no non-smokers where that is really a non-issue.

Thank you.

DR. SAMET: So let me just -- housekeeping for questions. If you have questions, fill out a purple card,

symposium question card, and turn it in at the desk.

Let me ask, for those of you who know the area, for those that need to go out and find lunch, does everybody need a full hour as opposed to -- yeah. Okay. So what about if we try to get back by quarter of 2:00? So that's an hour and five minutes or so and everybody will find a spot to eat. So quarter of 2:00 to reconvene.

(Thereupon a lunch recess was taken.)

AFTERNOON SESSION

DR. SAMET: We are back in session.

So we're now having a set of discussions for which we have lead-off remarks. And what we're going to do is roughly spend 45 minutes or so on each of these. The lead-off discussion, we're supposed to have about five minutes of some introductory comments.

And I think, Arden, do you want to go ahead, please?

PANEL MEMBER POPE: Thanks.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER POPE: I'm not going to spend very much time here. Just to make a couple of points.

I'm sorry. Back up one more time.

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PANEL MEMBER POPE: I've been asked to talk about which studies are appropriate to use to estimate the PM2.5-related mortality associations in California.

And so -- next.

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PANEL MEMBER POPE: I'm going to start with this slide of a study that was done in New York. These are -- this is a study in hyperlipidemic mice. Basically, they exposed half of their mice to normal chow or a normal diet

and they exposed half their mice to a high fat chow diet and then divided up both those halves into mice that got clean filtered air and then those that got PM polluted air. And those were environmentally relevant. In fact, they were about the levels that we get commonly in the valley where I live during inversion during the winter.

And basically what they observed is that the high fat chow diet contributed to the acceleration of these arthrosclerotic lesions, and that was especially true in the PM exposed mice. You saw the PM exposure influenced the normal chow mice and the high fat chow mice. But it is mice, and you might object what does this have to do with California people. It's not even the right species; right?

So go to the next slide.

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PANEL MEMBER POPE: Here's a study that was looking at ischemic heart disease events triggered by short-term exposure to particulate air pollution.

Now we're in the right species. These are humans. We can't sacrifice these folks to look at their coronary arteries, but we can use angiography to look at coronary arteries, do a case cross-over study of acute ischemic events. In this case, in about 13,000 well-defined and followed-up cardiac patients who lived on

Utah's Wasatch Front.

Bottom line -- next slide.

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PANEL MEMBER POPE: In fact, let's go straight to the next one.

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PANEL MEMBER POPE: The bottom line was that there was a significant increased risk of these acute coronary events in this group of patients, but especially in those that already had existing coronary artery disease.

You might say, what does this have to do with California? Well, it's the right species, but we have to move a thousand miles closer.

Next slide.

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PANEL MEMBER POPE: It turns out that you can look at subclinical arteriosclerosis using carotid ultrasound to measure this CIMT. This is a safe non-invasive technique that evaluates the burden of subclinical vascular -- basically arteriosclerotic disease.

Next slide.

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PANEL MEMBER POPE: And then there is some very

interesting study done by Nino Künzli and his colleagues. Basically, what they see is this sort of measure of subclinical arthrosclerosis was associated with increased exposure to PM2.5 in the L.A. area.

Next slide.

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PANEL MEMBER POPE: Of course, in California, there have been a number of really high quality studies have been conducted: Southern California Children's Health Study, a study of the air pollution effects on children's health focused primarily on lung function.

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PANEL MEMBER POPE: But this study shows that deficits in lung function growth amongst children living in cities or communities with different pollution levels. What you see is the deficits. That is, the reductions in lung function growth is higher in those cities where the children are exposed to more air pollution.

Next slide.

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PANEL MEMBER POPE: Another study -- this is just using basically the same panels of children. But instead of looking across communities with higher pollution, they're looking at children that are exposed to traffic pollution primarily based on distance to freeway. And

again, deficits in lung function growth are observed for those children that are exposed to more air pollution by living near the roads.

Next slide.

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PANEL MEMBER POPE: Now, this goes back to what I was showing earlier this morning. We have now a whole bunch of studies looking at mortality and long-term exposure. These are the results often emphasized by James Enstrom which are unquestionably some of the lowest results that we see across these studies. They are California specific.

Then we have -- there's the California Teachers' Study, unquestionably amongst the highest that we see in terms of effect estimates. I'm not -- you know, I guess I don't actually emphasize either one of them. I think they give us some evidence as to what range of results you get from some reasonable efforts to analyze data in California.

Next slide, please.

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PANEL MEMBER POPE: There have been a whole bunch of effect estimates from the California. So basically of these estimates that I showed earlier this morning, these are the published estimates using California-based data.

Michael's already done a nice job of talking more about the details of these studies.

Next slide.

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PANEL MEMBER POPE: So where do I come down in terms of what study should we use? I guess the question are hyperlipic mice in California less susceptible than those in New York? Probably not.

Are Californians' children's lungs and adult cardiovascular systems less susceptible to fine particular pollution than those elsewhere? The answer is probably not.

Is pollution from California cars, trucks, and other sources less toxic to humans than elsewhere? It's not as clear, but probably not.

I mean, the sources of fuel, the types of automobiles and trucks that we use in California are similar to those elsewhere.

Which health studies are relevant to California? Well, it's clear that some of the highest quality research on the health effects of air pollution has been conducted right here in California. And the results are roughly similar to those from elsewhere.

Again, we don't have time to talk about all the toxicology that's been done here, the panel studies done

here. But the reality is if you look at the overall evidence with regards to California studies relative to other studies, it's just makes you think that the hyperlipidemic mice here, the children here, the cars and trucks here are not that much different than those elsewhere.

So it's evident to me at least that well conducted epidemiological, clinical, and toxicological studies conducted both in California and elsewhere are relevant.

Thanks.

DR. SAMET: Thanks, Arden.

And Fred, you're up.

PANEL MEMBER LIPFERT: Hello, again.

And as I was saying this morning -- we don't have the slide, okay.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER LIPFERT: As I was saying, these are the data from the EHP study on the California teachers. And what I'm going to talk about this afternoon is how do we know which pollutant is real and which are not, which is a very tough question and not all studies even ask that question.

So first of all, you have to put all the

pollutants on a common basis, which means you can't use ten micrograms or ten PP. We calculated the risk on the basis of a mean concentration. And what I've done here is plotted the risk for the mean concentration against the pollutants correlation with OC.

Now, someone a lot smarter than me once said that all epidemiology results are due to chance, bias, or cause. It's got to be one of the three. So if we assume that OC is cause, then since all of these species have risks lower than they would have gotten just due to their correlation with OC, all of these are chance. Now, this is just one way to look at it.

The hypothesis is, for example, PM2.5, the hypothesis is PM2.5 risk is coming solely because it's correlated with OC, which is the real bad guy. Now you can accept this or not, but I don't know of another way to do it.

I'm going to come back to that in a minute. Let's go on and talk about what's collated with what.

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PANEL MEMBER LIPFERT: These are -- in this Veterans' study which was published last year, we calculated concentrations -- we had other people calculate concentrations for both these species and air toxics for every county in the U.S. They're based on emissions and

some very fancy dispersion modeling. It was not cheap. I know, because I paid for it.

And what we've plotted here are the relationship among these four pollutants -- five pollutants against elemental carbon, which is diesel. What we find is SO2 and SOX are highly correlated with diesel. Not a big surprise. PM2.5 is not. Sulfate is even less so. So this set of three pollutants are highly correlated with one another. That's what we learned from this.

Next slide.

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PANEL MEMBER LIPFERT: Now, if we go to air toxics, we have a lot more species to choose from. I think there is 180 in that set. And we only looked at 12. And this information is available on the web from the National Air Toxic Assessment from EPA. And they again have value concentrations for every county in the US.

So this time we're plotting it against traffic density, which is the number of vehicle miles traveled per year per square mile in a county. It's county averages. What we find is that up here nickel is highly correlated with traffic. Diesel, pretty much so. And POM is pretty much so. So these four are going to be difficult to separate.

If we look at some of the other toxics, benzene

has background levels so perhaps that might be separate. Manganese goes very much with traffic. Arsenic does not. So I'm pointing out to you that these are -- there are 58 data points on each one of those plots, one for every county. So when you go to this kind of a database, you're not limited to EPA monitoring any more.

Now one can argue, well, how accurate are they? We don't really -- we haven't really checked that. We find good correlation with measurements.

But the point here and the important point is whatever errors are in this database, they're pretty much the same on all the pollutants, if you believe the emissions, because they all come from the same model. Whereas, when you look at measurements, you have one set of problems with measuring PM2.5. You have another one measuring CO. They're in different locations at different times. This I highly recommend as a way of getting around that problem.

One more, please.

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PANEL MEMBER LIPFERT: Now this is from the speciated transnetwork nationally across the country. The same kind of thing, elemental carbon. We find zinc is highly correlated. Zinc comes from tire dust. Say hey, that relates. Silicon comes from road dust. That does

not relate. PM2.5, not so much.

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PANEL MEMBER LIPFERT: Okay. Next, please.

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PANEL MEMBER LIPFERT: I'm going to skip the words. You can read those for yourself and go to the next pictures.

One more.

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PANEL MEMBER LIPFERT: Now we're looking at stuff from the Veterans Administration study that I just mentioned was published in April of 2009. And what we've done is look at all the species that we considered and played some word games, saying, all right. What if benzene is the true bad actor? What if that? This is for all subject mortality, all counties for which we have data is about 200 counties. And we find here that no pollutant for all subjects has a higher risk than benzene after you account for the correlation. So we conclude from that, okay, sounds like benzene is a bad guy.

Next slide.

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PANEL MEMBER LIPFERT: If we play another game and say, all right, I'm not sure. I think maybe NOx is the one that's more important. We find that these guys

are sticking up above the curve. So that hypothesis is rejected, and where we are is that this group of pollutants here are all highly correlated. Look at the values of correlation. And these are subject weighted correlation, which is very important. You have to go where the people live. And when you have more people in a big city, you get a higher correlation. If you just look at the raw data, you get something quite different. But if people don't live in those counties, it doesn't matter.

Next, please.

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PANEL MEMBER LIPFERT: Now, we also found in this study that, whereas, the risk for all subjects were up to .1 , if we divide the data set in half according to traffic density and take the highest traffic density location, we get risks up to .2 that says all the risk is coming from the high traffic location. Lo and behold, we found a threshold. We didn't find it very accurately, but we showed it's not the same everywhere.

And what we have here is that the story is different. NOx and EC are sticking out against benzene. PM2.5 is not on this slide because we can't calculate PM2.5. There's too much water in it. But here's diesel. Diesel is no worse than anything else on this slide.

Next, please.

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PANEL MEMBER LIPFERT: And if we then do it again and plot it against NOx, we find benzene and formaldehyde are high. Diesel SO2, nickel are not particularly. So I'm just pointing this out to you is that there are ways to get around the limitations of ambient air quality data. And finally, we found some thresholds.

Next, please.

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PANEL MEMBER LIPFERT: These are two pollutant models where the second pollutant -- one is traffic against a bunch of other things one at a time. And you can see that benzene, formaldehyde, diesel, and NOx over here all with high risk combined. The traffic itself is not doing much. But when we come to SO2 and SO4, traffic is more important. So there are things you can do with two pollutant models.

Let's go on. Next.

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PANEL MEMBER LIPFERT: Next after that.

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PANEL MEMBER LIPFERT: Now, statistical significance is often used as an arbiter in epidemiological studies. You will read that we tested the hypothesis that PM2.5 was related to X, Y, Z, and

statistically significant, so therefore it is. However, what you find when you look at a whole range of pollutants is that some are more variable than others. And in any epidemiological study, you have to have variability in the pollutant. This is the last one. The pollutant that's constant is not going to show a risk for anything, regardless of how toxic it is.

So what we find is that there is an enormous range of variation. We found statistically significant effects of polypropylene and chloride at about one percent. But the reason we found them is because they're so highly variable that the statistical -- the risk for benzene and formaldehyde in diesel, et cetera, is 10 and 20 percent. So statistical significance is a necessary but not sufficient consideration.

I think that's all I have time for.

One more thing. Next slide.

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PANEL MEMBER LIPFERT: Next, please.

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PANEL MEMBER LIPFERT: Some correlations for 2,000 counties without subject weighting. Just want to point out SO2 has diesel PM .7. That's high. SO2 against traffic density .4. And if we look at the average correlation to see what pollutants are highly

inter-correlated with each other, we find benzene, diesel PM, and formaldehyde are pretty much correlated with a lot of stuff. Things like nickel are not.

So I would just try to advocate for the fact that we need to look at a lot of pollutants and not just the one that happens to be of interest.

Thank you very much.

DR. SAMET: Thank you, Fred.

Fred, just so I can make sure that we all have a clear grasp of what it is that you were showing us, when you went to the multi-pollutant data, you were trying to get at the issue of how would one know what component of the mixture might be important. And what you were showing us was a set of effect estimates based on the assumption initially that you put in a -- selected an A starting point pollutant and then put in others, estimated their effects. And one at a time there was --

PANEL MEMBER LIPFERT: John, the graphs with the diagonal lines are one pollutant at a time. So the hypothesis there is that each of those pollutants might be the one. Okay. The bar graphs are two pollutants at a time.

DR. SAMET: Okay. That's what I assumed.

Okay. Just to remind everybody, this session is entitled, "Which studies are appropriate to use to

estimate PM related mortality in California." And this is an issue, of course, that we were touching on before lunch.

And the question of whether a nationally based study, internationally based set of data, an amalgamation of data, California-specific data, et cetera, what should be used. And I think that's where we should focus our attention over the next 20 minutes or so as we continue the discussion. I think we've seen in a number of presentations the data that are available for different studies in California.

So let me open up for discussion on this point.

Roger.

PANEL MEMBER MC CLELLAN: For Arden, you seem to try to make the case that whatever kind of national data there was appropriate to California, the California data was rich and strong and kind of fit with the national.

I guess I come away with more a general view that says the signals that we're seeing in terms of what we look at the national data clearly there seems to be things that are very different in the industrial midwest and the northeast. And that causes me to -- I accept the notion that there's some things that are happening there. I'm not certain how much we should ascribe to PM2.5 or to sulfate or any individual pollutant. I tend to look at it

as saying there is a very clear air pollution effect in those areas.

I come out to California, and in my understanding, we've got a considerably different situation with regard to the kind of mix of air pollutants we have out here. Doesn't that cause you -- why aren't you a little bit more cautious in terms of taking an extrapolation from that national data out to California? I certainly think we should be rather cautious.

PANEL MEMBER POPE: Well, it's a pretty loaded question, frankly. I wasn't making an argument about how cautious you should be. I was making the argument that the human lungs, the human cardiovascular system, humans in California are similar to those elsewhere. I mean, there is no evidence in the overall data that --

PANEL MEMBER MC CLELLAN: (Inaudible).

PANEL MEMBER POPE: So I made that point.

The other point I made is that the sources of pollution, while somewhat different, they used to be a lot more different back when there were more steel mills and more coal-fired power plants. Admittedly, you don't have as much sulfate here. But the traffic-related pollutants, the consistencies are basically the same throughout the United States. And they're coming from the same fuel. They're coming from the same automobiles, the same trucks.

And furthermore, if you actually were to do sort of more -- sort of an overall empirical, the overall empirical evidence as I see it suggests that in California what you have is a small -- now, again, I'm perfectly willing to accept the understanding or accept the argument that pollution effects are smaller than many other risk factors. I mean, there are other risk factors bigger. But because we're focused on pollution right now, that the small relatively coherent effects of higher cardiopulmonary cardiovascular effects of air pollution and that general pattern existed in California just like they exist in Utah, just like they exist in Ohio River Valley.

And I've admitted right up front that I don't know which specific constituents of these pollutants are causing the primary effect or if it's a combination of the group. Right now, it seems to be more a combination frankly. But if you go to San Palo and do these time-series studies, in San Palo, you get similar results as you get in L.A., as you get in Steubenville.

And it's my judgment -- not an issue of being cautious. It's just my judgment that the studies that are being conducted elsewhere in the United States particularly but probably most of them in western Europe and some of them even in other parts of the world, those

studies are relevant to understanding what's going on in terms of the health effects in California, just like they are in Chung-ching, China or Pittsburgh, Pennsylvania.

PANEL MEMBER MC CLELLAN: You really wandered off wide. I mean, you spent time in China. I've spent time there. Anybody that wants to talk about air pollution in China as having relevance to California, I'd say, come on. Let's focus on the USA.

And I'm not as sanguine as you are in terms of saying, well, let's take the Midwest and upper northeast and relate it out here. You showed on the air pollution there in terms of (inaudible) made a strong argument for nickel coming down out of Canada as being part of that.

DR. SAMET: I want to draw the scientists sitting around the table into the discussion. And this is a question of what we might know about the air mixture sources in California and are there reasons -- so putting aside sort of whether -- because I think you're asking a very tough question if you want to say can we estimate epidemiologically whether risks are different in California from the nation as a whole and other parts. That's a real tough question. But there is an awful lot of atmospheric measurements that have been made in California. There is a huge amount of atmosphere the science is on. So what about those data and how they

might help us.

PANEL MEMBER LIU: The issue talking about the correlation between sulfate and sulfur dioxide and PM, talked this morning a bit. Not only the SO2 is gaseous monitoring, so it has much longer history, so it has better data and longer data, that's no doubt.

But also when you do this kind of analysis always a match population based data to concentration data is same basis geographical areas. And particulates tends to vary a lot from place to place. And SO2 is more homogeneous mix. So that might -- I would suggest that might be a reason SO2 could come out, have a much stronger relationship simply because that.

I think you're right. I mean, there are two pieces. One is the concentration. One is the health data. It's always difficult to really think about they actually talking about same areas. That concept has to be implanted. And a lot of the information that this morning presented east/west, you really have to look at, you know, how you correlate those data. I think that is probably the reason cause variation in different studies I would suggest.

Nowadays, in southern California or in California in general, most of the risks we're talking about is really relate to transportation and mobile source type of

emissions which is in urbanized areas.

DR. SAMET: Yes.

PANEL MEMBER MOOLGAVKAR: I wanted to come back to a statement that Arden made a couple of times.

This morning, he presented results from some of his studies and indicated that the smoking risks were higher than those associated with ten microgram change in fine PM, which is what one would expect. And he made that same comment here today.

But the game has changed now, because the Miller, et al, study and the Ostro study clearly show risks that are larger than the risks associated with smoking. When you come across studies of that type, then I have to disagree with Michael.

I don't think Rothman will say look at all the studies and the pattern of results. I think Rothman would say, well, I mean, eliminate the studies that clearly show evidence of some kind of bias. You don't want to take these into account. And if an air pollution study shows that air pollution at current levels in the United States is more dangerous or increases the risk of cardiovascular disease more than smoking 20 pack years or 40 pack years, I'm sorry, I can't take those results seriously because they are biologically totally implausible.

PANEL MEMBER POPE: The nice thing is I just

recently published a paper with my best estimates of the cardiovascular disease of the relationship with smoking versus environmental tobacco smoke versus particle pollution. Anybody can read it. It's in circulation of a few months ago. I forget the exact months.

PANEL MEMBER MOOLGAVKAR: I've seen the study.

PANEL MEMBER POPE: So that's sort of my best guess. And I -- not just best guess. Dan was involved with that paper as well. This was our best estimate based on the available data. And basically when you read that, you see that we largely agree with you. We think that probably the effects from air pollution are higher than what we think are reasonable in some of the studies and there's some studies where they're lower.

But we think the central estimate is relatively consistent across the environmental tobacco smoke data, the air pollution data, and with the cigarette smoke data. Although clearly in order to make that link, you can't assume a linear response relationship. It has to be a response relationship that is quite steep early on and levels off. But again, that's consistent with the smoking literature as well. I'll leave it at that.

PANEL MEMBER MOOLGAVKAR: Can I respond to that, John?

PANEL MEMBER ENSTROM: I'd like to disagree with

the way Dr. Pope summarized the California data. If you now look at the CPS I data that I have, the CPS II data that's been reported in the HEI 2000 report and what Professor Jerrett's reported today and you look at the data from the MCAPS cohort, there's clear variation between California and the rest of the country. I don't think there is any doubt about it.

The other two studies, the Adventist cohort and the Teachers' study are -- as Suresh pointed out with the Teachers' study, they're anomalous, but they're also very small relative to these three very large cohorts. So I think you would have to say that the overwhelming amount of available evidence at the current time shows a very clear pattern of no current effect in California. I just don't see how you can avoid that.

DR. SAMET: I'm going to make a suggestion. Perhaps this is a comment to the ARB that we've seen slides that summarize point estimates that have a substantial amount of work, analysis, and data behind them. Some of the distinct differences in data collection analysis may be leading the differences. And perhaps a very detailed assessment of each study, an attempt to understand why they're similar or different would be a good thing to do and to try and lay all this out.

I mean, I understand these points are different

heights on the graph and that's what we're all saying. There's many reasons why they may be different. I would also point out just one comment, because the Medicare study of necessity overlaps with the ACS Study. And the same people are dying and being collected in different ways in these studies. And they're not exactly independent. So there's some subtleties here in interpretation. But I think there ought to be an attempt to make deeper sense out of this.

One thing you can do when you go to one workshop is recommend another one. And I don't know whether that's the right approach here or not. But I think there's some roll up the sleeves kind of stuff here that perhaps needs to be done to get into this a little deeper.

Tom.

PANEL MEMBER HESTERBERG: Yeah, just another comment on Arden's presentation.

I was very encouraged, Arden, that you're now going into and looking at some of the human clinical studies and animal studies. Because from what I read on the ecological, you get associations. They're not necessarily that large. You know, 2 percent may go up to 20 percent. And what's recommended is you need to go in and find biological plausibility and confirm that.

The study that you mention I'm not that familiar

with. I need to look at the details of that.

But the same group did a study here recently where I strongly disagree with the model they used, the way they generated the end points they were looking at and the dose. That one was on diesel exhaust. In that particular model, I think they used the same mouse strain susceptible to cardiovascular disease. They tied off the femoral artery to the hind legs to generate anoxia. And then they exposed the animals to 1,000 micrograms per cubic meter of diesel exhaust.

Reading that study, it sounds like almost half the animals died. Anoxia generates angiogenesis. That's a well known phenomenon. Diesel exhaust at that level increased the angiogenesis.

Now, the bottom line conclusions of those researchers was that because you get angiogenesis in cancer late stage, we all know it's a totally different mechanism on diesel caused angiogenesis. Therefore, a two-month diesel exposure to diesel exhaust will cause cancer. And that's in the press. I mean, those types of studies don't demonstrate biological plausibility. And I think it causes issues for all of us.

Now, the specific study you mentioned, I would like to dig into that. And maybe the dose of the PM they used was appropriate. But the devil is really in the

details of these studies. And I would like to look into that. And I think a lot of them cause more problems than they solve.

PANEL MEMBER POPE: Well, I respect you and I'm not a toxicologist. Your judgment on that's essentially better than mine. I don't know. And in fact that study, even though I can read and understand it -- I don't know. I like it. I think it's a pretty neat study, frankly. And I think it makes a pretty need slide, too.

DR. SAMET: Aaron -- (inaudible)

PANEL MEMBER POPE: Let me just say something so I don't have to go over this anymore.

My point isn't that any one study is better than the other, that or anything else. My point is I would consider it a mistake for the state of California to not use the richness of data that exists out there and try to focus on their own studies alone, because there is a substantial body of literature that's relevant to California that goes beyond its borders. It's a very simple statement.

DR. SAMET: Melanie.

PANEL MEMBER MARTY: Just a couple things.

With regards to the toxicology for particulate matter, there is a humongous amount of literature now, lots of it showing biological plausibility to affects on

the lung and the heart.

So you're talking about one APO mouse study. There's more than one study. There's other studies that did not use the crush injury model that you do get in fact increased atherosclerotic areas in the vasculature. That's one thing.

I think we're arguing about angels dancing on the head of a pin a little bit here. And I would just like to point out there is a lot of studies on the cardiovascular effects on particulate matter done across the world with different mixes of pollutants, different geographies, different lifestyle, different genetics, all kinds of stuff. And they're all pointing in the same direction. That is one of the reasons U.S. EPA has determined there is a causal association between PM2.5 and cardiovascular effects on mortality. It is biologically implausible to think that Californians would somehow not be susceptible to these same biological insults.

DR. SAMET: Actually, I thought Californians were just so much healthier than everyone else.

PANEL MEMBER HESTERBERG: Can I respond to that? I've looked at a lot of these studies, and dose is an issue in a lot of them. They go to very high doses. And the dose determines the poison and the mechanism oftentimes. Some people rationalize doing mechanistic

studies at high dose because we get an effect, but the mechanism may very well be different. So dose is very critical.

DR. SAMET: I don't know if you want to comment on some of the compilation of evidence and the plausibility as developed in the ISA.

PANEL MEMBER ROSS: Dose is very important. And one of the things I would mention is we deliberately focus on toxicology studies that use lower doses. And we generally say within an order of magnitude of ambient is the lower end. It's not in the thousand parts per million that you're talking about. So in the plausibility -- in the discussion itself in the integrated science, we don't talk about high concentration studies. We only focus on the reasonable concentrations given their animal studies, yeah.

DR. SAMET: Roger.

PANEL MEMBER MC CLELLAN: I'm concerned that we are leaving -- left on the table a view that air pollution in California is just like it is in the rest of the country. I'm sorry, but if that's your conclusion, you're not reading the literature that I am. And I'm shocked that people like Dan aren't standing up and saying, "I've looked in detail and it's very different."

And you, Arden. It is different. Why are you so

silent?

DR. SAMET: Actually --

PANEL MEMBER POPE: I think I've been talking too much, frankly, although --

PANEL MEMBER MC CLELLAN: John --

DR. SAMET: I would say that the community that really needs to speak to this are those who are carefully studying the atmospheres in California, those who are making comparisons elsewhere.

With all due respect to my epidemiological colleagues, they are not atmospheric scientists. And I think the question of whether there are important differences that figure into the health risks need to be adjusted.

Susan --

PANEL MEMBER MC CLELLAN: And you're separating the world into epidemiologists versus aerosol scientists. Come on. You as an epidemiologist understand the exposure.

DR. SAMET: Roger, I think you and I have set around the same multi-disciplinary tables for years discussing these issues with colleagues because we know we need the depth of scientists represented.

Go ahead.

PANEL MEMBER PAULSON: I don't think that anyone

would argue that any particular location is exactly like any other. There is a whole -- we all know there is a whole spectrum of pollutants that are present in different proportions in every different location. But their main features that are similar in California as they are in many other places in the country and other features that are slightly different -- like there's more sea salt in Los Angeles than there is in a lot of inland areas. Nobody thinks sea salt is a big project. There's huge amounts of diesel exhaust and gasoline vehicle exhaust. That's very similar obviously than lots of other places. There's generally a little bit less sulfate. There's a higher proportion of some types of secondary organics aerosol, lowers of others, higher anthropogenic, lower biogenic. Slightly different proportions of inorganic salts. But the general features are, you know, in slightly different proportions played out pretty much everywhere in the country.

And also in some locations, like New York, there are more wintertime pollution problems. Those have somewhat more similarity with some wintertime pollution areas in California. And then the photochemical smog problems that we have in the summertime in southern California are more similar with other parts of the country.

PANEL MEMBER PHALEN: I think that's a good summary.

But the thing that to me seems most relevant about the difference in California is the higher contribution of fine soil to our PM2.5 that you don't see in many of the large open centers back east. We have more in the L.A. basin for sure and other areas in California, too, the agricultural areas. We just have a lot more soil in the PM2.5. And that creates a little bit of a problem if you are trying to reduce the concentration of PM2.5 and you go after something like diesel emissions. It's more difficult here to get a lowered level because we can't really effect the soil levels that much.

In fact, one industrial hygienist was complaining to me in California that at least some of the samplers that he was familiar with were near fields that generated lots of dust. And he was quite concerned about exceedances when the wind was blowing the wrong way.

So I think the low humidity, it doesn't change everything, but it just makes our PM2.5 more difficult to understand and control visive anthropogenic emissions.

PANEL MEMBER PAULSON: Without belaboring it, I think you're really overstating the contribution of soil dust to PM2.5 in the major urban areas in California.

PANEL MEMBER LIU: On that subject, I think

there's always something that describes southern California as the same. We have a chart of the future path put on the maps. You're going to see color varies from place to place. So obviously our central urbanized areas is pitch black. It's not soil.

DR. SAMET: Dan, I see you're roused up here.

PANEL MEMBER KREWSKI: I don't know if I'm roused, but I have something I can offer for the discussion, John.

The discussion that's taking place over the last several commentors may fall under the general rubric of one of the ten research priorities for my NRC Committee. There's I think -- is there more than three of us here? Roger, John, myself, Dan. Who else? Lots of us.

One of the ten research priorities was defining the toxic constituents of the complex mix of air pollutants to which we're exposed. If we look at air pollution in California, air pollution in the midwest, air pollution in Europe, there is going to be quite a bit of variation in what that's comprised of. We can observe different population health impacts from those different air sheds. But then we can also dig deeper and try to identify the toxic constituents.

And if you think it's difficult, Suresh, trying to disentangle the six different criteria pollutants, if

you give me 20, 30, 40 elemental fractions and ask me to sort those out and then if we start looking at different sources and trying to get the relative contribution of those, it becomes a difficult problem.

I don't have a solution, but I think that's the problem that maybe we're discussing a little bit. What are the components of the air pollution mix that we need to be concerned about.

A partial solution, John, might be something -- I think it was you even that could -- we take some of the major population-based studies, the cohort studies, not just across the U.S. but internationally, Europe and Asia, because the more heterogeneity that we have in the pollution exposures, the greater the opportunity to try to sort out the effects of the different types of mixtures. So that might be something we can think of for your next workshop and look at the international pooling of cohorts of air pollution studies.

DR. SAMET: Fred.

PANEL MEMBER LIPSETT: I'm going to put my atmospheric analysis hat on for a moment and ask a question and then make a comment.

My question is: As I understand California air quality, nitrate is a big contributor, especially in places like Riverside and places where the PM standard is

not met. Is there someone here that believes that ammonium nitrate is toxic? Show of hands. One. Okay.

Question. We've also I think reached some agreement that traffic problems are pretty much ubiquitous. If you read the European literature, that's all they talk about. That's where it's at. And to a certain extent, Asia. And the fact that we have uniform emission control standards in the U.S. and the same number of violators seem to be in different parts of the country says traffic is ubiquitous.

So my question to ARB is when are you going to study traffic? Let's go to the source and stop getting confused with all the different ambient measurements that can be made.

Thanks.

DR. SAMET: That's possibly a rhetorical question I think, but we'll see if it's answered later.

George.

PANEL MEMBER THURSTON: I just wanted to follow up on Dr. Paulson's remarks.

I really agree with what you said. The differences across the country are -- there's not a dramatic difference in the aerosol. It's a quantitative, not a qualitative, difference. In other words, the same sources pretty much are present around the country, but to

different degrees. And coal essentially is concentrated in the east. But fossil fuel combustion is present throughout the whole country to a different degree. In some places, more oil. In some places, more natural gas and coal. But fossil fuel is combustion.

And that's really what the studies that we've done with the ACS and the other studies have sort of been pointing towards is there is a problem with fossil fuel combustion. And it seems like the pollutants coming from fossil fuel combustion are associated with the -- most associated with these health effects.

And so it's really more a matter of degree of the various sources than some great very contrast that could say oh, well, the particles in California would be non-toxic. That's dramatically different. I think the remark was made, well, the people in California, yes, they're healthier than the country. But, you know, people don't think that suddenly they're invulnerable to air pollution. And in fact, I was thinking part of the reason probably they're healthier is a smaller percentage of smoke in California.

And, of course, the biggest relative risks we have that we found in the study are for non-smokers. So that means non-smokers have a higher relative risk. There's more of them. And California might be a place

they want to worry about air pollution. That's a bigger share of their risk. But by the same analogy, the aerosols in California are not sufficiently different you would say they're suddenly non-toxic.

PANEL MEMBER MC CLELLAN: I never said they're non-toxic. But, George, you have to take a hard look at the changing composition and levels of air pollution across the United States going from our earliest data in the 1960s, 1970s up to today. And I can tell you California is not like the Ohio River Valley, Pennsylvania, New York. And for to you suggest that somehow there is a great similarity is wrong.

DR. SAMET: Okay. George, let's not debate. I think we actually need to move on.

I just want to remind everybody that we were talking about the selection of studies to estimate PM mortality in California. I think there were two elements to this. I think a lot of our discussion about the nature of air pollution in California air quality, the database, probably exists to make a more detailed comparison. There have been countless dissertations generated at Cal Tec on air quality in southern California. And I think there is substantial data to look at.

I think this question of why the estimates are different and the different studies could merit some

additional scrutiny and review by ARB or by ARB and bringing in some of the investigators to really sit down and look at that.

Let's move on to our next topic, which is how should uncertainties in the concentration-response function and exposure assessment be addressed in developing a methodology, presumably a mortality estimation methodology.

So this is Zack first.

PANEL MEMBER PEKAR: So I'm Zack Pekar, and I work for EPA, the Office of Air Quality Planning and Standards.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER PEKAR: I'm in charge of designing the risk assessment for PM, NAAQS along with the folks I work with.

And what I was asked to do -- I guess I should talk into this, shouldn't I? I have a booming voice. I count on that sometimes.

I was asked to provide a little background for the basis for our selection of the concentration-response function use in the national scale risk assessment. And then to talk a little bit about the way we attempted to characterize or assess our confidence in the risk

estimates that are generated using that response function.

So once again, I'm focusing here on the national scale risk assessment in support of the national ambient air quality standard review for PM. And I'm going to talk about long-term mortality estimates which is what I think our discussion is here.

Next, please.

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PANEL MEMBER PEKAR: So the goals of the risk assessment are first to assess to characterize the nature and magnitude of public health impacts from long-term exposure to PM to public health. Again, this is at the national level.

The way we do that is part of the NAAQS review -- let me stop for a second. I actually realized that I wanted to set this up a little bit. We're reviewing the NAAQS standard for PM, for particulate matter. We are in the process of reviewing that. The risk assessment I'm going to talk about, we just completed a second draft of that risk assessment that is currently open for public review. So if people have comments on the analysis, they can submit those.

In early March, we're going to be having a peer review meeting with the Clean Air Science Advisory Committee, which is a peer review group, to discuss the

design and issues related to the PM NAAQS. So I thought I'd provide that background.

So back to this. The risk assessment is designed to characterize the nature and magnitude of public health impacts from PM 2.5.

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PANEL MEMBER PEKAR: We do that by modeling a number of urban study areas. L.A. is one of the study areas, but these include cities throughout the country. There are 15 of the cities. Obviously, a second part of that is to try to assess our overall confidence and characterize uncertainty in that estimate of risk. It's probably pretty important just given the discussion here.

And then finally, we try to evaluate the degree to which the estimates that we generate are representative of the broader nation. So we've modeled 15 cities. Obviously, there are more than 15 large cities in the U.S. So one of the questions is how representative are the urban areas that we've modeled of the rest of the country, urban areas in the country.

Next, please.

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PANEL MEMBER PEKAR: So when we conduct the risk assessment at the national level, we generate two types of risk estimates. We generate a corset of estimates. And

what we've done here is looking at the literature -- and it's in all the literature we've been talking about today, we identify the set of studies or these studies that we think we have the greatest confidence in. That's the qualitative assessment that the EPA staff makes.

Then we bring that assessment before KSAC, which is a peer review group with a number of members here, and we get feedback from the public on this. And based on that, we generate -- we extract concentration-response functions, which I'll briefly talk about, from that core study. And we use those to simulate or estimate long-term mortality risk for a number of different health end points. That's our core estimate. So if you imagine a series of risk estimates here going from low risk to high risk, several of these -- the two red dots represent the core risk estimates that we generate.

The other risks we generate, we conduct a sensitivity analysis to generate a set of additional analyses. While we may -- and I'll talk about this in a second. We may have greater confidence in one of the U.S. EPA studies for reasons I can explain. Obviously, there is merit. A number of other studies have support in the community and the literature. So we use additional epidemiology studies and extract concentration-response functions from those studies and generate an additional

set of risk estimates.

Now, not to get too technical here, but this is not representative of an uncertainty distribution. What we haven't done is tried to put confidence weights on each of the studies and generate a whole set of risk estimates that give you a confidence distribution. Means, here's our best estimate. Here's the 90th percentile or 95th percentile. We haven't done that. You do that, but conducting a probabilistic, a Monte Carlo analysis basically. But in order to do that, as I just explained, you have to be able to take a look at each one of your studies and the concentration-response functions and put a confidence level on that.

That was done to a certain extent in a certain context with a solicitation which was mentioned earlier today. But that analysis, that work is now a few years old. So what we did, given time, is we essentially generated two core estimates, a set of additional risk estimates, and together those represent a range of risk estimates that management can look at.

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PANEL MEMBER PEKAR: So what I'd like to do now is provide background on the core epidemiology studies and concentration-response functions that we selected and why, and then a little bit of detail on the additional set of

analyses that were used in the sensitivity assessment.

So for the core, for selecting the core study, we went with the Krewski 2009 extension of the ACS Study which has been discussed a lot here. Our reasons for that are points that have been made earlier. And once again, I'll just emphasize the fact we're conducting a national analysis. We're considering this in the broader context of the nation. So just to be clear about that.

So it included extended air quality analysis up to 18 years. It had rigorous examination of a range of concentration-response functions. A lot of that stuff gets fairly technical. But there were some new things in terms of looking at random effects, the clustering of data as we were talking about that that I think was done to a certain extent for the first time in this particular version of the analysis, a range of ecological variable controls, consideration of exposure time windows. The fact that study attempted to look at that didn't find a lot of differences between those windows, but the look at that we thought was valuable.

And then finally the fact that as the basis or sort of the sub-analyses of this larger national scale analysis we included -- they included the study design. Study authors included a look at L.A. in detail and New York City in detail. Also provided us with additional

support that that data set and a comprehensive way included some dimensions that we really liked. And finally, it's a very large data set, which is just described here.

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PANEL MEMBER PEKAR: So then now that we've selected the Krewski 2009 study, anybody who's looked at that study knows it's 150 pages, 160 pages. Very detailed analysis. There are many, many concentration-response functions presented in that analysis. I think it's one of the strengths.

So we spent a fair amount of time looking at which of the concentration-response functions we should really use from that analysis. Ultimately, we went -- and this gets techy, but just to put it out there. We went with the Cox model with adjustment for the ecological covariate. That's something that we've talked about a little bit here. The reason we went for that concentration-response function was it allows us to define that concentration-response function based on two air quality periods.

I think a point was made earlier that the effect estimates were not that different from these two exposure periods. And I would say if you run instances -- numbers for a large city like New York to effect estimates, you

get differences of a thousand deaths in a year potentially.

So the point is that these effect estimates run for the different air quality periods from a public health assessment standpoint could be significant. So rather than selecting one or the other, we have a response function or effect estimates concentration-response functions for both of those air quality time periods.

And just to mention this. A higher risk assessment approach was reviewed by CSAC a few months ago, and we received support and obviously a lot of comments and suggestions for working on, but broad support for the selection of these concentration-response functions.

And then just to be clear, we did consider the inclusion of one of the more sophisticated models, without getting into a lot of detail. It's the random effects model which allows that clustering, that covariates looked at. And the reason we didn't go for it as the core analysis is because we couldn't define it for both of those exposure periods. It wasn't specified like that in the study.

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PANEL MEMBER PEKAR: I only have two more slides. Supposed to be short on this.

So for the sensitivity analysis, we wanted to

include additional concentration-response functions from the Krewski study, because we felt there were other dimensions that should be included. So we did include a log where you have the log of the effect and the log of PM. That gives you a steeper slope. So we included one of those models.

And we also included the random effects model defined for one of the exposure time periods that was given. We also included Krewski 2000, because that allowed us to look at the Six Cities Study.

We considered using Laden, but I don't know if this point has been made. The Laden air quality, the PM2.5 data for Laden is based on visibility estimates, and we didn't want to go with sort of an interpolated metric like that. We wanted to use direct PM2.5.

DR. SAMET: You might want to point out that's further follow-up.

PANEL MEMBER PEKAR: That's right.

So then if I can go all the way back to the second slide.

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PANEL MEMBER PEKAR: So just to point out, this plot actually is the set of estimates that was generated I believe for IHD mortality. I don't have numbers down here.

But the point that I wanted to make was generally we selected a corset of estimates; generated it. Then we had additional sensitivity analysis estimates around that.

What we found was that most of those sensitivity analysis results where we used other viable models ended up giving us actually higher risk estimates than what our core estimates were. So it's just I think a point to make.

There were a number of studies that we mentioned here that we couldn't use in the risk assessment, because we don't have baseline incidents data or other things you need to run risk estimates for. But those will be considered as part of the evidence analysis which is a very critical part of this whole contribution which is a second part of the review that I'm not going to talk about.

So anyway, that's it.

DR. SAMET: Thanks, Zack.

Suresh.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER MOOLGAVKAR: I thought what I'd do is take the set of slides that Arden showed and find out why they don't support his conclusions. Just kidding. Just kidding.

PANEL MEMBER POPE: No, you're not.

PANEL MEMBER MOOLGAVKAR: But in any case, the point I want to make is if you start out with the assumption that fine PM is killing people and you make that your central assumption, then any observation can be fit to that or explained on the basis of that assumption. And it seems to me that a lot of members of this panel have gone beyond the issue of asking whether that assumption is true or not. In other words, a number of members of this panel are making the assumption that there is a causal relationship between exposure to fine PM and mortality, particularly cardiovascular mortality.

I want to talk about the uncertainties in the original studies that led a number of people in the panel to that conclusion.

So if I might have the next slide, please.

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PANEL MEMBER MOOLGAVKAR: So first of all, we have only a meager understanding of factors that effect health and human population. In particular, the role of socioeconomic status is very poorly understood. And if you look at Steenland's paper in 2004, one can see how poorly we understood the role of SES in determining mortality.

Talked about the inadequacy of the currently used

statistical model. I'll come back to that in just a minute.

And the results are highly model dependent. Namely, depend upon the statistical model that is chosen to perform the analysis. The estimates of personal exposure are not available in epidemiological studies, and the range of reported risks is huge. So, for example, originally we thought that there was uncertainty and we're to address uncertainty because we were trying to tease out small risk from noisy data. But all of a sudden now, we have these studies that attempt to characterize exposure better, like the Miller, et al, New England Journal of medicine study and the Ostro study, in which the risks are so large that they're totally implausible.

Next slide.

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PANEL MEMBER MOOLGAVKAR: So here is an example of how bad the Cox proportionate hazard model can be. This is the total mortality rate ratio for 40-plus cigarettes per day. This is taken from CPS I. And the points on the graph, these are not modeled. These are actually data points, because the data set was large enough for the rate ratios to be actually computed, estimated. This is taken from one of the National Cancer Institute model graphs on tobacco smoking. I think it's

Monograph 8.

So if you look at 40 cigarettes per day and look at the rate ratio starting from age 35 up to age 85, you see this. I put a smoother through the data. But you see the risk increasing to about the age of 50 and then going down all the way to almost one or 1.25 by age 85. And this is the phenomenon that Arden referred to earlier this morning.

Well, if this model -- if the proportion has the model correct, you would get a horizontal line that goes across this graph. Well, if this model is used to control smoking or control for other confounders in which the same kind of phenomenon might occur, clearly you're going to get biased estimates of the risks associated with smoking.

Next slide, please.

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PANEL MEMBER MOOLGAVKAR: So the first is the point that I already made.

The second point I want to make is that just because a covariate is entered into the regression and you enter many, many terms does not mean it has been adequately controlled.

And again, I'll take the example of smoking. Pack years is a poor measure of control of cigarette smoking, because the risk clearly depends very strongly

both in independently on both intensity and duration of smoking.

Next slide, please.

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PANEL MEMBER MOOLGAVKAR: So now the second point that I made is that results depend on modeled choice. And here again I've chosen an example that I already talked about this morning.

Let's look at the long-term studies of the reanalysis of CPS II as reported in Krewski, et al, in 2000. This is taken from Table 37. If you look at single pollutant analysis, the fine PM relative risk is 1.20. Highly significant. The SO2 relative risk is 1.49. Again, highly significant. If you look at two pollutant analysis, the fine PM relative risk falls 1.03. Becomes highly insignificant. That for sulfur dioxide remains robust and significant.

I don't think this finding and such a strong result can be explained on the basis that sulfur dioxide is simply a precursor for sulfate and therefore should not be included in the analysis. I mean, that is just sweeping the problem under the rug. This observation needs to be explained and has not been addressed in all these studies of ACS II that have taken place after this one.

Next slide, please.

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PANEL MEMBER MOOLGAVKAR: There are inconsistent results. I've just chosen a few. But I can point to many more. Krewski, et al, 2000 finds a much lower fine PM mortality effect in California than in the northeastern U.S. This has been alluded to a couple of times earlier today. However, when they do the spacial analysis in 2009, the report no effects in New York City, but a positive effect in Los Angeles and a fairly large effect there. So the conclusions from these two studies is somewhat different. And that might be attributed to maybe better exposure in the second study, better exposure estimates.

Now, I know that John is not going to like this point I'm making here. But when you look at the first stage NMMAPS analysis, finds a significant effect in New York City, but not in L.A. And the comment has been made that you should not be looking at the first page NMMAPS analysis because they were not meant to be looked at. That's like saying you can take 90 meaningless results and combine them into one meaningful mean estimate in the country. And that simply cannot be done.

And there's also a statement in the NMMAPS results that says if the city is large enough, then you

can take the estimate seriously. I contend that L.A. is a large enough city in the United States for us to look at.

Next slide, please.

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PANEL MEMBER MOOLGAVKAR: Biologically implausible results. Pope, et al, circulation 2004 reports significant protective effect of fine PM on respiratory mortality. So you can -- this is his Table 4 reproduced. You can look at the relative risks here.

Now, I'm not suggesting that one run behind a diesel bus and inhale deeply. All I'm suggesting is that this is a biologically implausible result. And if this result is reported in these analyses, why should the other estimates reported in the paper be taken seriously? I mean, we have to talk about the limitations of observational studies when we see results of this type.

Next slide, please.

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PANEL MEMBER MOOLGAVKAR: One more point I wanted to make on the previous slide is that in that paper Arden points out that there is a synergistic effect between smoking and air pollution risk. And this morning, George Thurston has mentioned a couple of times that, in fact, we see the biggest risk among non-smokers. So again here there are not entirely consistent results.

When scaled linearly, risks are implausibly large in some of the studies. So let's look at Miller, et al, New England Journal of Medicine 2007, that reported fine PM associations that were much larger than those reported in earlier papers. And a simple calculation shows that their results imply that a woman moving from the least polluted city, namely Honolulu, to the most polluted city, namely Riverside, would increase her risk of cardiovascular mortality more than if she smoked 40 cigarettes per day. This defies biological plausibility.

Next slide, please.

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PANEL MEMBER MOOLGAVKAR: The same can be said for the Ostro, et all, paper on environmental health perspectives that has already also been discussed earlier today. Here are the relative risks in 95 percent confidence intervals associated with incremental exposure to sulfates, a component of fine PM.

All-cause mortality, the relative risk is 21.5. For cardiopulmonary mortality, 27.7. For ischemic heart disease, 100.

Now, this simply defies biological plausibility. And to me, it indicates that both the Miller, et al, study and the Ostro, et al, study may actually be picking up socioeconomic effects, SES effects, when they tried to

characterize exposure more finely than has been done in the past.

Next slide, please.

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PANEL MEMBER MOOLGAVKAR: So this is my last slide. I'm repeating again my conclusion from the previous one that Miller, et al, and Ostro, et al, could be explained by residual confounding by SES. The attempt to better characterize exposure may actually lead to estimation of an SES effect. Regulation is a policy decision in the face of considerable uncertainty. Attempting to justify specific regulation on the basis of causality in my opinion leads to a distortion of the science. Data that are used for regulation -- we've discussed this earlier today. Data that are discussed for regulation should be available to all stakeholders.

Thank you.

DR. SAMET: So I want to remind everybody of what the topic was that we began here. How should uncertainties in the concentration-response function and exposure assessment be addressed in developing a methodology. And I think I would for the moment prefer that we focus on that issue.

I think Suresh spent a fair amount of time both in the earlier discussing some of the issues around the

limitations and strengths of particulate studies. And I think you've highlighted some of those again.

But again I think for starting and I think for a discussion that would be most useful for ARB purposes I think if we could initially address I think some of the more general concerns/issues related to underlying models, model selection, and the actually addressing of the uncertainty how it should be characterized, described, and so on, I think that would be useful.

I think we have the possibility of looking at one methodology from Dan. But I think if we could move to a more general level in the discussion, I think that would be most helpful for ARB.

Fred.

PANEL MEMBER LIPFERT: I would have to agree with you, John. And it seems to me in listening today that the one topic that we don't hear a lot about -- maybe it's just implied -- is the uncertainty due to model selection. Very often, especially in large studies, the difference between alternate models is much larger than the confidence limits from any one model.

And by model, I mean how you slice the data, what confounders you use, how many pollutants you run.

And I think an issue that's underlying here that no one has really come to grips with yet is the issue of

the age of the subjects, because those effects are quite different between time-series studies which effect the elderly and long-term studies which appear to effect middle ages. So the notion that somehow you can compare those two kinds of studies I think is flawed and needs to be addressed a bit more fully.

Thank you.

PANEL MEMBER GREENBAUM: Yeah, I would agree with what Fred is saying.

I would just make a more general comment for especially for people who are of not familiar with epidemiology studies.

Generally, when you look at different populations in different parts of the world, you have different mixes of exposures. And as Melanie said before, at least with time-series studies that have been done looking at hundreds of cities throughout the world, the relationships between PM and mortality, for example, are pretty consistent. But when you look at just confining the analysis data, some of these longer-term studies, you are looking to people who have different age distributions but they're going to have differences with susceptibility based on what -- in part on the extent to which people in a particular population have more underlying disease, whether it's like cardiovascular or whatever, you have

different information quality of information about their exposures.

For example, like some of the major studies that we're talking about used a single monitor to represent an entire population in a city, like with Mr. Enstrom's study, with the ACS Study, with the Harvard Six Cities Study. And so that would indicate that people who might live at different -- like three, four, five, six, seven miles away from the monitor all get assigned the same kind of exposure in this kind of analysis.

And one of the principles when you have that kind of exposure mass classification in epidemiology, the more exposure misclassification, the more likely it is that you're going to obscure a real relationship, assuming a relationship like that exists. So you get a bias towards the null effect. And you bias your estimates downward.

So to the extent that you try to improve your risk assessment, as was done in the Women's Health study or the Teachers' study or some of these other, there is a real effect. You are likely to see higher effect estimates. But the quality of the exposure assessment will make a big difference on what you see in your ultimate estimates of risk.

And then the confounders, these are things that might be associated with the exposure and with the

outcomes. They're different across all these different populations. And all of these things enter into what the ultimate results are. And so you can't -- because of this, you can't make -- do any regulation. You can't make any conclusions on a single study or two studies. You have to look at the vast body of evidence to see if things -- if you get results that are reasonably consistent across different populations with different studies and hopefully with different kinds of models as well.

DR. SAMET: George.

PANEL MEMBER THURSTON: Well, I just had a couple of responses to Suresh's talk which I really feel have to be asked, even though I know you want to stay on methodological.

One was moving from Honolulu to a high pollution area. I think that's not a proper use of the results, because you know you have to average over their lifetime. And the assumption of the study is that people have lived there for many, many years. So if they move, then you have to say, well, they had this low exposure and they moved to this higher place. And that may be 1/50th of their exposure. So then you average the two. You just can't suddenly take their measurement that year and say that's their lifetime exposure. So I think you're way

overestimating the difference. I don't have the numbers. It's very difficult to respond.

The other comment is with this whole SO2 discussion that you keep bringing up. In the HEI reanalysis, they pointed out very clearly this association with SO2 and they said the absence of a plausible toxicological mechanism by which sulfur dioxide could lead to an increase in mortality further suggests it might be acting as a marker for the mortality associated pollution.

And you know, I think you're ignoring that whole argument which you're doing this that there is a whole body of information which we didn't really present very much here, but Arden put up that slide showing all these plausible mechanisms by which particles could be killing people. And we don't have that for SO2, do we?

PANEL MEMBER MOOLGAVKAR: No, we don't.

PANEL MEMBER THURSTON: So if you look at causality, that's a big factor.

PANEL MEMBER MOOLGAVKAR: Which is why the finding is an embarrassment.

PANEL MEMBER THURSTON: No, it's not. It's consistent actually with the results that it's part of the mix.

PANEL MEMBER MOOLGAVKAR: -- debate at the moment, but I would like to respond to your first point.

PANEL MEMBER THURSTON: I know you don't want to.

PANEL MEMBER MOOLGAVKAR: What I'm saying is that a woman who's 20 years old, she can either choose to take up smoking 40 cigarettes a day or move from Honolulu to Riverside. And by the time she's 65 years old, she will be at a higher risk of cardiovascular disease if she decides to move.

DR. SAMET: And the Honolulu/Riverside debate we really don't want to take up.

PANEL MEMBER THURSTON: I just think the calculation is misleading. It's not a proper use --

DR. SAMET: It turns out no one has ever moved -- never mind. I might get myself in trouble.

So Dan.

PANEL MEMBER KREWSKI: John, thank you. Let me raise a broader question about uncertainty analysis. You're challenging us, Mr. Chairman, to think about uncertainties associated with the concentration-response function. I'm not sure that's the -- you're focusing us on uncertainties associated with concentration-response function, which is important.

But I'd like to ask the question what are the major sources of uncertainties and estimates of air pollution on population health. And the concentration-response function will have an impact.

But largely we're measuring population health impacts within the response range. So any sensible flexible models, as long as we don't go too far to different exposure levels, is probably going to be reasonably consistent.

But let's think about something that was just discussed. The exposure data, what happens if we use exposure as ecologic exposure at the SMSA level and what happens if we use them at the ZIP code level. In L.A., like Schwarz showed, there was a factor of three. I can't think of a single concentration-response function choice that would lead to that big of a difference.

If I think of other sources of choice of analytic technique that could lead to large or small uncertainties adjustment for individual covariate, we've done that extensively. Doesn't seem to be a big deal. I think the exposure assessment to my mind could be one of the dominant ones and much more important than the choice of the concentration-response function.

I had another one that's a big one, too, that's slipping my mind.

DR. SAMET: So in terms of what EPA is doing, the risk assessments, you've done now I think a much better job of setting out systematically the sources of uncertainty and trying to characterize them.

Zack, can you make a comment on that?

PANEL MEMBER PEKAR: So I laid out up there the variety of functions and studies that we considered. But for instance, we actually considered trying to run the more detailed sort of Jerrett-based estimates for L.A. with that kind of detailed profile and just given time and methodological challenges, we couldn't adjust the surfaces down to look at alternate air quality standards. Sort of the what if. It was too complex for us given that time.

But just to let folks know, just even if your uncertainty -- we haven't included those higher slopes that come when you address exposure misclassification or exposure error, which I think is a pretty important thing.

So we talk about that qualitatively. We say that the range of risk estimates we've looked at are essentially based on the primary national scale analyses. But we say some of these more detailed looks are starting to suggest exposure profiles -- addressing those factors can increase the slope more.

PANEL MEMBER KREWSKI: I thought of my other big ticket item.

Pardon me for jumping in, John.

If you look at adjustment for copollutants, we talked about SO2 mitigating the PM2.5 effect when they're included in the same models but not the other way around.

So the choices of the exposure metric, the choice of the copollutants that go into the two models I think would be to my intuitive thinking probably the two biggest sources of uncertainty we would have to contend with.

DR. SAMET: And again, perhaps in a suggestion to ARB. And I think Roger and Dan and I once sat around for a number of years estimating the risks of radon. Do you remember that? And somewhere in this massive risk assessment there was a huge table of uncertainty. And you may remember that. It was a useful exercise to develop such a table because you could begin to say which ones are the most important. It's probably a useful exercise. Suresh listed some of these. And it's hard to say either qualitatively or by expert judgment or quantitatively it's not hard.

But you can begin to make some estimates of which are most important, which are most critical and line those up and begin to try to do whether it's a sensitivity analysis as we saw from EPA or other methods to try to understand what are the most critical uncertainties as you make decision. Again, that's a useful exercise. We've only potentially touched the surface of how long that list might be.

Mike.

PANEL MEMBER JERRETT: Thanks, John.

Just a few comments.

And I think bar on what Suresh was commenting on but also on the uncertainties that we face, the Women's Health studies and the Teachers' cohort both produce risks that are much larger than what we've seen. So if they were biologically implausible, we might say there's too much uncertainty there, we should throw out those risk estimates.

But both those cohorts have very low levels of underlining cardiovascular risk. So even small increases on a relatively low baseline are going to in a relative sense look quite large. So it's entirely plausible that those are reasonable estimates and never smoking cohort of women or in a cohort of women where the baseline prevalence is five percent and there is no significant occupational exposure.

So I think that that's one -- looking and trying to understand the underlying population differences and their absolute versus relative risk is something we need to think about a lot in doing the burden estimates.

When we look at the effects in New York City, which have come up time and again, I want to emphasize there were significant effects there for ischemic heart disease. There was a 20 percent increase, which if I scale it to the same exposure contrast as Los Angeles,

it's actually a bigger increase. It's 1.56 relative risk, significant. So very significant.

Now here's another case where you have to understand the underlying exposure and population, because the underlying population is subject to the highest exposure. It's probably one of the healthiest populations in the world. You have Manhattan, upper east side, good access to health care, good diet. They're walking a lot. They're exercising. And they're getting the highest level of exposure that we can detect on what's arguably the most biologically plausible outcome and effect, even in this healthy population I think it's quite remarkable.

And to me, it lends that it's even stronger evidence that air pollution is asserting an effect than a weaker one. It's not a negative study at all, and it's one that we think about in this broader body of evidence that people are talking about it strengthens the base.

Now, the scale of variability in the pollution, going back to what Dan has mentioned and what Suresh is mentioning, I think everybody views SO2 as a marker for near source effects. And if we want to have ARB and/or government regulatory agencies do something, we need more measurement at fine scales that represent high gradient exposures near traffic and industry where we're likely to see these bigger effects. We can't develop exposure

models without the underlying data. And we can't go out and get the data every single time we do a health study. So that's something I think when we look at reducing uncertainty, there's going to have to be a complete rethinking in the way that government monitors pollution.

Just a couple of factual corrections. The reanalysis never tested a California-specific estimate or tested a southwest estimate which includes at least four states. So there's no specific evidence from the reanalysis study on that.

The respiratory effects that were shown to be -- or thought to be biologically implausible, we have subsequently investigated those, published in the New England Journal of Medicine last year in our article investigating ozone. And when we put ozone in a model with PM, we nullify any of those negative risks because we show that the mixture that's associated with ozone is associated with mortality. So we have to look at these mufti-pollutant models.

And just one final point. We did test for proportionality hazard assumptions for key confounders like smoking and air pollution in the first reanalysis when there are only nine years of follow-up and a lower likelihood of non-proportionality, and we found no likelihood of it.

So if you're thinking about not using the national level ACS Study because you're concerned with that, we don't have any evidence that's a problem yet.

DR. SAMET: Okay. I think -- Suresh, just quickly, because I think we're going to do one other thing.

PANEL MEMBER MOOLGAVKAR: Yeah.

With the kind of departure from non-proportionality that I showed you, I don't think statistical tests would detect that kind of departure, because it's not monotonic departure from proportionality.

Having said that, I think I buy your explanation about healthy populations to some extent. But they can't explain the magnitude of the risk, I don't believe.

And finally, I think talking about the shape of the concentration-response function, there is this paper by Abrahamowicz. I think Dan Krewski is also a co-author of that paper. And that finds clear evidence of non-linearities and for thresholds like behavior for sulfates. And for some reason, that paper has been completely ignored today.

DR. SAMET: So in our last three minutes before break, Dan is going to spend a few minutes talking about expert solicitation I guess, Dan, as a way to characterize uncertainties. So go for about two or three minutes and

then we're going to break.

PANEL MEMBER KREWSKI: While the slides are being retrieved, Mr. Chairman, we call it expert elicitation, not solicitation.

DR. SAMET: I think experts are also solicited.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER KREWSKI: So turn the clock on and see if I can do this in three minutes.

This is a presentation I made earlier this week at the Public Health Agency of Canada. Took me two hours. I'm going to do it in three minutes.

Next slide.

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PANEL MEMBER KREWSKI: So this slide was already shown previously -- next slide --

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PANEL MEMBER KREWSKI: -- where we saw the experts that were providing guesses of what the best risk estimates were for particulate air pollution.

Which one were you again, Arden?

PANEL MEMBER POPE: I'm Dr. J.

PANEL MEMBER KREWSKI: Who am I? I'm Dr. -- I don't know.

But this is an example of a quantitative expert

elicitation and you discuss --

DR. SAMET: Dan, maybe for the sake -- this has not been very well explained what the data are up there. So would you just take a moment to describe for everybody what we're actually looking at?

PANEL MEMBER KREWSKI: On the vertical axis, you have the relative risk. So relative risk of where it's one is no increase in risk relative to background. And here you would see a central estimate of about two --

UNIDENTIFIED SPEAKER: They're not relative risk. They're percent change.

PANEL MEMBER KREWSKI: Sorry. I can't see the slide.

So 2 percent increase in risk and sort of a 50 percent uncertainty interval around that and a fifth to 95 percent uncertainty interval.

So one expert said I think this is the best guess. I'm half sure it's in here. And I'm pretty sure 95 percent it's in this range. And all of the other individual experts -- you can pool across experts, but the way these numbers get put up on the board or the way these experts get put around the table to discuss the data, they discuss each other's data, sources of uncertainty, strengths and weaknesses. You modify your original opinion, at least I modified mine. Arden, you may have

stuck with your original opinion knowing that yours was right and mine was wrong. I don't remember.

But this is an example of an expert elicitation that's quite useful. But the one we weren't to show you was on the next slide.

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PANEL MEMBER KREWSKI: We went through a very intensive expert elicitation process for prion diseases, which are a bizarre class of diseases we don't know how they occur. Mad Cow Disease is perhaps the best known. What you do is ask the experts a series of questions to which you know the answers. You calibrate their knowledge. And then you ask a whole series of questions to which you don't know the answers and you give the experts who calibrated well more weight than the others.

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PANEL MEMBER KREWSKI: I'm just going to show you one or two of those questions.

Next slide.

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PANEL MEMBER KREWSKI: So these are the experts. We gave them 22 unknown answerable questions. The 22 target questions after they were calibrated. This is the center room at the University of Ottawa.

Next slide.

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PANEL MEMBER KREWSKI: And here is the first question out of 22 that I could show you. What's the likelihood that we'll encounter another disease like BSE, but it's not BSE? So another zoonotic disease transferable from animals to humans within the class of transmissible spongiform encephalopathies? BSE is mad cow disease. What's the likelihood there is another mad cow disease lurking out there that we haven't discovered?

This slide shows here we have eleven international experts. One expert would give his or her best case. In this case, it's 40 percent likelihood that we'll find another such disease. But that expert expressed uncertainty going from ten percent likely to 80 percent likely. You can see a fair bit of divergence among the experts.

If you just take a simple average, the red line, the overall average is about 60 percent likely. And this is averaging the -- taking the max of the upper and lower limits, if you take the weighted average right up here, 98 percent with the knowledgeable experts of another TSE. So you may see a lot of uncertainty here.

What sense can I make out of this?

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PANEL MEMBER KREWSKI: Qualitatively, I think it's fair to say the experts find it highly likely that there exist animal diseases that may affect humans other than BSE. So that's a clear indication of direction from the experts.

What's going to be the headline in the Washington Post?

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PANEL MEMBER KREWSKI: "Experts think it's 90 percent likely we'll have another disease beside BSE."

So we have 22 of these questions, some of them are more quantitative. Some are more intricate.

I just wanted to show you how the process works. And the reason I wanted this air time, John, is we should think maybe within the California Air Resources Board this is a possible tool. Get a group of experts together, calibrate them with respect to their knowledge of PM2.5 risk issues, and then ask them a series of questions to which you're not quite sure what the answers are, where there's some uncertainty, and use this approach as a way of potentially gauging uncertainty.

How much time did I take?

DR. SAMET: Okay. Great. Thanks, Dan.

So I'm going to suggest that we take about a ten-minute break and then reconvene.

(Thereupon a recess was taken.)

DR. SAMET: We're starting again.

George -- so the next topic is what studies are appropriate to use to estimate health impacts from specific sources such as diesel PM.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER THURSTON: And I guess I just say forward on the slides.

Okay. I'll be very brief, because I just have a couple of minutes.

As you said, I'm going to try to cover a very, very broad topic that requires far more discussion than I'm going to give it. But I will follow it up. Talking about how to estimate premature deaths from long-term exposure to PM2.5.

Next slide.

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PANEL MEMBER THURSTON: So this is like so many other environmental and pollution studies that there are basically three groups of information: Animal studies, controlled exposure studies, and then occupational studies of people who work and get exposed and then epidemiological studies.

We look at a large population. And that's really

what we've been discussing this morning are the population studies. And there is information that can be gotten from each of them and there are strengths and weaknesses. In one line, I tried to summarize those. So it's obviously very abbreviated.

But in the animal studies, the big advantage is it's controlled conditions. And you can use specific pollution emissions to expose the animals, like mice. And then you can see what the effects of specific things are.

The challenge in other situations is that there is a mix and you can't -- it's difficult to break out how much is from each component. Here, you can apply a component. You can add things in, subtract them. So there are advantages to these kinds of studies, especially in looking at mechanisms is biologically plausible which components could have an effect on living things.

The disadvantage is that you're giving up the realistic mix of pollution that, in reality, people aren't exposed to just one pollutant. They're exposed to a variety of things.

And also there is a species extrapolation required. There's people are not the same as mice and there is a lot of differences. And so you have this whole problem of extrapolating, especially in terms of trying to get a dose-response, how much pollution for how much

effect. And so quantitatively you really can't use these studies for risk assessment, but you can use them as a way to look at biological plausibility.

And then there are occupational studies. For example, toll workers who get exposed to air pollution and predominantly traffic pollution and the advantages that they're human population with real pollution mixes, not just one pollutant. But the disadvantage is that they're very high exposure, so they're not like the general public.

And also there is -- generally, any time you look at an occupational group, you have to worry about are they different from the general public? Is there a selection bias that goes on? The type of people who get these jobs and keep those jobs might be different from the general public. And you probably don't have the most susceptible individuals in that population.

And so when we talk about occupation, one of the big concerns people have, is there a healthy worker effect. So it makes them not representative.

So basically the concern would be that they're getting very high exposures, but they have lower effects per microgram. So you end up with very high estimates of effects.

The epidemiological studies have advantages.

Those are real people getting real exposures. And it includes everybody in the population, including who might be susceptible in the population. So that would be like people with preexisting diseases, older children, pregnant women, those populations.

But the disadvantage is that then it's hard to differentiate out how much is from one component. For example, diesel versus on the component, oil burning. And so that's the challenge.

Next slide.

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PANEL MEMBER THURSTON: So of the epidemiological studies, you know, basically I broke them into three groups.

One is proximity to roadway studies. And the advantage of that, you know, again, they are real people and they have large traffic exposures. I think in Europe it's more of a diesel exposure, but in the United States it's more of a mix.

And disadvantages of those is again how much is diesel, how much is other traffic pollution, if you find an effect. There is always a concern -- well, in all studies really possible socioeconomic status. The people who live near the roadways in the case of the study, are they the same as the people who live further away?

As a really nice summary of all this, there is a recent -- just last month an HEI special report 17 that goes through all these studies. So that's worth looking at and I think should get into the process. And maybe Dan will want to maybe summarize the findings of that or if you want to add to that, or you could assign it to Aaron.

Two slides.

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PANEL MEMBER THURSTON: But basically in that report, if I can try to summarize it, even though I am not the expert on that report, it seems to me what they were saying with the long-term studies was that the results of looking at proximity to roadway were consistent with studies of air pollution in general, but there weren't enough studies that have been done where they took long-term cohorts and analyzed this to be able to come to some decision about causality.

And correct me if I'm wrong.

So that's very relevant to look at. Special report 17, I think it is.

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PANEL MEMBER THURSTON: And then epidemiology studies looking at particulate matter. We've been talking about those all day with their relative risks or hazard ratios.

And the advantage of those, we do have many studies and we have representative exposures and the general public that's studied. And so they're very relevant.

But the disadvantage is if you're trying to apply this to diesel, that you're assuming that the toxicity of diesel is not significantly different from all particles. In other words, that you're saying that we can't really say whether diesels are more or less toxic than PM2.5. So we're going to say it's similar to other PM2.5 and treat it that way, if you're going to use particulate matter studies.

Now, there is another option, which is epidemiological studies looking at the particulate matter component such as by constituent, a trace element, or even doing source apportionment where you take the mass and apportion some of it to coal burning and some to traffic. And there are studies like that beginning to come out, but it's in a very early stage. And so while it has the advantage that would yield results of mass deaths per amount of mass, let's say, or relative risk, that's more specific to traffic and to diesel.

The disadvantage is we don't have that many studies yet. So it's not really possible to have a body of knowledge to come to that estimate yet. And I think

the basic, you know, situation with that whole area is what Mary Ross was really speaking to this morning is that we don't have enough information to say that one component is much more toxic that another component yet and that one thing is very much more and that one is very much less. And right now we can't answer that question with sufficient confidence.

So I would say, you know, based on our studies, it does seem that the fossil fuel combustion component, the kinds of things that Arden Pope was talking about, the fossil fuel combustion component would be among the more toxic.

But I think a conservative assumption is to say, okay, we are not going to say it's the most toxic. We're going to say it's similar to other PM2.5. So while not the best answer -- I would love to have more studies done of components. I think that's a conservative approach to that. But so that's it. And so maybe that will get some discussion going. Something to shoot at.

DR. SAMET: Tom.

PANEL MEMBER HESTERBERG: Again, my name is Tom Hesterberg. I'm Director of Product Stewardship and Environmental Health at Navistar, Incorporated.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER HESTERBERG: We're the major U.S. manufacturer of trucks and engines and buses, school buses, as well as RVs, military equipment in the U.S. There are European competitors. But especially in the intra-city vehicles, the pick-up and delivery vehicles, you'll either see Navistar or international on most of them around the city. So we are obviously very interested in this topic.

I don't see Mary here. But thank Mary Nichols and Bart Croes and Linda Smith for inviting me and organizing this. I think this is a fairly balanced discussion of the issues not only around PM, but I'm going to talk more about diesel on my topic.

I want to mention, too, in your packet -- I wanted to thank CARB for including -- there is a short white paper that I wrote that's going to go into more detail than I can go into in five minutes. And there is also some of the recent review articles that I published in a peer reviewed publication on diesel exhaust.

And I wanted to thank George too for a good intro to what I'm going to provide, because I didn't go into the pros and cons of these different studies. I'm going to cover the ones that you covered focusing primarily on studies that have been done on diesel exhaust.

One that I don't think you mentioned is human

volunteer clinical studies. And those obviously have the advantage of controlled exposures, controlling the environment, but also obviously a lot more relevant to humans. They are relevant to humans.

Next slide.

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PANEL MEMBER HESTERBERG: I'm not going to go into the details. I mentioned earlier I'm not an epidemiologist, but it's clear there is a lot of uncertainty around the ecological studies. Model selection is one that a few years ago there was a lot of discussion around that because that can certainly impact the results. And you know, there may be a tendency to select those models that provide the increases and the associations.

Treatment of co-pollutants. I brought that up this morning. I'm still not comfortable that the potential co-pollutants are being dealt with as confounders. There are thousands of other potentially toxic and some known toxic agents in the atmosphere that aren't being measured in these epidemiological studies. And a lot of those go up with PM, go down. There's some recent studies, Joe Monalie's group and others, filtered out the PM from diesel exhaust. And a lot of this toxicity is still there. There's not that much, and it's

at high doses, but there's still toxicity when the PM are gone. So there are a lot of other components, seasonal trends -- I'm not going to go into all these.

But I think because of these uncertainties and because the relative risks are small -- and I mentioned earlier the Boffetta paper that said unless you're over two in terms of relative risk -- and for these we are down around .2, .1 to up to .4 or higher. We're down in the lower range of relative risk. I think there are other studies that need to be done to provide the biological plausibility and understand mechanism, et cetera.

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PANEL MEMBER HESTERBERG: I wanted to point out also in terms of going forward the idea of focusing on epidemiology studies of diesel exhaust. One of the biggest problems there is that there are no valid markers for diesel exhaust. HEI conducted or oversaw a study several years ago where they brought in the experts. And the bottom line is there are no specific markers.

One of the problems is that ambient PM in the monitoring sites and cities, most of that pollution is coming from the side streets. And a lot of that is automobiles and not diesel.

So I know that CARB has proposed the possibility of using NOx as a marker. If most of that NOx is coming

from automobiles, that's not going to be a very good marker. And we're going to discuss that. I think, Bart, we talked about that yesterday and the idea is we ought to conduct a separate workshop just on that issue alone. There are appropriate markers. Are there good markers to use going forward?

The ratio of PM and NOx emissions varies. When the exhaust is hot in the diesel truck, you get a lot more NOx. When it's cold, you get a lot more diesel PM. So it's going to depend on the driving conditions. And a lot of our vehicles in the city never get that hot.

And then there has been a study published in JAWMA, Journal of Air and Waste Management Association, 2003, that show NOx goes down. It's well known NOx goes down on weekends. You have fewer trucks. PM does not necessarily go down depending on the city. So there's not necessarily a correlation.

And then there's going to be a workshop on that probably in the next couple of months by CARB to really dig into that in more detail.

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PANEL MEMBER HESTERBERG: Want to talk more about the laboratory inhalation studies. I think they have some utility. I mentioned earlier you have control. You know exactly what you're exposing the animals to. And there

have been a number of studies of -- I call it TDE, traditional diesel exhaust. This is pre-1990 diesel. It's quite a bit different than what I'll talk about later, the new technology diesel exhaust where most of the PM has gone.

But in a six-month study that was completed by Lovelace down in Albuquerque -- and this is actually part of a NERC study where they're comparing a lot of different combustion sources -- exposures were to whole diesel exhaust. And I want to point out that the PM is only about a third of the mass. Two-thirds of that mass are gaseous components. So any effects you see you can't necessarily attribute to the particulate matter.

As I mentioned earlier, in fact, when you filter out that particulate matter, a lot of that effects are still seen.

But basically what they saw even at very high doses, a thousand micrograms per cubic meter, and they drop to 300, 130, they saw mild pulmonary and some cardiovascular effects. A lot of those were transient. Essentially didn't kill any of the animals. There was no mortality, even at a thousand micrograms per cubic meter, two or three orders of magnitude higher than you see in a city where the exposures is two to ten micrograms per cubic meter.

And I realize we don't have the "susceptible" population here, but no mortality, no real indication. And also in the NERC studies, they're comparing not just diesel, but they're comparing that with gasoline exhaust. And wood smoke and a lot of those same mild effects are seen at similar levels. So I don't think there is any -- you can attribute any unusual toxicity diesel exhaust particles to any other exhaust particles.

If you put a particle trap on it, Jake Lovelace put a trap on a Yanmar engine and compared before and after exposure. Even those mild effects went away when you put that particle trap on.

Now, the trap is a catalyzed trap. It not only removes the particles, but it actually burns the hydrocarbons. So hydrocarbon is going down. Everything is going down with these particle traps.

And then in terms of cancer, one of the reviews in the packet there -- we reviewed all of the studies out there. You only get lung cancer in rats at overload levels, higher than a thousand micrograms per cubic meter. You get below that, there is no cancer. There is no cancer even at those massive levels in mice or hamsters either. So I think it's pretty well accepted this overload is an unusual thing. Probably doesn't get to those levels in humans. And certainly the animal evidence

does not support diesel being a carcinogen.

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PANEL MEMBER HESTERBERG: And I don't have a slide on this, but I've also reviewed the occupational studies. The trucker study is a major one. And there is a railroad study. The issue with those studies is that although they find a small increase, the odds ratio is about 1.5. Maybe a 50 percent increase. It's consistent across all exposure levels. In fact, that same 1.5 was found in truckers before dieselization of the trucks. So I think that's pretty weak evidence there.

In terms of the human volunteer studies, we reviewed about 50 of those studies that have been completed. There's little or no consistent impact observed at the primary exposure levels that have been used are 100 or 300 micrograms per cubic meter. Again, those are fairly high compared to the ambient exposures of diesel exhaust which are on the order of two to ten micrograms per cubic meter.

And there is some recent studies. They haven't been published. But there are essentially abstracts where they put a particle trap on the human volunteer study exposures. And even those subtle pulmonary and cardiovascular effects that we're seeing completely disappear when they put that trap on. That's Kent

Donaldson's group at University of Edinburgh.

Next.

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PANEL MEMBER HESTERBERG: I want to point out that I think future studies should focus on the new technology diesel exhaust. We've done some analyses, part of the ACES study that's being overseen by Dan's group, HEI. We've got some of the data on the emissions. The emissions when you compare to old diesel, they are actually more similar to CNG, compressed natural gas. And CARB has been involved in some studies that have collaborated that.

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PANEL MEMBER HESTERBERG: And final slide just to summarize.

I think epidemiology studies still have quite a few uncertainties. I'm uncomfortable about one. I know there is a huge (inaudible) of chemicals and potential toxins in the ambient air. When you measure PM, that tends to go up and down with those. Those are not being measured. We don't know -- those are unmeasurable in many studies. Unmeasurable confounders. They're not being taken into account. There is no marker for diesel exhaust in terms of going forward. Maybe we'll come up with a marker with Bart's group next month.

I think some studies that do have some utility are sub-chronic and chronic animal studies, human volunteer studies, occupational studies in humans. And bottom line is when you get down to ambient or even occupational levels of diesel exhaust, there is not a whole lot going on. When you compare it with other combustion sources, it's not very different from wood smoke and some of the other sources.

And again, in the future, ten years from now, most of the vehicles on the roadways here in California and throughout the U.S. are going to be new technology diesel exhaust emitting vehicles. And these are extremely clean. There's no black soot coming out the back. You can't smell anything. It's as clean or cleaner than compressed natural gas exhaust.

Thank you.

DR. SAMET: Thanks, Tom.

So I'm going to suggest that to make certain that we give as much time as possible to the questions that have come from the public that we take 10 minutes, 15 minutes for discussion here and then move on to the questions, because we have both questions from the public to discuss and a wrap up from Dan.

So why don't we open this up for discussion for a while and then move on.

Fred.

PANEL MEMBER LIPFERT: I just want to make a quick comment, because I've forgotten about it and I think it's relevant.

A couple years ago, I was cruising the autobahn with some relatives, and we got stuck in traffic. And to my amazement, when you look out the window of the car, about 18 inches off the ground you're looking at a diesel exhaust pipe. European trucks don't discharge in the air. They discharge on the ground. So when you're looking at European studies, I think that's something that one might really want to think about.

And also as you probably all know, when you cruise the autobahns, you don't go through towns in Europe like you do in the U.S. But the central streets, the regular streets do. And many of those houses have no set-back. If you look at the exposure study for the Hoke, et al, epidemiological study for a few years ago in the Netherlands, the minimum distance from the roadway was sited at ten centimeters. So we got a lot of apples and oranges to sort out here.

Thank you.

PANEL MEMBER ENSTROM: I would like to propose that based on the information particularly that Tom presented and the new diesel technology and the great

reductions in diesel levels that CARB reconsider the designation of diesel particulate matter as a toxic air contaminant. I think there is a process for that. And I think it should go forward because of all the advances and the information that's been presented today. And I think I'm proposing that. I believe that it should be done, because I think there is a lot of irregularities in what was done in 1998 and I think it should be straightened out.

That's my proposal.

DR. SAMET: Okay. Other comments?

Roger.

PANEL MEMBER MC CLELLAN: Just a general comment.

As I emphasized earlier, you know, at the end of the day, the regulator, the policy maker, the politician has to use whatever science is available. And the science has to inform what is ultimately a policy decision. We might even be able to estimate to some degree some level of risk associated with a particulate level in the environment. But ultimately a decision on how that's used then in setting some standard involves acceptable risk. And that really is a decision that scientists can't make but is left in the hands of the policy maker.

The point I wanted to make is that the challenge for the regulator is to look to the future, and one of the

things you're going to do in terms of the future but using the science experience of the past. And that's why in some of my comments earlier I dwelled on what I viewed as important factors in terms of past exposures that we are now weeding out, if you will, in our epidemiological studies. And essentially as I've looked at the data over the last 30 to 40 years, there's no question that we have made major advances in terms of improving air quality across the United States.

To paraphrase, one of my friends and colleagues said the problem we have is that we've never decided on what's the rule for success. And I think that kind of is imbedded in that policy decision in terms of the regulator in terms of putting any new regulation in place or making a change is how much more is needed in terms of going lower.

As I said, as I look at it, I see that there has been a lot of changes in terms of air quality over time. I'm not certain where we are on that path in terms of how much "cleaner" it should be. But I think those policy decisions ought to be made not looking just at the information through our little magnifying glass on this issue, but taking a broader view of all the factors that influence human health.

DR. SAMET: Okay. Let me ask again -- going back

to our charge on studies to be used for estimating health impacts of diesel, other comments? We heard from both George and Tom.

Because if not, we have lots of questions from the public. To use a metaphor, this panel looks a little out of gas. And it could be that we should move on to the -- roused up Arden.

PANEL MEMBER POPE: I actually have to go to catch a flight. So I'm going to wait for a few public questions.

But on this, I want to just say one thing. And it kind of relates to what Suresh said earlier in that there is a number of us he said that have latched onto PM2.5 and thinks it's it. That's not true. And it's not true with diesel emissions either.

Just very briefly, when I got involved with this, my first studies used the word "community" air pollution, because I had no idea which pollutant was mostly responsible. My buddy here, George, and others tried to convince me that it was acid aerosols. So we spent years chasing the acid aerosol effect.

The reality is the acid aerosol doesn't pan out, so we started looking more closely at inhalable particles, PM10. That didn't pan out so well, especially in those long studies where the PM2.5 consistently --

PM2.5 and not acid aerosols, but sulfate and other sulfur oxides consistently outperformed our other indices of air pollution.

The bottom line is it's been the data that has led us to PM2.5 as being the index. And it seems like that works in areas where you have a lot of truck traffic, a lot of gasoline automobile traffic where you have steal mills, where you have copper smelters, where you have coal-fired power plants. Why this is the case, I don't know. But it turns out -- and we tried to go to ultra fines. Ultra fines don't seem to work as good as PM2.5 right now. So the bottom line is it's the data that's driven us to PM2.5.

I will agree that the different sources of PM2.5, they don't -- none of them seem to be any worse than the others. That includes diesel. It doesn't seem to be particularly worse than gasoline or steel mills or coal-fired power plants.

And this is one of the problems with public policy is, you know, the different industries want it to be the other industry that's really the source of the pollutant that matters the most. And it's sort of bad news that us as epidemiologists are giving, and that is we're saying it looks like all of the sources matter. And that's the best answer we've got at this point.

So my most -- I guess the plea I have is for the public and everyone else to understand is that the movement toward PM2.5 and the various sources of PM2.5 as being contributors on the adverse health effects that we see has not come by any personal vendetta against PM2.5 or diesel emissions or coal-fired power plants or whatever. It's that's where the data have led us.

Now where it's going to lead us in the future as to whether diesel is really way more important or not, I don't know. But right now, it appears that where we're at is that the various sources of PM2.5 contribute maybe not equally, but contribute in a combined way to adversely affect human health.

Thanks.

DR. SAMET: Suresh. And then we have two other commentors, and then we're going to go I think to the public.

PANEL MEMBER MOOLGAVKAR: I just wanted to make one comment, Arden. And that is if you look at combustion source particles, each cigarette contains about 16,000 micrograms. So you're clearly saying that combustion of fossil fuels is far, far riskier than the combustion source particles that we get from cigarette smoke. Is that what you're saying?

PANEL MEMBER POPE: Cigarettes are way worse. No

doubt about it.

PANEL MEMBER MOOLGAVKAR: On a per micrograms basis, you're saying that air pollution is a lot worse than cigarettes.

PANEL MEMBER POPE: The evidence suggests that environmental tobacco smoke as well as urban air pollution both on a per microgram basis is more toxic than active smoking. Why that's the case, I can't tell you. But that's certainly the evidence.

PANEL MEMBER MOOLGAVKAR: Well, you're talking about your paper in circulation. But that paper doesn't explain anything. All it does is --

DR. SAMET: We're heading off track here. We're heading off track.

Melanie.

PANEL MEMBER MARTY: I'm answering the question: What studies are appropriate to use to estimate health impacts from specific sources such as diesel PM?

Roger said you have to use the science you have. Right now, we have lots of data on PM2.5. It's robust. There is effect estimates we can choose from. It makes sense to me. And we have, as a sister agency -- the ARB said that we are comfortable with them at this point in time using those effect estimates to look at diesel PM.

DR. SAMET: Okay.

PANEL MEMBER MC CLELLAN: I missed your comment you attributed to me. What was it you were attributing to me?

PANEL MEMBER MARTY: That you have to use the data that you have.

PANEL MEMBER MC CLELLAN: Yeah. Absolutely.

DR. SAMET: Michael.

PANEL MEMBER JERRETT: I just wanted to raise another issue I think is important, and that's the concept of intake fraction. We've heard a lot from some of our other presenters that levels of diesel exhaust are going down. But what has happened though is the vehicle miles traveled have gone up at a rate of three to four times population growth over the past 20 years. So our roads have become more crowded and more congested. There are more roads. There are more people living in proximity to heavy traffic. And some of that is diesel traffic.

Very good studies in Los Angeles along the 710 freeway unequivocally shows the difference of on-road exposure -- Scott Froines has done the best studies. He's at UCS in John's department. Unequivocally showing massive increases in black carbon, ultra fine particles. Virtually all of the major constituents of toxic PM are on the road with a lot of trucks compared to roads with cars. So we have a lot more people living close to these areas.

And someone said earlier the dose makes the poison. But the place also makes the poison, because these place conditions how much of the fraction that is emitted actually enter into the lung. And unless we start taking that into account in our studies -- and Zack and I had some interesting discussions about how that might be done by looking at proximity to roadways and the level of population exposed. I think that's another consideration when we want to look at diesel particulate to see how we can do these risk assessments. Because we're going to have to understand the intake fraction as well as the levels that are coming out of the exhaust, because the vehicles miles traveled have gone up so much and they're in proximity to huge populations.

PANEL MEMBER LIPFERT: I just want to make a quick response.

Arden, there is a certain circularity in your argument, because the reason you have PM2.5 data is because EPA decided to measure PM2.5. If they had put a similar effort into ultra fine or benzene or benzo[a]pyrene or formaldehyde, we might have a different situation. We can't answer that question. It's just part of the evils of the system that we don't have an independent monitoring agency that doesn't have a regulatory agenda in mind.

DR. SAMET: Okay. I'm actually -- Tom, to the diesel point?

PANEL MEMBER HESTERBERG: A quick point on Michael Jerrett's comment, and I think it's a good one. But it's not just vehicle miles traveled. I think it's density on the freeway. And that's probably not going to change. The L.A. freeways, I mean, you're in creep mode and almost like a parking lot or you're flying along. I'm not sure that's going to change on the roadway. And we know from studies that the PM drops dramatically as you get 200 feet away from the freeway.

So I'm not sure vehicle miles traveled is going to necessarily increase the exposure to people's --

DR. SAMET: I'm going to suggest we're probably drilling down too deep, and I think we have probably not enough time to cover all the purple cards that are in hand. So I think we need to move on. But after 5:00 you can continue this discussion outside.

There were three kinds of questions that came in. There were simple ones that I think I can just quickly run through myself and maybe give a ten second answer that hopefully no one will disagree with. There are a number that I think need sort of a full response by the panel. And then there are a number that really relate to matters of policy and the ARB itself.

And what we're going to do first is turn to I think Mary for some general responses to these comments, and then the panel will focus on those that are less policy related.

AIR RESOURCES BOARD CHAIRPERSON NICHOLS: Well, I have been listening to the science debate. And it's been really interesting for me, because you know, I tuned into this topic when I was at EPA in the Clinton administration and was involved with the original setting of the PM2.5 standard and checked out for quite a long time. And now obviously I'm back here at ARB responsible for implementing our programs. So I have appreciated how much work has gone on since those early days and how much of the controversy that swirled around the whole issue of moving from a focus on all particles to smaller particles has now moved on to a much more sophisticated kind of discussion.

There are about six questions here that are really policy questions. And they probably reflect a lot more of what people who have been here -- I think some of them had to leave. But I know there were a number of people in the audience who are here because they are involved with some of the industries that are being regulated, especially trucking, construction, and so forth. And so their questions are much -- they tend to be

pretty practical about why are you doing this and what's your excuse, basically.

So I just wanted to take a step back for a second and say how I think we're approaching the issue of regulating PM2.5 and how we think about these questions at the Air Resources Board, which is a policy agency.

So first of all, Air Resources Board is the agency created under state law to do basically two major things. One is to come up with a plan and develop the regulations to meet federal air quality standards or any state ambient air quality standard that we create. And the other one is to deal with reducing exposures to toxic air contaminants.

I want to tell you that having had this job, the same job I'm in right now, you know, 30 years ago, the levels of public concern about air pollution wax and wane, mostly in regard to economic conditions more than they have anything to do with the measured air pollution.

The comment about how people ought to realize that we've really done a lot to clean up the air, that's interesting to me, because I know we've cleaned up the air. I've lived through a lot of that experience. And there's no question that we measure many pollutants at far lower levels than we did when I moved out here in 1970.

On the other hand, public concern, especially in

some communities, has not gone away about air pollution. People, even those who lived through the period when it was much worse than it is now, still feel that air pollution is unacceptable. They're worried about different things. They might be worried more about toxic chemicals than they are about ozone. But they're still -- the pressure to continue the work of cleaning up the air is strong.

Okay. So with respect to PM2.5 and what we're doing with that, one of the things that I think has created a lot of concern and understandably so is that the very controversial report that came out with the information that suggested higher risk of mortality and premature death from being exposed to PM2.5 came out shortly before the ARB adopted some regulation or while we were in the process of adopting some regulations dealing with particulate emissions from diesel engines.

And those two things are sort of related, but in some ways they're not related, because the truck rules and the off-road diesel equipment rules that the ARB has adopted and is implementing were adopted under the State Implementation Plan that we have to submit to U.S. EPA for meeting the federal fine particle standard. We are not at liberty to decide that we don't like -- that we don't think PM2.5 is a problem. We have to submit a plan on

pain of being sued and losing our freeway funds and so forth if we don't show how we're going to meet that federal ambient air quality standard.

And the plans that the State had developed over the years, particularly for the South Coast air basin and for the whole central valley, seemed to show that we had done just about everything we could do to clean up stationary sources, all the power plants and refineries and canneries and everything else. Everybody had controls on. And so you're going to have to go by logical steps. We cleaned up fuels, and the next step was to go look at diesel equipment. And they have been the last group to be regulated. And there is a good reason for that. It's important economically. It's characterized by a lot of small businesses. So it's much more difficult and expensive to regulate in that area. But the time finally came to adopt those regulations.

Now, do we consider effects of the economy or do we consider the economy? Yes. I've already said that cost effectiveness in terms of regulation is a key issue for ARB. We look at cost effectiveness relative to other things that we could control. So every time we do a rulemaking, we try to look at it in comparison with the cost of other rules that we've already adopted and not to just jump into things that are way more expensive.

We also look at the fact that the economy can change and sources can change in terms of their contribution to the problem. So for the diesel-related industries, both construction and trucking, the current economic downturn has made a big difference in the inventory. We know that. And so we are both slowing down in terms of enforcement of rules, and we are actually looking at reviewing those rules to see what can be done or what needs to be done to continue the progress that we're making on meeting air quality standards but to do it in a way that doesn't over regulate or cost more than it has to.

I guess the last issue is about the toxic aspects of diesel particulate specifically, which I realize is some of the main concern of some of the people that are -- whether the toxicity or the identification of diesel particulate as a toxic air contaminant was correct when it was first done or whether it should be re-looked at again in terms of current information. And I guess that process is not under the control of ARB. It's something that we take -- we receive our information on that through the Office of Environmental Health Hazard Assessment. But my view would be we should regularly look it up and indicate our toxic assessments if we have new bodies out there. It would be wrong not to do that. Science moves on, and

particularly relative information about what's important and what isn't.

So I think that actually answers the major questions. There was one question somebody asked why we had so many industry representatives here to manufacture doubt. I would just say to that I don't think of anybody as either an industry representative or an environmental representative here. I know that people have disclosed their salaries or research is funded by different groups. I think that's a fact that can be noted. But I guess I believe that science is science and the great thing about a symposium like this is it does allow people to expose each other's ideas, challenge each other's positions, and I think people have done that very effectively.

So I think that covers what I was assigned.

DR. SAMET: Good. Thank you, Mary.

(Applause)

DR. SAMET: Okay. So I think Dan is going to wrap up. So we have a big stack of purple slips. And I'm going to run through a few of them that I think I can answer quickly.

So one question is have any of these studies demonstrated a relative risk ratio of two or higher, the standard used by federal courts for admissibility of scientific evidence?

I'll just make a quick comment. I'm quite familiar with this issue and the federal reference manual used to train judges. There's not a bright line for relative risk. This has sometimes been construed that way for individuals, but not on a population level.

Another question related -- I think this has been an important issue in the discussion. The clear definition of premature mortality and the comment is versus harvesting. And early on there has been a substantial discussion. Here really the issue is for these premature deaths, how much life shortening has gone on?

Historically, when these day-to-day studies were first done, the question was how much life shortening is there? And these longer-term studies became very important, because they pointed to a longer degree of life shortening, not just a day to day, but perhaps some matter of months to years, something of public health significance. So there's no a definition that we care about one day of life shortening, ten days of life shortening. None of us would want to have our lives shortened from a public health perspective. But there's not a bright line in this discussion.

Bob, do you have any addition?

PANEL MEMBER PHALEN: On the question on the

relative risk of two, to me, the question is related to indicating that you're looking at surrogates for the real factors. In other words, when you have a relative risk of two or so, there is a -- historically, there is a strong indication that what you've measured is not the cause. So I think that's the point.

DR. SAMET: Let's not go there. I think it's largely based around calculation of attributable risk and those are exposed to a factor and probability of causation. And you're a little bit off. But we can talk about that privately.

There is a discussion here about tire tread rubber, very high percentage of carbon black as filler material. How is it separated from the carbon of diesel exhaust in those studies since there is obviously heavy tire wear in the same locations as the fuel usage?

I know around the course PM fraction there has been discussion of the potential contribution of materials from tire wear. Perhaps there is somebody who can comment specifically on any separation of the carbon in the tire material, the tread from other sources. I suspect what's collected is mass on a filter and analyzed, it's probably just carbon I suspect. But you're hearing that from an epidemiologist.

PANEL MEMBER JERRETT: There's research being led

by Frank Kelly in London, England, to look at the toxicity of particles that come from tire wear compared to other elements of black carbon. And as far as I know, it's showing up as toxic.

DR. SAMET: And then a question: Are sulfates toxic? And I assume this means sulfate, per se. And I think this is actually looked at in a lot of critters. And isn't the answer pretty uniformly not; is that correct? Roger or Bob, somebody help me out.

PANEL MEMBER MC CLELLAN: You have to expose animals to extraordinary concentrations. The ability of the respiratory tract to handle and inhale sulfates at levels well above those is typically seen as quite remarkable.

PANEL MEMBER PHALEN: There are some exceptions, like vanadium sulfate, for example.

PANEL MEMBER THURSTON: Can I respond to this? Because this is a subject that comes up a lot and has been looked at. There is a recent British study report that looked at this evidence. And basically, you know, if you look at sulfate alone, then you have to go to really high levels to see effect.

However, it's never alone in the atmosphere. What they're finding is that it interacts with things like transition metals, that it's an effect modifier. So

places with more sulfate that seems to imbue the particles with more toxicity, not because of the sulfate, per se alone, but its particle is an interaction of many things. And so that's really the thinking right now is that it's an effect modifier. It makes the particle more toxic. It's not itself the cause all toxicity --

DR. SAMET: I don't want to dwell too much. We have some much more complicated questions to go on to.

So another question that I'm going to read, and I think it's an important question of explanation. Can you show us one death associated with diesel particle emissions exposure in California?

And I think this is a very useful question and relates to understanding of the fact that indeed these are calculations of attributable numbers under models and assumptions. It's not that anyone can go to a particular person and say this is the person who was a victim of diesel exhaust, radon, or anything else. Essentially, with some exposures, we become far more susceptible to lung cancer in a heavy and sustained smoker.

But these are calculations at a population level, and they don't go down to specific individuals. And I think this is something that's very important to be communicated as ARB or anyone else who does these estimates tells the public about them.

So let's go to the tough stuff. And there are three in my hand that primarily relate to changes in diesel. So here's a question. As engine technologies improve and particle emissions decline, will the health effects decline into insignificance? If so, when?

Sort of related to that is a question that I think Tom alluded to in some of his presentation. All the major studies are with "historical diesel." How do we calculate the risk of today's diesel?

And another question just related to the change in the fuel, the removal of sulfur and what the implications are. I think these questions relate to how do we, in fact, use some of the historical data to deal with now and I think the future.

So Tom.

PANEL MEMBER HESTERBERG: Just one thing to keep in mind is not only the particulate matter levels are coming down to near zero in terms of diesel emissions, but a lot of other things are coming down. The NOx is coming down. Hydrocarbons, as I mentioned, that particle trap is catalyzed with platinum so it burns off not only the particles, but the hydrocarbon comes down to near zero. We're not going to know -- just like now we don't know in my mind attributable the health effects to particulate matter.

Once all these new technology diesel engines are in place, it's not just particles; it's a lot of the pollution. That's probably a good thing. Maybe we won't know exactly what was brought down was attributed, but I think the studies Dan is overseeing at HEI is going to give us a handle on that.

PANEL MEMBER GREENBAUM: We actually are testing newest diesel. But in addition, there is a set of studies that we're doing, several of them in roadway tunnels, that have tracked quite dramatically reductions in emissions over time as new rules have been put in place showing a reduction in the diesel emissions. There haven't been such a set of studies, but there probably should be now that we are seeing much, much cleaner diesels. So as that mix increases, that's only been for the last two years, there would need to be increase.

I would say our ACES study, which ARB is happening to fund, has published its first report on dramatic emissions, including ultra-fine emissions from the heavy-duty diesel trucks and buses even during regeneration of the filters.

PANEL MEMBER HESTERBERG: Just a quick corollary to that is -- I think Dr. Lipfert touched on this. The high emitters I think are the issue now. There is a lot of low-hanging fruit out there. And the emissions program

here in California apparently isn't working, because those are still there. I don't know exactly why. But I think if there is a focus on that, that would be the next step. Rather than putting more and more after treatment and controls on the new vehicles and new diesel new cars, let's go after the high emitters. And some of those are new vehicles. It's not necessarily just the old vehicles that are high emitters.

DR. SAMET: Roger and then Melanie.

PANEL MEMBER MC CLELLAN: I just joined the answer to that -- back to the question you were asked about has anybody seen a death from diesel exhaust. You went through a very logical explanation, which you said that going down the line of assumption and calculations one could calculate -- make that calculation. Using those same assumptions, we'd say based on the same number of vehicles operating today we'd have a 99 percent reduction or greater using the same models, because the new technology really is that effective. It's a combination of the engine, the control system, the exhaust after treatment, and that ultra low sulfur fuel.

DR. SAMET: Melanie.

PANEL MEMBER MARTY: I was just going to say that the risk estimates are based on per microgram per cubic meter. So as that drops, yes, your risk estimates drop.

DR. SAMET: Okay. So any other comments to this set of questions?

Should we be monitoring more pollutants? Which one would we use of these data? Bob.

PANEL MEMBER PHALEN: I think definitely the biological aerosols. You know we've been very slow to recognize their potential importance. And they're very, very potent. I remember one MD pulmonary physician said one potential engrain in a sensitive enough asthmatic can trigger an attack. So I would propose the biological components as worthy of more measurement.

DR. SAMET: Other commentors on this? I'm not sure we've satisfied the questioner.

Melanie.

PANEL MEMBER MARTY: I would just say as time is moving forward, we are slowly looking at the individual components of particulate matter, and more of those types of studies are needed and better measurements of those are needed.

DR. SAMET: I would essentially add from the perspective of the epidemiologists, there are a few epidemiological studies that have the resources to establish their own monitoring network and any population context we rely on what is there.

I think Roger and others have pointed out we

study what we have at hand, because that's what we have at hand. You know, I guess the question of whether a group could sit back and say here's our best candidates for health risks, whether it's biological aerosols or something else. And this is what somebody should be thinking. I don't know how ARB thinks about this. But essentially it means every time the monitoring changes, because it involves money and implementation of new a monitoring network is costly, of course.

Yeah, Roger.

PANEL MEMBER MC CLELLAN: I think that epidemiologists, scientists, we love more data. We'd love to have more specificity out there in terms of what's in the ambient environment, link that in terms of our health effects studies.

But I'll sort of state the obvious. A monitor has never protected anyone. So the public shouldn't be confused by putting more monitors out there that we protect them. We may gather more scientist data, whatever.

I think there is some element of a need to step back and make a little more common sense approach in terms of -- we've heard a comment from Tom, low-hanging fruit. I think all of us understand that we have high emitters out there on the road. How do we deal with those? That's

a real tough political policy issue, because the American public by and large doesn't like regulation that comes down and impacts on them. They're quite happy in terms of impacting somebody else.

But in terms of Michael might be -- there's a little different sort of thing. But I think we need to step back and be very cautious with regard to suggesting more monitors help us out in some way in protecting public health. I don't think they do.

DR. SAMET: George.

PANEL MEMBER THURSTON: Well, I would say the information we gain allows more efficient public health decisions to be made so that once the information is gathered, the monitors itself -- if you don't use the data to learn more, then you're right. But if you take that data and that information and you learn more about what's causing the risks and what's not causing risk, then public policy makers can make better decisions to more efficiently and hopefully, you know, at the lowest possible cost get the maximum public health benefit.

And along those lines, I think we're moving more towards, as we discussed, trying to look at things in a more holistic sense and look at sources and the mix of pollutants coming from them. So separating that out is a challenge.

And EPA is now setting a standard for roadside monitoring of NOx, nitrogen oxides. And that would be an opportunity to look at organics. And there are new methods out there.

What we lack -- years ago, we had a very good tracer for automobiles at least because we had lead in gasoline. That was not good that we had that, but it did allow us to focus in and target. We could say, okay, we see lead along a roadway. That's from automobiles. And then we implemented catalytic converters. And because the lead poisoned the catalytic converters, we took the lead out. It really didn't have so much to do with the fact that it was lowering IQs in children. It had to do that we had the catalysts. And eventually we learned more about the effect of lead, so it's a good thing we did that.

So we don't have a marker for -- a very good single marker for automobiles versus diesel. But there are new techniques out there looking at organics coming out of various sources and able to differentiate where the particles come from based on that. So we have trace elements from the network, the speciation network.

What we don't have is any data along the lines of these JMA -- HEI has been very active in promoting research into this area. So -- right, Dan? And so those

kind of data would be very effective in trying to discriminate out how much of the particles are from which sources. And especially I think this roadside monitoring that may result from a proposed standard at this point, NOx. It's final now. I should know that.

PANEL MEMBER MC CLELLAN: A single purpose monitor doesn't provide you much in the way of scientific information. If you learn nothing today, again, it's you can't go out and look at a single marker and somehow try to draw an association.

PANEL MEMBER THURSTON: So you're agreeing with me?

PANEL MEMBER MC CLELLAN: No. I'm agreeing it's worth less to put out NO2 monitors along roadways. If you're going to put out more monitors, you've got to be looking at the mixer of what's there. Single purpose, single indicate for monitors are not very useful. But that can't be regulatory -- (inaudible)

PANEL MEMBER THURSTON: (inaudible) We have an opportunity to better characterize emissions and the exposure along roadways by enhancing, not just doing the single pollutant, but adding in organics. If you want to promote adding in other pollutants as well, that's if you want to propose that.

But I think the most cost effective -- if I had

to focus, target in on one thing I would add, it would be these organic compounds so that we can better -- because each source has its own fingerprints, organic fingerprint, it's a little variable. But the sources are different in that. And that could very well be a way to get to the next level.

DR. SAMET: I think the person who submitted this question was trying to stir up trouble.

Mike.

PANEL MEMBER JERRETT: I think these are valid points. But what we do need a lot more of is not necessarily measuring many more pollutants. We need to decide on what are reasonable markers and measure them at many more locations than what we do routinely.

And New York City has just set up a very interesting program where they're measuring in over 100 neighborhoods. They've come up and found something that nobody expected. It's buildings with oil -- level four oil in their boilers and have some of the highest particulate levels in any of the neighborhoods in New York. So that's a system that's going to cost money.

But when we look at the societal investment we have to make in diesel regulations or any of the other ancillary costs that come along with trying to protect public health, the investment in getting better

information to inform the science is relatively trivial.

DR. SAMET: I think this discussion is useful largely for pointing out it would be useful to have questions that you want to answer in implementing whatever additional monitoring is being done. And going beyond that to making decisions about what you might do targeted at particular sources or particular classes of compound is I think a lot of work.

I'm going to move us on. And there is a question -- it's more of a comment. I'll read it, because I think we've touched on it already.

Couldn't the exposure to pollutant mix in large California cities be different than other large non-California U.S. cities due to California emission standards for on-road mobile sources which are more stringent than U.S. emissions standards for time periods for many of the cohort studies? Engine control technology may change not only the inter-pollutant mix, but also the PM characteristics such as size, distribution, et cetera. I think we've touched on these issues, and I think this is in the complexity of understanding the air pollution mixture and its source from place to place.

Mike, here's a question for you. How can you relate the association of PM to elevated death in the California Teachers' study -- and I think there is an

important issue buried in here -- for individuals that spent a majority of their life indoors? What does this have to do with diesel PM?

And I guess teachers -- this is actually an out of date question, because it says why not chalk dust PM? But I'm not sure that chalk dust is in -- chalk is as much in use as it used to be. But historical chalk dust exposure might be.

PANEL MEMBER LIPSETT: Teachers are not the only people who spend most of their lives indoors. In fact, ARB did some time activities studies back I think in the 1980s and early 90s indicating that virtually everybody spends 85 to 90 plus percent of their time indoors.

And with respect to exposures to PM2.5, there are a number of exposure studies that have indicated that these particles remain airborne or suspended for long periods of time and do actually penetrate indoors. Homes are not -- maybe this has changed over time as homes have become better insulated and weather stripped and this sort of thing. But in terms of the overall and compared to like coarse particles or PM10, for example, they do tend to penetrate much better.

Now, John has just opened a recent review article on this as well. But overall, these fine particles do tend to get into schools. Certainly the doors are open a

lot more in schools than individual homes, but these other kinds of long-term studies that have investigated PM2.5 have investigated impacts in people who spend most of their lives indoors. So from that standpoint, teachers are not really different from any other people.

DR. SAMET: Dan.

PANEL MEMBER GREENBAUM: I just wanted to say that we have funded a number of studies measuring personal indoor and outdoor levels of a variety of pollutants in hundreds of households, including the elderly, including families, including caretakers of children. It's hard to measure them directly with children.

And in general, two things. One is -- and this is a place where sulfate, whether or not it has effects, can be useful, because there's not a lot of indoor sources of sulfate. But we do find very strong correlations between the outdoor levels of sulfate as a marker of the particle mixture and sulfate indoors.

At the same time, there are some things that are outdoors that don't show up as primarily coming from outdoors. For example, formaldehyde and acetaldehyde, the principle exposures of the people that we measured in our studies are from indoor sources, not from outdoor sources.

But for particles, it seems pretty clear there is a strong measure, even for the elderly who spend the most

time of anybody indoors.

DR. SAMET: Tom.

PANEL MEMBER HESTERBERG: I just wanted to make a comment before you get to the next question, and that relates to the talk that Mary Nichols gave. I thought it was very good.

And you mentioned that you want to go back and look at the diesel URF and then also go back and look at some of these new regulations that CARB has to speed up the process of replacing the traditional diesel exhaust vehicles on the road. And given that it seems to be a real burden, particularly on a number of the smaller trucking companies, I would encourage you to delay those, as I indicated, I think with the current reg.

The 2007 regulation that's in place, the current replacement reg, the 2010, in ten years, all of those are going to be replaced. I think what you have to weigh is often is there going to be an advantage to speeding that up to putting a huge burden on companies out of business, putting -- increasing the unemployment, particularly when we now have studies that are indicating diesel exhaust.

I don't think it really is a carcinogen, unless it's at really high concentrations. These are new studies and new analyses since the last URF was passed. And also the human clinical studies don't show much --

DR. SAMET: I'm going to take us back to the public questions.

PANEL MEMBER HESTERBERG: -- 100 micrograms. Anyway, just want to encourage you to re-look at those things.

DR. SAMET: I have two questions in my hand that essentially relate to how do we know the relationship between exposure and risk, the form of that relationship.

So one asks could there be possibilities of thresholds and could the relationship be such that there is a threshold at lower levels?

And the other question I think relates to how -- it says if there is a health effect for PM, shouldn't there be a concentration-response function where greater effects are shown at higher PM ambient concentrations? That is essentially what is being modeled in the data. But I think if anyone would like to speak to how modelers sort out what the shade might be and could sort of look at what the alternatives are -- and again, I think this is often where there is debate about the right model, the form of the model.

But perhaps either Zack or Suresh or both could give some generic response to this question.

PANEL MEMBER MOOLGAVKAR: Well, in modeling concentration-response relationships, I think one has to

distinguish between short-term and the long-term studies.

In the short-term studies, the technique that has been widely used is to use what's called regression. And to use what are called splines -- flexible splines to look at exposure-response relationship. So one starts off with the assumption that the relationship could be linear and then moves to other model forms to see whether there are non-linearities or any indication of a threshold.

For the long-term studies, the standard statistical methodology that has been used so far has been the Cox proportional hazards model. And again, one starts out with the assumption of linearity. Actually, it's linearity on the logarithmic scale, but then moves on to other kinds of exposure-response relationships to examine the question of thresholds and non-linearities.

Again, it's a pretty technical subject, and it's not an easy question to answer very quickly. However, I will say that for the long-term studies, as we discussed, there is one paper out there. I'm sorry that Dan Krewski isn't here on the panel now. But there is a paper by Krewski that clearly shows indications of non-linearity and also indications of a threshold for the sulfate dose-response relationship.

PANEL MEMBER ROSS: There is an issue -- actually, a number of these are issues we've been talking

about for some time. And we've considered them in previous assessments and continue to consider them.

And one of the things we've talked about, and many of you heard this before, is the possibility that in a population you have a whole mix of people. So what's a threshold for someone is not a threshold for somebody else. So while individuals may be more or less -- there may be a threshold for me, for example, for what levels of pollution can affect me. But across the whole population of people, babies to grandmothers, you can't discern a threshold in these community-based studies.

DR. SAMET: Roger.

PANEL MEMBER MC CLELLAN: I think that's an excellent question and obviously very complex. We spent pretty much all of today, with the exception perhaps of Zachary's presentation where he started to move into this issue of now we have an assumed relationship between the concentrations and the response. And we're going to use that to estimate deaths, body count if you will.

So you have to have some assumptions as to the exposure of that population, the concentration and that response function.

I think that there's some very important issues in that and that the distribution of exposure across the population -- and without going into the details of it

when one starts to calculate risk, the largest number of people are actually those who have the lowest levels of exposure. And it's only a few individuals up at the top. So your body count, if you will, is very sensitive to how far down you assume that linearity goes. If you assume the linearities goes to the first micrograms of material, you're going to have a larger number.

Now, we know realistically when you attempt to roll back in terms of regulation you're not going to do that uniformly. So there's complications there. My view of always when I look at this is that these are estimates in italics with double parentheses around. They provide guidance to the policy makers. We should be very careful to make sure they don't represent reality.

DR. SAMET: Fred, I'm going to move us on for the sake of time. We're moving right on with this one.

Another question, many questions raised this morning about the potential role of SO2 and mortality. Are there mechanistic data that would support this link. I just would say that for SO2, per se, and mortality, except at extremely high levels, the answer would be no.

And some other questions have come in. I'm just going to highlight them. We really have to move on to Dan's wrap-up.

A suggestion that one group to study would be

heavy equipment operators, like a member of the Operating Engineers Union. Certainly some groups have been studied that are heavy diesel exposed. I'm not sure this particular group has been -- this union itself -- yeah. Okay. All right. So much for that one.

And then I'd say more of a comment that there are groups that are heavily exposed to particles. The comment about those with massive indoor exposures in developing nations, little evidence of a cardiovascular signal from these massive exposures in developed lower and middle income countries.

Any comment on that, Aaron?

PANEL MEMBER COHEN: Well, it's the case of absence of evidence rather than evidence of absence. That really hasn't been studied, except to a limited extent in a randomized control trial of clean stoves in Guatemala. And in that study by Kirk Smith at U.C. Berkeley, actually they found effects of very high levels of indoor particulates from burning solid fuels on blood pressure.

DR. SAMET: Okay. Well, thank you.

There is a last comment or question I simply can't read. It's a tracking of PM and life expectancy against each other in California noting some inconsistencies. So I think we've had a long day. Dan has been sitting next to me capturing the essence of what

we've been saying and is going to summarize the meeting.

Dan.

(Thereupon an overhead presentation was presented as follows.)

PANEL MEMBER GREENBAUM: And for those sitting behind me and saw me working on my computer, no, I wasn't doing my e-mail. I was trying to capture this all.

So I'm going to very briefly try and recap what I heard today and in as fair and honest a way as possible. I'm sure there's more and we can figure out ways to capture that, too.

Remember that good science is messy and takes time. There are multiple paths and dead-ends, so it's not surprising there's all these questions in some ways.

And our understanding does grow with the number of studies and different types of studies. If that were not true, a lot of the scientists in this room would probably have given up a long time ago.

We heard life is risky and we all die. And some causes of why we die are well understood. There are a lot that are not well understood.

I'm going to talk about five questions I think we tried to address:

What do we know about PM and premature mortality nationwide?

What do we know about PM and premature mortality in California?

What study might we use if we were trying in California to estimate those things?

How should uncertainties be included?

And what do we know about the constituents and the sources of PM, including diesel?

--o0o--

PANEL MEMBER GREENBAUM: Just hit this until it fills the screen.

Bart Croes asked me to very briefly tell people -- because although many of you know who we are, not everybody does.

So HEI is a nonprofit. We've been around for nearly 30 years, and we're dedicated to providing impartial high-quality science on the health effects of air pollution.

We have joint and equal core funding from U.S. EPA and the motor vehicle industry, all of the companies worldwide who make vehicles for sale in the United States. Also other agencies and industry balance funding, U.S. DOE, highway administration, CARB, but also the oil, chemical, steel, and other industry.

We have an independent board and science committees, so we are not affiliated with these sponsors

who oversee our work. I described that a little bit in the history today.

And we've done over 200 studies on a whole range of these things. We primarily do new research. But we also occasionally, when asked, do reanalysis and special reports, like the traffic report, which George Thurston mentioned.

--o0o--

PANEL MEMBER GREENBAUM: Now go on to what we've been talking about.

There are a number of larger epidemiology studies of PM and mortality which generally find positive associations with some exceptions. And there are some. Some of the largest of these studies have been subjected to extensive reanalysis and extended analysis.

The U.S. EPA and the Global Burden of Disease effort have reviewed these as well as a range of relevant toxicology and intervention studies, which we didn't talk about today, but studies like the one in Utah where we know that a steel mill shut, that pollution went down and a number of health effects went down. And then they went back up after the plant opened up again. And based on that, they have determined that PM exposure causes premature mortality of certain types.

And Mary described that process I think quite

well this morning. There are, however, a number of remaining challenges. Regional variability, not every study has found results in every part of the county. On one hand, the Medicare cohort didn't show effects on the west, whereas the NMMAPS study showed stronger effects in southern California, New England, and industrial midwest, but not really in the rest of the country.

PM, we've talked about this a lot, is not a single pollutant. And we need to know more about the individual components and other pollutants, the gases and toxics. I'll get back to this more later.

Residual confounding, although some of these studies do a lot, much more than past studies to try to control for individual confounding possibilities, there was also the possibility that some degree of remaining confounding is in the studies we talked about. Socioeconomic status as being an example of that.

And we have the challenge of the rising age of the cohorts we've been working on and the likelihood they become less useful as they age and the likelihood they will being less sensitive to any effects we might be trying to tease out.

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PANEL MEMBER GREENBAUM: The story in California is not radically different, but there are somewhat fewer

studies, but several epidemiology studies that have tried to estimate PM mortality risks in California. There's the ACS Study in Los Angeles, the California Teachers' study, AHSMOG study, the follow-up to the California Cancer Prevention Society I study which did find positive associations.

The second follow-up to that study -- and it's a little unclear, but the AHSMOG male results did not find such strong association or did not find associations at all.

We also saw a preview not yet peer reviewed of the ACS in California study which seemed to find cause-specific associations but not for all-cause mortality.

There are questions. One of the key ones, how does California air differ from the rest of the U.S.? There is some difference. For example, sulfates are higher in the eastern part of the country. But the carbonaceous species from the traffic, for example, in some fossil fuel combustion seem to be very similar. How does the fact that California's healthier factor into this? I was pleased being from Massachusetts to see that the life expectancy from Massachusetts is better than California actually. But I don't know to what attributes to it. Our weather is much worse than yours.

Is there a reason that all-cause mortality might not be positive in California when it is elsewhere? And that's the question that came up from this most recent analysis that is being done. And we don't know the answer to that piece yet.

A key question is which study to use for analysis, if you want to estimate risks. And EPA and the Global Burden of Disease have reviewed the evidence and they have selected the Krewski HEI 2009 work on the American Cancer Society Cohort as the basis for their work. And I think that the reasons most -- it's the most recent fully peer reviewed analysis of the most extended population. It's based on a study with extended individual characteristics and community characteristics. And it had been subjected earlier to extensive reanalysis.

Some other studies we talked about seemed to have very high estimates, for example, the Women's Health Initiative and the California Teachers. And not that that automatically says you shouldn't use that, but it does raise questions about whether those are the appropriate studies to use.

And I think the key question for ARB to ask in this: Is there good evidence that the risk in California is notably different from that found in the Krewski study? Is there something that's dramatically different or

markedly different that would say you shouldn't use that? This is not wearing my HEI hat, but I think that seems to be the question that we were all wrestling with.

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PANEL MEMBER GREENBAUM: Uncertainty is a certainty in these studies. And it's very important as we've talked about to figure out how these effect the result. As Aaron Cohen talked about, the Global Burden of Disease is moving to quantify uncertain, too, in all aspects of their analysis: The exposure measurement, the geographic variation, and the modeling approaches that they use.

And they're comparing that not just from the Krewski study they're using, but other studies they use. U.S. EPA is quantifying uncertainty from a number of different scenarios. We did talk about two in particular. This list could be longer. But the panel identified two very important areas: Model selection in which models and approaches you use and the exposure metrics and/or method of estimating exposure that you use that you have to try and estimate what the uncertainties are for that.

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PANEL MEMBER GREENBAUM: Last, but not least, we talked about PM effect and the mix of pollutants. And it's not a surprise to anybody it's a complex mixture and

part of an even more complex mixture with gases that have their own effects.

And I put that in quotes, because often when we use these terms, those are everything, the gases as well as PM are markers in some ways. And each source has its own mix of emissions. There's no one pollutant that comes out. And it's not always easy to specifically identify a source. For example, as Tom Hesterberg noted, the markers for diesel are by no means perfect.

Studies of PM and other air pollutants are inevitably studies of a marker of some less well known set of components. And we did hear from George Thurston that no single type of study toxicology -- and that could be animal or human occupational epidemiology -- is perfect to tease out the different effects. And what we really need for the future are systematic multi-disciplinary efforts and bring together both toxicology and epidemiology to understand the toxicity of the PM components and the gases. And both we at HEI and I know EPRE and ARB have been trying to fund studies that would get us to this better information.

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PANEL MEMBER GREENBAUM: A few concluding thoughts.

We did hear a little about data access today. I

think there were a number of comments that that was important to enhancing the underlying confidence and result.

The next one is my comment, it's not a comment we heard from the panel. I think it's useful and that we generally follow this. Civility is a good idea. I think it's important in these science meets policy and contentious arenas to remember that ARB officials and scientists that critic are trying to advance knowledge and the public good, as a general guide.

Twenty years of hard work has advanced our knowledge. I don't think anybody would doubt that. And led to some beneficial decisions. We have much cleaner diesel on the road today than we did 20 years ago. And a lot of good work on the part of industry and others leads to that, even as questions have continued.

And last, but not least, we should remember that good science is messy.

Thanks.

(Applause)

DR. SAMET: Thanks, Dan. That was a terrific recap.

I think just a few last comments. As an epidemiologist, I just have to say that epidemiology has done society a lot of good. You've heard about

epidemiological studies in a very difficult area.

But if you look at accomplishments more broadly, heart disease mortality is now one-third of what it used to be. Half of that is prevention driven by epidemiology. Cancer rates are dropping. We now know what causes cervical cancer, and we have a vaccine.

So the tool, the method has proved remarkably valid and useful in many arenas. It is our core science of public health. But we can wander into very difficult questions, and we've been talking about one today. And it's a question that involves looking around the table and in the room, not just epidemiologists, but a whole range of scientists that have to come together to look at difficult questions.

And I think Dan made reference to the fact that, you know, when you have difficult data, gray, and you have to make it black and white, decisions like to regulate or not regulate, it becomes I think difficult. A lot of questions of the science goes on and it should go on.

So just a last remark from me, and I want to thank everybody.

PANEL MEMBER MC CLELLAN: I have a question for you, John. As an epidemiologist, there was one point that Dan -- and I thought was an excellent summary, Dan. Excellent. Almost matched Mary's.

The question about looking at cohorts -- and I'm not exactly at the tale of the age distribution curve and dropping off, but I would take strong exception with it. I wonder if you would also.

DR. SAMET: I don't want to reopen the whole methodological discussion. I think we need to have a different way to have cohorts. Maybe Medicare is a way. We need serial cohorts.

PANEL MEMBER MC CLELLAN: But the question was we're not getting much value out of looking at these end-of-life cohorts. And I'd say maybe Michael made that. Whoever made it. I just disagree.

DR. SAMET: Well, I think the easy answer -- and again, we're ending up here. We need cohorts that cover the full age span, and we need to keep having them come -- you and I can talk about this later.

Let me see if ARB wants to make any last remarks. I want to thank everybody for a lot of input, a lot of discussion. And I think it was a great exchange on tough issues.

If there are no further comments, then we are done. And we didn't do too badly with time after all. So thanks to all.

(Thereupon the CARB Symposium concluded.)

CERTIFICATE OF REPORTER

I, TIFFANY C. KRAFT, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing hearing was reported in shorthand by me, Tiffany C. Kraft, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said hearing nor in any way interested in the outcome of said hearing.

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