

July 11, 2008 CARB Teleconference on PM2.5 and Mortality

Participants:

Linda Smith, Ph.D., CARB Research Division
Lori Miyasato, Ph.D., CARB Research Division
Deborah Drechsler, Ph.D., CARB Research Division
Hien T. Tran, "Ph.D.," CARB Research Division
Bart Croes, P.E., CARB Research Division Chief
Bart Ostro, Ph.D., Epidemiologist, OEHHA
C. Arden Pope, III, Ph.D., BYU
Michael Jerrett, Ph.D., UC Berkeley
Richard Burnett, Ph.D., Health Canada
James E. Enstrom, Ph.D., UCLA

Audio File (<http://scientificintegrityinstitute.org/CARBTeleconference071108.wav>)

Transcript of Audio File

0:00:05

Smith: Let me just give you a little bit of background information and then I'll ask Hien to facilitate the meeting here. First we'll go around this room so you know who is here. I'm Linda Smith, Lori Miyasato, Deborah Drechsler, Hien Tran and Bart Croes. OK. To give you a little background as you all know the Air Resources Board does estimate health impact exposure to air pollution such as PM and ozone, including premature death and other end points. And we do this not as part of our regulatory policy or a requirement of regulation but more as an illustration of the impact of our regulation. So we're not going to go into regulation at all rather we're just going to focus on the science here. This is as an outcome of Dr. Enstrom's concerns of how we have or have not looked at his research. In fact Dr. Enstrom did testify or show testimony before the legislative hearing confirming the chairman of our board, Mary Nichols, and asked that we look into his research a little bit further. And Mary Nichols said she would respond and part of that response is this conference call. So with that background, I'll turn it over to Hien who will start our meeting.

0:01:26

Tran: OK. Good Morning everyone. I hope you have all received the agenda and listed there are the key issues that Dr. Enstrom would like us to touch on. And the first one is on his paper, his 2005 paper on Inhalation Toxicology. And I know when we addressed his paper there was a critique by Brunekreef and Hoek that Dr. Enstrom provided response that we discussed Dr. Enstrom's paper we might want to blend in the 2nd item,

which is his response as well. So with that let me begin with Dr. Enstrom. Do you want to touch on the key issues you want to bring to our attention?

0:02:13

Enstrom: Yes. Thank you very much. I appreciate your putting together this teleconference. And since I've never actually met any of you personally I'd just like to state a few things about my background to give you a little more information. I'm a native Californian I was born in Alhambra, which is just east of downtown Los Angeles. And for the first 11 years of my life I lived in Rosemead which is just east of Alhambra. And so the reason I'm mentioning that is I've been familiar with smog and air pollution issues in California going back to the 1940s. And the reason that the epidemiologic research has come up is because for the last 35 years I've been at UCLA conducting epidemiologic research and during the last six years I've been involved with air pollution epidemiology using a database that I acquired from the American Cancer Society, known as the Cancer Prevention Study I. I acquired that database in 1991 because my dealings with the American Cancer Society go all the way back to 1973 when I started my epidemiologic career and they played a major role in not only initiating my career but funding the first part of my career. And the reason that I'm involved in this call now and that I testified before the Senate Rules Committee is because I've been disturbed with the way the Air Resources Board has dealt with my paper that I published in 2005. And if this was just an academic exercise I wouldn't particularly consider it that important, but the regulations dealing with diesel particulate matter have become an extremely important issue in the state of California in terms of the economy and there have been estimates made that the regulations that could result from these deliberations that are involved in your staff reports could range up into the billions of dollars. So we're talking about a real economic problem here in addition to an epidemiologic issue. And so with regard to my 2005 paper, I felt, based on the treatment that it's received in 2006 when you did an earlier version of this May 22nd report that either there is a misunderstanding of what my paper does or there is a lack of what I consider fair consideration of my paper. It seems like it should be given the same kind of consideration as other major papers. For instance if you go back to when it came out in late 2005, it's really never in my mind or from all the records I can find, it's never even been presented to the Air Resources Board in terms of notifying them that it exists. And I've gone through the various slide presentations that are given to the board and then it was, in my mind, mischaracterized in the 2006 Appendix A, as it's known as. And then it was not included in the deliberations that went on for what resulted in the ballot initiative known as Proposition 1B. And then after Proposition 1B was passed, this proposal to spend \$1 billion reducing diesel emissions in California has sort of preceded on without any consideration of my paper or other evidence in California that's specifically related to the issue of diesel particulate matter. So I became concerned enough to submit comments on April 22 regarding one of the deliberations at the April meeting of the board dealing with the goods movement emission reduction plan. But I have never received a complete response to those comments. I did talk to Dr. Smith and she was as helpful as she could be but the number of the people that could have responded have not really done so. And then I was surprised in the May 22nd report to the board there was really no mention of my paper at all and no mention of my April comments. So my feeling is that there has to be a better means of

considering all the evidence and as part of my comments that I submitted in April, I pointed out something that was in my response to Brunekreef and that is that the reanalysis report that was done in 2000 by the Health Effects Institute shows a map suggesting that there is tremendous geographic variation of fine particulates and mortality across the United States. And that map indicates findings similar to my paper that is the relationship is very weak in California and is concentrated in the eastern part of the United States, particularly around Appalachia. So I would like some of this addressed in a better way and I'd like ideally if some of the staff people that were involved in preparing the 2006 and most recent May 22nd reports could possibly explain to me why they have chosen to characterize my study in the way they've characterized it. That would be helpful to me.

0:09:05

Tran: Dr. Enstrom thank you for the introduction. I've mentioned in the staff report dated May 2008 we chose to rely on the U.S. EPA expert elicitation results and the experts were given all the relevant literature. They were free to choose from all of the published literature and came up with the uncertainty behind the relationship relating PM2.5 exposure and premature death. So at this point I'd like to turn the discussion to your peers who have reviewed your paper to address the strength and weaknesses and there by justifying how it was used in that report. So should I begin with Dr. Pope?

0:10:03

Pope: Yea, well, I have been sitting here, sort of putting down sort of thinking about what Jim had said with regards to this. You know I have a number of thoughts and I don't know that I have them carefully organized yet. But first off with regards to your specific question and expert elicitation, there is no, it's not confidential information. Everybody knows that I was one of those experts that were solicited to be involved in that as was Bart and so he can speak as well. You know two of the things we were asked to do: 1) was to basically come up with a point estimate of the effects of particulate pollution on mortality and 2) to come up with some sort of level of uncertainty. And in the end we really came up with these distributions. But in essence what we're talking about is, you know, what do we think is the most likely effect estimate and what is the uncertainty. And for me, I look at the literature and you kind of have some extremes. You have the Women's Health Initiative with sort of what I consider to be unrealistic, probably way too high estimates, not because the study wasn't done well, these were superb researchers that did a great job, but there is a lot of stochastic variability that goes on here. And they got a very high estimate. Then you have the Six Cities Study which is a fairly high estimate but substantially lower sort of more into the norm. You have the ACS, and we better be careful here because, you know, the CPS II analysis, but you know my original work in the mid 90's and then the reanalysis by the, Krewski and Burnett and that other group, and Rick is on the phone he can talk about that more. And then of course some reanalysis and extended analysis we have done with it. Then there is a couple of papers on the low end, this Enstrom paper from California and Fred Lipfert's paper, you know, they kind of give us the low end estimates. And so, if I look at it I estimate, you know I think of this Enstrom paper as a very valid paper. One that should be looked at and it influences how much uncertainty we have to place with regards to our estimates and I

was one of the experts, as part of the expert elicitation that didn't think that there was, you know I did think that there was a non zero possibility of there being no effects of air pollution and largely it's Enstrom's paper that influenced my view on that. I still think it's small. I think that the likelihood of there being a significant health effect from air pollution, even mortality effect, is extremely high well over 90-95%. But the Enstrom paper and the one Fred Lipfert paper kind of make you wonder. So in the end the way I look at the Enstrom paper is it has it's warts like all of these studies do. It comes in at sort of the low end. It does see in the early part of the follow up period it sees an effect comparable to what we saw in the ACS analysis. The Woman's Health Initiative gives effects that are larger than what I think are reasonable. And I think they sort of are the two lower and upper bounds of what the reasonable effects estimate should be. And relying on that expert elicitation is probably as reasonable approach as I know and it comes in with an effect estimate higher than what the Enstrom paper gives, lower than what the Women's Health Initiative gives, and even lower than what the Harvard Six Cities Study gives, but you know that's the way it turned out. So I thought it was a fairly reasonable exercise and I don't fault Dr. Enstrom for weighting his particular paper more. I will point out that of the two probably most important papers focused in California we have the Jerrett et al paper and, Michael is here he can talk more about it. It gets effect estimates higher than is being used in this analysis. Its effect estimate is more in the range of the Six Cities Study. And then the second paper is this Enstrom paper which gives effect estimates lower than what's being used and then of course a large multi city, U.S. study, gets effect estimates sort of similar to what is being used here. And, I don't know, when I look at this whole exercise I think it's been done reasonably well. Now that shouldn't surprise anyone, given that I was involved with it. So, I'll quit rambling and there is where I'm at.

0:15:47

Tran: OK. Thank you Dr. Pope. Let me ask Dr. Ostro to follow up with additional thoughts on the overall expert elicitation effort as well as Dr. Enstrom's paper.

0:16:03

Ostro: I would have to say that Arden as usual has summarized the issues very well and I think what he said pretty much covers my own feelings, that we decided to use the expert elicitation and judgments of the number of experts involved in that study rather than doing our own expert elicitation of the whole thing. And speaking as one of the experts, I also took in all the studies that were available and clearly they influenced the ranges of uncertainty that I projected during the exercise. So I think all of the papers played some role. Like Arden, I also would not say it's 100% certain, so I leave a little room for a no effect estimate. And, you know, given the variation of the studies, again I think our estimates that we came up with with the ARB is fairly reasonable.

Now, in terms of the two things that were stated by Dr. Enstrom I just wanted to address and then I'll turn it over to some of the people doing the analysis on the ACS studies. First, this paper specifically relates to diesel PM and it clearly doesn't, it's PM_{2.5} measured from the IP network in 79-83. And it's probably catching some secondary particles from, that started from diesel, but it's clearly missing all the primary particles that are closer to road ways because of the monitors were sited such that they wouldn't be

effected by local sources. So it may or may not be specifically relating to diesel PM. And a second issue is that even if one doesn't get into the long term exposure studies there's many studies out there now, both in terms of toxicologic human critical studies as well as epidemiologic studies that clearly show very serious effects from diesel particles. I'm not just talking about cancer effects but cardiovascular effects as well. So clearly to have a zero estimate wouldn't make sense given some of these time series studies and some of these clinical studies and some of the animal studies as well with the very serious effect. And if anything, we might postulate that the effects of diesel might be even stronger than a generic PM2.5 effects that has been shown from all of these studies. The relevant issue is, you know, that the pollution effect is safe small relative to all the things that are causing cardiovascular mortality that I'm always surprised that you find anything in these studies. The fact that some of these studies have come out and shown effects is pretty compelling.

The only other thing I want to say at this point is, in looking at the study itself, the thing that struck me as really important was the age of the cohort. And one thing I tried to do is get a comparison of the group. In 1982-83, when the IP network was used and, as Arden indicated, when one looks at the cohort during that period, the risk estimate is almost identical, 1.06 to the original Pope et al study. So the age of ACS II, if I'm not mistaken, you guys can correct me on this, my understanding was in 1982 the age was around 57, the average age. Where in the cohort that Dr. Enstrom used the average age is 74 at that period. So there is a cohort effect that occurs and as you're following this cohort into their late 80's to 90's there are all sorts of other effects that begin to take hold some are pretty obvious and some are pretty subtle. And I know Rick Burnett has looked at this issue and cohort and probably be better to talk about it but I was very concerned about the effects of looking at a very much older cohort. Not only in terms of controlling co-variants but also survivor effects and many other things as well. So those are some of things that went into my thinking in terms of usefulness of the study in California. So I'll stop here and listen to some other comments as well.

0:21:03

Tran: OK. Thank you Dr. Ostro. I will now ask Dr. Burnett to expand on your comments and perhaps touch on this survival effect that you just mentioned.

0:21:15

Burnett: I don't know what all the fuss is here because I'm looking at Dr. Enstrom's response paper, Table B, adjusted 1973-1982 follow up that 10 year period. That's 1.016 relative risk highly significant which is about in the ballpark that we find in the national ACS cancer prevention study II. So, and this is exactly what we see in the ACS, the national ACS study is that as the cohort ages two things are happening. One thing of course is that your proportional hazard assumption starts to break down. The mortality risk is dependant on the 7th power of age, so as you age your hazard, baseline hazard goes way up and the chances of air pollution having the same relative risk as somebody at 50 and 90 is, it just can't be. So what you're seeing is a diminishing of that relative risk over time because the proportional hazard assumption doesn't fit the entire age range. So the relative risk goes down as you follow the cohort. And the second, probably as important, thing is that all the action we see, or most of it in the ACS study is with cardiovascular

death. Which in our study the average age at death, at cardiovascular death, is 67 years. For instance, respiratory death is at 78 years. So what's happening is when you follow all causes of death, you know all the association between PM and mortality is occurring in the cardiovascular years, which are younger. And so all the deaths in the 80's and 90's and so on are not contributing to the association between PM2.5 and mortality. So there you're getting a lowering of the risk and we see that same thing in the ACS. So, I really looked at Dr. Enstrom's study and I'm saying, as Arden pointed out, every study has strengths and most of these studies have a lot of weaknesses. And I don't think this one has any more weaknesses than any of the others, but we got this problem of following the cohort too long for all causes of death. And I think it would be fascinating to go back and do this analysis for cardiovascular death and see if we get a more stable risk estimate over age and over time in the study. But, I certainly, if I had to pick out one number out of that study that I had the most confidence in then the one I just quoted would be the one with the shorter follow up period. And I think that's perfectly consistent with any other results of our study and of other cohort studies. So I think that's the critical issue, is that following the cohort for maybe too long a period. And we had discussions with people at the American Cancer Society because we are continuing to follow the cohort and they have a lot of concerns about that saying, you know, "I think you're following them too long." So that's a major issue and to really look at the specific causes of death and not just the all causes of death.

0:24:49

Tran: Thank you Dr. Burnett. I would like now to ask Dr. Jerrett to chime in.

0:24:59

Jerrett: I've read the expert elicitation and seen what went into that and I've looked at all the other data that's available. I think that this study was taken into account in the expert elicitation from my reading of that document so I don't think that it was ignored in the analysis. I think that, when I looked at this, I mean it looks like a carefully conducted study that has risks and would consider fairly similar to ours. As Rick has pointed out, when you have the follow up in the earlier part of the period, there's also, you know in follow these cohorts too long, beyond the risk growing to the power of 7, it's also, the people that are left at a later period tend to be survivors. So if you survived to age 85 without chronic disease of cancer, heart disease, diabetes, there is a very good chance you're going to live even longer. So what concerns me when I see the really, what must have been an age level well into the 70's on average with the big proportion of the cohort well into their 80s, that many of these people maybe robust survivors. So I think that there is some literature on it, I have to go and look at the pages and certainly discuss with people like Ira Tager in following up cohorts. There is a survivor effect. I would be concerned that the people that were seen at these longer follow up periods, the people that were pegged for lifestyle or reasons that they didn't have early life exposures in these places, all of those reasons could be getting to a survivor effect that diminishes the importance of many other risk factors. These people are part of the population that inherently are probably going to live longer regardless of the risk that they're facing. So when I look at the air pollution literature in total, I start to think that there are very subtle sensitivities there and subgroups that we don't understand very well yet. I was just at a

workshop all day yesterday with John Froines at the Particle Center on all the mechanistic and chemistry behind and the genetics behind air pollution and health effects. While there have been incredible advances within the last 5 years I think that we're really just starting to scratch the surface on who is susceptible to air pollution. So it's entirely possible that, in these early periods, people that say don't have the GSTM 1 onogene or the ones that are dying earlier and what you're left with are robot survivors where numerous studies of respiratory disease or anyway you could show the risk are half that of the normal population. A pretty big piece of the gene pool is about 50% of the population. So I think when I look at this that would be one of my main concerns, but I don't think that it should be down weighted in any analysis. I think that there are certainly studies that we have coming out, there is one in NY city where we attempted to replicate the Los Angeles study and we don't find effects that are very large compared to Los Angeles except in ischaemic heart disease. And New York City has a very different dynamic that the population is living in the most fluid area in the central part are also some of the most healthiest people in the United States, probably in the world, which are people in Manhattan. But you know we're reporting that, it will be published very soon that'll go into the risk estimate. People will consider that. I think, looking at that study in comparison to Dr. Enstrom's we don't find any elevated risk of all caused mortality but we find a risk of ischaemic heart disease there which again we're going back to the biological and toxicological evidence I think its got its strongest plausibility being related to air pollution health effects. Minor risks, it's almost the same as what it is in Los Angeles maybe a little bit bigger. So I echo Rick Burnett, again that probably it would be very interesting to see what that earlier period of the cohort where the survivor effect is probably not as big an issue whether or not cardiovascular and ischaemic heart disease are influenced by air pollution and what the risks are compared to other studies. You know looking at this paper too, the other concern that I had is that, if I read it correctly, there are 11 counties with pollution. One of them is almost certainly going to be Los Angeles and if we compare pollution levels in Los Angeles to, you know, across the Los Angeles basin and now (30:50) with seven different exposure models and the raw data itself show that the exposure contrast in that area is greater than what you see across the continental U.S.A. measuring at central site. So that in particular probably has, you know, if this cohort is in relation to population, I didn't have an opportunity to go through how much of the cohort comes out of Los Angeles county but it's probably a big proportion if it's anything relative to the total population of the state it's at least $\frac{1}{2}$ to $\frac{2}{3}$ probably. And for that $\frac{1}{2}$ to $\frac{2}{3}$ you probably have a lot of exposure measurement error within the region so you have levels that drop down to below the national average and to get into coastal and northern coastal parts of Los Angeles and then as you go inland you have levels that are the highest in the continental U.S. So having a very small number of exposure contrast with only 11 and having one of those areas probably dominate the cohort with a lot of exposure measurement error. That too could be an issue in terms of pushing risks toward the null. So I think Arden said it best that all these studies have warts and you know I could go through all the warts on my study and on any of the other studies that have been published and I think it's really the total evidence that we have to look at. When we look at the evidence here and I think it's sort of, for me it's remarkable how close the risk estimates are in the study by Dr. Enstrom when it's fully adjusted and when it's in that earlier period of the follow up. I mean it's virtually identical to what

Arden reported across the entire cohort with a younger group. So I think looking at that, looking at what we know coming out of the various acute studies the studies that were done in other countries like Canada and the Netherlands and Norway. I think it is, you know the expert elicitation did a reasonable job in taking that data and its totality into account. So I think it has been taken seriously, well certainly I have anyway. It wasn't available for citation when I published my paper, but it will certainly be cited in future work. And I think that the expert elicitation, two people on the panel have taken this into account. So I'm not sure, you know I haven't had an opportunity to go through page by page of the new CARB report, but if there is something in there that somehow discounts it or says that it wasn't included I think that probably should be changed because it does sound like it was included. And it sounds like looking at the risk there and the most reliable ones that are available they are very similar to what we see in the other literature or at least on the low end of the other literature which would be Arden's paper and perhaps a few others. You know I hope that Dr. Enstrom doesn't see that as a criticism. I think that it's terrific to have more people engaged in this field. We need to have as much evidence as we can from as many different angles as possible because the cost of remediation are getting high for society and the stakes are high too because there are large numbers of people exposed. So those would be my summary comments after a long day at UCLA where I got up at 3 in the morning and got home last night at 11 so I hope that wasn't too incoherent, but that's my summary from reading the paper.

0:35:13

Tran: Thank you Dr. Jerrett for that coherent summary. At this point before we move on to the next item on the agenda I'd like to ask Dr. Enstrom if you have any questions to clarify the issue on the comments you've heard.

0:35:25

Enstrom: Yes, yes I do. And I think this goes to the last part of what I was proposing be looked at. And that is that no one mentioned the Reanalysis Report in 2000. My point is that there's a geographic variation in what I would pose particularly to Dr. Burnett is: has there ever been a specific analysis where you limit the subjects to California only either in the Reanalysis Report of 2000 or in the Pope 2002 paper of which you are a co-author on both of those investigations. Has there ever been a limitation to the California subjects only to elicit a relative risk within California?

0:36:27

Burnett: Well, we haven't done that specifically for California but I think Mike...

0:36:34

Jerrett: Yeah, we did though. I think we did, but...

0:36:37

Burnett: Well I don't remember if we did California. We did break it down....

0:36:41

Jerrett: We have an ongoing grant with the Air Resources Board. That just started a year ago so we're still very much in the preliminary stages and analysis.

0:36:50

Burnett: But we are doing a detailed analysis now of the roughly 95,000 California residents of the ACS II study.

0:37:02

Jerrett: I think when we used metropolitan areas in California, there are really only 6 in our database.

0:37:09

Enstrom: OK, but please explain the map that I pointed out before that shows there really is no excess, the way I read the map, there is no excess mortality due to fine particulates in California based on that map.

0:37:25

Burnett: Well there are 2 issues here. 1) that map was based on the early part of the follow up from 82 to 89.

0:37:35

Enstrom: Yes, which addresses your concerns about my follow up being too long.

0:37:40

Burnett: No but, but the map, the way I read the map, well in fact I know exactly what the data is saying, is the residents of L.A. had moderate survival after adjusting for all the smoking and everything and they had moderate PM2.5. So they were actually right on the dose-response line. Now what has actually happened is that the picture, which we have never published, but the map, the survival map of the U.S. has changed quite a bit in the 90's. And the other parts of the country have caught up to the rust belt and in particular into L.A., so the subjects in L.A. which had moderate survival compared to the rest of the cohort in the 80's have now accelerated their mortality compared to the rest of the cohort and they've also had a little higher pollution too. So now you're seeing, when you look at a longer follow up for cardiovascular outcomes, in particular, the L.A. residents are not doing so well. So things have changed, but certainly in that early part of the follow up, L.A. was right on the dose-response curve. You know, it was fairly consistent with...well I wouldn't characterize as low mortality they certainly had more average mortality and more average pollution. And they weren't extreme they weren't like, for their amount of pollution they had way higher mortality rate, they were consistent with the rest of the country.

0:39:26

Enstrom: Well, it's a little hard to translate that map into relative risk, but I would like, as I proposed in the second part of my agenda, which is page 2, to have analysis done

based, in other words take the Pope 2002 study and just break it down for California residents only and also break it into the follow-up period of the 80s and 90s. Is that possible for you to do?

0:39:58

Burnett: Well we, like I said, like Mike Jerrett said, we are doing a major analysis of the ACS cohort, the 95,000 subjects in California now, we're in the middle of that project. Where we're looking at detailed, several detailed complex exposure models for PM with those subjects. So, we are doing a major piece of work on that right now.

0:40:28

Enstrom: Is it possible to do it the way that I framed it? In other words, for the 11 counties, and I got this day directly from the Hinton reports that the EPA published back in the 80s, to do it the way it was originally published in the Pope 2002 but breaking it down for the county's, the same counties that I used in my paper. There are 11 California counties that have PM 2.5 data in that 1979-83 period. Is it possible to do that?

0:41:09

Burnett: Well, I guess I don't know.

0:41:14

Jerrett: It's not on our agenda at this point.

0:41:17

Burnett: No, I think we're trying to do a much better job of exposure assessment.

0:41:23

Pope: Arden here. I think to make a point on that, of course it's possible to do that, but what we think is going on is we're very much aware now that aggregating pollution and risks across the metro areas, while it was informative and directed and we do see effects, we're now fairly convinced that that is not exactly the best way to do it. And it turns out that in the United States the greater L.A. area, because of the better monitoring network they have and because of the data that's available, Mike and his colleagues have done a nice job of saying "alright let's focus on an area where there's a lot of variability and exposure across the metro area and see if the effects go away or see if they get bigger." Well in fact, they got bigger in L.A. and smaller in New York. Is that correct Michael? And so we don't know exactly what's happening but we do know now, we're less interested in just using sort of aggregations across the areas. A better exposure assessment than that.

0:42:48

Enstrom: Ok, so let me simplify this. Most of what is in this May 22 report relies heavily on your 2002 paper which is, I guess, considered the gold standard. What I'm asking is a very simple...

0:43:06

Pope: Incidentally, I don't think so anymore. I think it's considered by most that read this literature carefully as the bias as being toward the null. I mean, I think this is true as well, I think that given the way that that study was designed, it is unable to see the effects when you have better spatial resolution with regards to exposure and in fact even the expert elicitation folks, most of them argue that the Pope 2002 paper probably underestimates the effects.

0:43:45

Enstrom: But it's given the highest rating in the May 22nd draft report. So as of the time that draft report was done it's rated the highest, at least my reading of that.

0:43:57

Pope: You notice, almost all of them, not all of them, but many of the experts actually have their point estimates at something higher than the ACS study. So the idea generally is that, yea it's a good study and it's informative but the biases in it, the dominant biases in that study probably cause us to underestimate the effect estimates versus overestimate them. My concern would be we're only taking 70,000 subjects and having very crude, of course the IPN network data, and I've looked at every single piece of that data, believe me, I think is very sparse. In fact in places like Fresno, we only had two observations, two 24 hour period observations. And we've thrown out Fresno in all of our subsequent analysis because of that. So to go down to a small number of subjects and I know that 80,000 seems like a lot but doing this kind of work it isn't, and to use really I think, very sparse IPN network data at a more micro level because you have to remember that really the orders of magnitude different things that are being said here. One is: we know that the fine particulate pollution is generally higher in the east than the west and so that kind of grading that we have nationally, you know maybe it's partially acceptable to use relatively crude measures of exposure, like averaging all the ambient data and any MSA but once we get down to smaller geographic levels then, as Mike pointed out, we have huge variation in PM2.5 and we're making a much stronger statement. If I were just saying I think Steubenville has more pollution than L.A., you know more fine particle pollution than L.A. on average, and that's probably a fairly correct statement, but now if I go down to a smaller geographic level I'm then using very sparse and very limited data to make very complex estimates on exposure which can be totally wrong. And so that's why Mike is spending so much time and effort with the California analysis to come up with what we think are highly superior exposure estimates and that's where we see a comfort level of going down to this smaller geographic level is only if we have much better exposure data. And I don't think that we'd want to do it without....

0:46:37

Jerrett: If I could chime in, we spent a lot of time through the extension the Health Effects Institute gave us some further funding after the reanalysis to look at the extended spatial and temporal models and one of the outcomes of that study with all that new and very powerful random effects estimation software. So we can look at 2 or 3 different levels of influence, but the other thing that we can do is we can calibrate a properly specified time dependent covariate model that essentially looks at the risks over time,

over calendar year, so that what we're going to see, you know, I did, there is another paper that I know Fred Lipfert and some of your colleagues have seen that we published more of a methodological piece saying, you know, if you want to ascribe air pollution risk to specific government interventions not general ones, there are a lot of complexities to that. And that we broke the follow up period into subgroups and you do see some interesting patterns there, which I won't go into in detail. But we were always concerned with that analysis that you know, breaking into these smaller chunks, you're throwing away a lot of your statistical power, the chance, every time you break into a subset of having some random variation enter and affect your results goes out. What we really want to do with this next analysis and what we will be and what we are funded to do is to take this powerful new modeling framework that allows for time dependent co variants and to look at that risk of pollution as a continuous function over time. We have pollution data, not for PM2.5 but for all the other pollutants going back to 1988. So we're calibrating very detailed models, we're doing a lot of work to improve the estimation of PM2.5 based on land use, remote sensing, auxiliary satellite information and a lot of other data on traffic and truck traffic so that we can come up with an estimate that's going to give a much better estimate of exposure but also look at that effect over time in a properly specified model. It's breaking into these smaller subgroups, I think in retrospect has a lot of issues and having done one paper using that approach now. So I think we could do a replication analysis of your study, but I don't think that it would be, you now unless you want to start a dialog in the literature where we put something out and you comment on it. I don't know, you know I think there are certainly, there are some signal that we generally find at the national level when we have enough contrast between the cities that on average that it is a useful analysis. But at this point, you know, some 6 years after his paper we feel that we could do better and that's where we want to put our efforts to work. So, I don't know, you know we don't have any further plans on the books to do more studies that are based on these metropolitan area comparisons. We are looking at, you know there are some instances where that's the only way we're going to get at the issue because we need the statistical power for some subgroup analyses on particular health outcomes, we may still have to rely on that. As we start to understand more and more what pollutants tend to associate with which health outcomes. But you know it's not something that we're funded for and if the ARB asks for us to do that then we could certainly look at it and some sort of estimate of the cost to do that initial analysis. But I don't think that, you know, we need to go down that path because I think that we're all fairly convinced that we can do a better job now and our understanding has changed since 2002.

0:51:22

Tran: Thank you very much Dr. Jerrett, Dr. Burnett and Dr. Pope. I think that looking over the agenda, I think we covered all of Dr. Enstrom's key issues. Dr. Enstrom I did, because we have about 5 minutes left, did you have additional questions?

0:51:40

Enstrom: Well, I would still like those analyses done, the ones I have listed as 4A, B and C. In order to address the concerns that were raised about my paper being an elderly cohort and the fact that in the 80s it was a lot larger contrast the PM2.5 levels have fallen

quite substantially since the early 80s. And, so there's a large contrast and I think that it's valuable and I would like it done. Is it possible that it could be done?

0:52:21

Tran: Dr. Enstrom, like Mike Jerrett has explained, the current contract with ARB we believe that we have better exposure models to address those questions that you raised. So it would be like going back in time to use the older methodology when the science has advanced further already.

0:52:49

Croes: This is Bart Croes. Dr. Enstrom is there option in your, with your cohort to take advantage of some of this better exposure information that will be available?

0:52:59

Enstrom: I believe, certainly. If there is a willingness to accept an older cohort, it's definitely an older cohort, but that would be a contrast worth looking at if you're willing to get more input. I think it's very important in science that you get diverse opinions and I'm very concerned that certain types of approaches and certain individuals are not being given fair consideration here and that's what I raised when I spoke before the Senate Rules Committee. And I'm very concerned about that. So if you would be willing to, you know, have me give independent input and a number of investigators that I work with, that would seem quite fair. And I think then we'd really have maybe more of a level playing field. So certainly I would welcome that, but again you're dealing with an older cohort here, but I think one of the points that you've made is that you think that the fine particulates influence older residence more. They may be more susceptible to these problems. So, I think it's a valuable cohort and it's one that I think should be further analyzed.

0:54:22

Burnett: Dr. Enstrom, this is Rick Burnett. You have access to cause specific deaths, do you?

0:54:26

Enstrom: Yes.

0:54:27

Burnett: Have you ever looked at any cause specific deaths?

0:54:31

Enstrom: No, because my funding levels are minuscule compared to the ones that you're using. So I've just been able to do the limited amount that I've done, that's it. But it is available, it's just that I have not been able to fully process all the information to put it in a format that can be analyzed.

0:54:59

Burnett: I think that moving on this way, I think because of this age cause of death issue, further analysis of the CPS I cohort really has to look at cause specific death to be I think, fully informed.

0:55:18

Jerrett: I'm willing to share exposure estimates, but I would point out that that would require a separate ARB approval and we'd have to get all the locations and approvals from ACS because the location is here. I have...and the CPS II data are being hand delivered, flown out here, to be picked up in Atlanta on Monday and coming out Tuesday and then I'm putting them into an 1800 pound safe that's got a 2 inch metal door on it, you know, highly secure. So, this is not something, we don't ever exchange these data by mail or any other means. So it's going to mean that we would have to go back out to Atlanta and geo code this older cohort. We're not going to get as good an address match because the GIS files going back in time are pretty sparse. Then we would have to bring it to our lab and assign the exposures as we're assigning the other ones. Because the data are so massive we don't create a complete grid of predictions for the entire state. We're predicting at places that we need to predict to visualize the data and make sure it's adequate in terms of face validity in what we're seeing, but most of the predictions and the actual prediction statistically is happening only at the locations where the subjects live.

0:56:53

Enstrom: Well, I'm kind of confused. What are you relating your most recent conversation to?

0:57:01

Jerrett: I'm relating it to, we want to work, if you want to take advantage of the exposure assessment that we're doing and assign that to the CPS I. And the whole premise of this is that we want to get to their home address and look at the near source effects of roadways and we want to look at this with an exposure model that is capable of taking that into account. That it's something that would take a fair bit of time and resources to get through the process to get that data for analysis. That's all I'm pointing out. You don't have their home address do you?

0:57:38

Enstrom: Yes, I have. As far as I know the only investigative that was ever allowed to trace CPS II, excuse me I misspoke, CPS I subjects and that's based on, starting from their original address in 1959 and also follow up information that I got from 1972. And it's because of the expertise I developed in following my other cohorts using databases like the DMV and other name and address databases that I've followed these subjects successfully now for 45 years. And I have specific addresses on all the individuals over that time period, except the ones that obviously died in the early follow up period in the 60s were already deceased. So, yes I have specific address information. I've been doing this since 1991.

0:58:42

Pope: Do you have permission from ACS to have that released out of your custody?

0:58:50

Enstrom: Well we went through an elaborate procedure. I've had it continuously approved by UCLA as an ongoing project and so the ACS has no involvement at the moment because they basically gave me the California portion, it's 118,000 out of the original one million, approximately, 70,000 that were in CPS I cohort. So I've basically done this as a UCLA study since 1991. Although, I had cooperation with Clark Heath and Larry Garfinkel. I worked primarily with them on this in the earlier years, early 90s. Before Michael Thune took over. So I have all that information, so there is no need for any clearance. I have to keep it all confidential but in terms of aggregating subjects that's possible and so you know again....

1:00:07

Jerrett: We need the address level data though to do the assignment.

1:00:09

Enstrom: Pardon

1:00:10

Jerrett: We would need to have the addresses so that we could assign a longitude and latitude coordinate to those.

1:00:20

Enstrom: Well is it possible that you can provide the, you know, that we could work out some, I mean if there's a way to work out some kind of an arrangement where I give you addresses or something. I don't know, it seems possible. I could give you addresses without a name and then link it back or it seems possible to do. You know I've been doing this stuff successfully at UCLA for 35 years so I have a track record involving numerous cohorts. I've had no problems with breaches of security and I've done high quality work for that entire period. So I believe that there is a way. If there's a will there's a way to get this done.

1:01:23

Jerrett: Well it's really up to ARB. You know, and whether or not they want to supply additional funding for that. I'm happy to attempt to do the geo coding and find the exposures to the addresses of this earlier cohort.

1:01:47

Tran: Dr. Jerrett this is Hein Tran, I think if we follow your input there is a lot at stake here, we need to go back to the table and evaluate the scope of your contract and then we would take all of Enstrom's suggestions into consideration.

1:02:05

Jerrett: I think we're still going to have the problem that the best and the most reliable data that we have for PM2.5 is really what is coming out of 1999-2000 and we can't really change that. It would be a huge leap back going to this earlier cohort, I'd say that that's representative and then the other gashes, pollutants and PM2.5 because of major changes and the monitoring network and the equipment that was used is basically controlled by the most knowledgeable ARB staff that we shouldn't go back to anything prior to 1988. So I think there's a question about, certainly we can technically assign the data, but whether or not it's going to provide any sort of valid exposure assessment to this very old cohort is still a question that you may want to take into account in your deliberations.

1:03:12

Croes: Right, right and that's a very good point because you know we can only go back to the late 80's.

1:03:16

Jerrett: Yeah, so we're going to have, but, you know technically it's possible and I think the other thing that would or that I would have to do to make 100% sure that I need, before doing anything with anything to do with ACS data I need to have some discussions with my colleagues that have been involved in this study much longer than I have. I particularly need to talk to doctors Thun and Calle who are really our main contacts at ACS and have been collaborators. I really wouldn't want to do anything to jeopardize or compromise that relationship with them. So they would have to be onboard. As Rick already said, they basically have been very concerned about giving us any further follow up and there is a study that has been funded by the Health Effects Institute to the tune of 4.5 million dollars to look at speciated particles. I know that the PI on that, Mort Lippmann and the Co-investigators, George Thurston and Kaz Ito specifically tried to get a follow up period in the past to increase their chances of getting a grant and they were told "no" by ACS. So it's entirely possible but I think that ACS is very concerned that whatever their cohort is used for that it's an appropriate use and that the inferences that are going to be drawn are valid. And if they're concerned about that current cohort being too old they might have some similar concerns about this one. I can't speak for them until we actually consult with them.

1:05:10

Pope: Yeah, I'll second that. I do know that we have to be real careful here and I also know that what we're finding in terms of the aging cohort, Rick and Mike have both mentioned this already, but as we follow this cohort longer and longer we do see that the effects of air pollution tend to diminish a bit and there's several reasons that that's going to happen. Let me just make one other point and that is, I can't speak for the rest but I can speak for me, I've known you by reputation James for some time and my impression has always been positive so when I looked at this paper I always thought it was a competently done paper by a well respected scientist and I've always treated it as such. And than one other point I'll make is that if I can't, given the circumstances that I'm in and I don't have

lots of funding but I have lots of support and if you wanted to work together briefly, I couldn't do this I couldn't make this a huge effort, but if you wanted to work together briefly, look at some cause specific estimates have a sit down and go through this I have no objections to doing some of that. Now again depends on how the data are situated and you know it might involve a trip out to L.A. and doing some runs or whatever but I have no objections there either.

1:07:01

Enstrom: I appreciate that, that's very nice of you. But again, my operation is quite small and as you can tell from my publications I have very few compared to all of you, but I still believe that it's highly relevant to California and that's the reason that I'm pushing it and I think that if some of the regulations could be slowed down while some of these issues are worked out that would also relieve me. I'm very concerned that a number of these regulations are going to move forward based on, well for instance the Pope 2002 study when more studies are forth coming and I think that if there's an effort made by the ARB to slow down the regulatory process that would relieve a lot of my concerns.

1:07:56

Pope: That's something I wouldn't get involved with one way or the other. I'm interested in the science and I hope that the regulation is wise and uses the science in a reasonable way.

1:08:10

Croes: This is Bart Croes. Yeah, the regulations are to meet the PM2.5 standards which are exceeded by quite a bit here in California. So that needs to continue but you know we certainly want to try to improve the science and that's why we've been funding work on the California specific part of the ACS cohort as well as the Children's Teachers Study. I appreciate Arden's offer and we have a lot to think about here and we'd like to follow up maybe individually with each of you and discuss implantations further.

1:08:44

Burnett: And this Rick Burnett, working with Health Canada, and the Canadian government. We have no problem slowing things down but it's just natural bureaucracy.

1:08:53

(laughing) That's not our problem.

1:08:55

Jerrett: Yeah, I don't think that, as Hien correctly pointed out and Linda that this report is not about regulations it's about trying to get some assessment of the benefits that may accrue from the potential of regulatory actions. There are always implicit or explicit economical concerns that weigh into that and that is something that fortunately gets left to other people to consider. I'm not about to comment on whether regulations move too quickly or too slowly because I don't think that's my job here. I'm just trying to supply the best science that I can. To help make those to be as informed as they can be. So I

don't think this report, from my read of it, was about specific regulations or the pace thereof. It's about trying to get the most reasonable assessment of the science. I think that based on the EPA elicitation and the numerous other studies, this is the best that we have now and your study and others have been taken into account. And I kind of feel that they should have probably given more weight to my study and I'm sure that other people think that they should have given more weight to, you know Doug Dockery feels they should have given more weight to the Six Cities Study, has that feeling about their own study.

1:10:32

Everybody likes their own studies more.

1:10:34

Yeah, it's funny isn't it. So...

1:10:37

I actually agree, Mike, and James just so that you're fully aware of what I think. I think that we have underweighted the Jerrett et al study. I personally think it is one of the most carefully done studies in California with some of the very best data and I think the fact that they ended up using estimates substantially lower than the Jerrett et al study is sort of an indication that there is at least some conservative people involved with this.

1:11:14

Croes: And you know, just for the record, the people from Woman's Health Initiative study weighed in and also were upset we didn't give their study quantitatively that the higher risk estimate was in common with the record with the use of that study in California. So we are getting it from both sides.

1:11:38

Enstrom: Ok, this is Jim again. I think there is a little bit of a misunderstanding. It wasn't so much that my study was underweighted it was more in the lines that it was mischaracterized. And it's also, I believe the May 22nd draft report does not try to focus on California specific evidence. That's what I'm trying to get at. I believe there's enough evidence out there that the focus can be on California specific evidence. So, it's not so much that I'm concerned that my study be given great weight and that's why I'm proposing these additional analysis of the Pope 2002 study which is not even my study. So I just wanted to get that clarified.

1:12:34

Croes?: Fair enough.

1:12:37

Jerrett: Yeah, I think the other issue, the important scientific issue for me, is given all the work that we are currently doing with the CPS II in California with a much younger cohort. You know how much more information are we going to get out of the CPS I. I

think that's going to be something that we're going to have to think about. You know, is there more geographic coverage, are we getting some areas in California in that cohort that we wouldn't be getting in CPS II because as the cohort, you know as you follow that cohort on the risk estimates become smaller and smaller and less informative and the early years we had probably no idea what exposure would really be like. So I think there are some serious issues that we have to think about here.

1:13:35

Tran: Thank you very much everybody for bringing those issues to the table. I would like to summarize the discussion today that Dr. Enstrom has brought up to the attention of the importance all of you have elaborated on and it is important to look at age, age and survival effect of the cohort, pay close attention to the exposure estimate as far as taking into account spatial resolution and the detailed analysis that is currently undergoing under the Jerrett contract with ARB. I assure you that when we revise the May 2008 report we will carefully address all of Dr. Enstrom's comments. And again I want to thank you all for your participation.

1:14:27

Pope: I just say one thing that you didn't mention, which I think is cause specific deaths.

1:14:32

Tran: That's right.

1:14:35

Pope: I mean, the action in the CPS II is mostly ischemic heart disease a little bit of additional cardiovascular, but it's not all causes and I think that's really important to keep in mind, that's where the information is, it's not all causes.

1:14:51

Jerrett: Dr. Enstrom could go back to his original funder, EPRI, he might be interested in that as well. It's another avenue if he's interested in looking at that and has the resources to do it. That would be a very good follow up and something that may seem to help.

1:15:12

Smith: OK well, thank you very much. I think we're going to be cut off, we only have the phone line for another few minutes, but I would like to thank you all for your participation. Like Bart and Hien had said, we have a lot to be thinking about and we will follow up with all of you very soon. So, thanks again and have a good day.