US ENVIRONMENTAL PROTECTION AGENCY

SCIENCE ADVISORY BOARD (SAB) STAFF OFFICE

CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE

(CASAC)

OXIDES OF NITROGEN PRIMARY NAAQS

REVIEW PANEL PUBLIC MEETING

MARRIOTT AT RESEARCH TRIANGLE PARK

4700 Guardian Drive

Durham, North Carolina 27703

OCTOBER 24, 2007

8:40 A.M.

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U.S. ENVIRONMENTAL PROTECTION AGENCY
CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE
PUBLIC MEETING
October 24, 2007

DR. NUGENT: Good morning everyone, and welcome to the Clean Air Scientific Advisory Committee, Oxides of Nitrogen Primary Review Panel.

And today and tomorrow the panel is convened to do a peer review of the first draft, integrated science assessment of oxides of nitrogen.

And tomorrow the panel is going to be reviewing, is going to be providing a consultation on a draft Agency document on the NO2 health assessment plan.

My name is Angela Nugent and I am the Designated Federal Officer for this panel. And I serve in the EPA Science Advisory Board Staff Office.

I'd like to make a few remarks in my capacity as Designated Federal Officer or DFO and then introduce the first two speakers on the agenda for their remarks.

So this panel, the CASAC Oxides of Nitrogen Primary NAAQS Review Panel is a federal advisory subcommittee and by EPA policy its meetings and deliberations are held as public meetings, they're

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noticed in the Federal Register, all in written and public comment are invited, minutes are kept and the public is kept informed.

So the panel operates as part of CASAC which is a chartered federal advisory committee that the CASAC, chartered CASAC is empowered by law to provide advice to the Administrator.

So far for this panel meeting there's been three request for oral comments and I've just received one set of written comments, that was the only set received and it pertains to the NO2 health assessment plan and I'll distribute that to you at the break and make it available to the public for tomorrow's discussion.

Let's see, as you can see on the agenda there is time set aside this afternoon at the very end of today's discussion for this panel to summarize the major review comments and recommendations related to the integrated science assessment.

So the plan is to distill down the recommendations and advice of this panel at the end of the day today.

There is a second public comment period tomorrow morning and interested members of the public who would like to provide additional public comments,

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please contact me, either in person or by email by 8:00 a.m. tomorrow.

Let's see, I'd also like to note just as a matter of record that the members of this panel are in compliance with federal ethics and conflict of interest laws that pertain to them. So we're good to go for this meeting.

The Agency has arranged for a recording and a Court Reporter for this meeting. So I ask every member of the panel and every member of the Agency and the public when they speak, to please identify themselves by name at the beginning of their remarks.

Let's see, and I think that's it.

Let me now turn to Doctor Vanessa Vu who is the Director of the SAB Staff Office, and then to Doctor Rogene Henderson, Chair of the Chartered CASAC and Chair of this panel for their opening remarks.

DR. VU: Thank you, Angela. Can you hear me? Yes, that's good. Good morning everyone. I'd just like to also add my welcome to everyone to the meeting of the Clean Scientific Advisory Committee, the panel, the nitrogen oxide panel that will deliver advice to the Administrator regarding the revision of the NAAQS for the health effects, or the primary standards of the NAAQS for nitrogen oxides.

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On behalf of the Administrator I would like to thank members of the CASAC and members of this panel for your time and taking your time away from your busy schedules to provide advice to the Administrator regarding the subject matter that Angela had talked to you about in her opening remarks.

I'd also like to take this opportunity to thank, special thanks to two outgoing members of CASAC, Doctor Frank Speizer and Mr. Rich Poirot for their long, valuable service to the Agency in the past six years as members of CASAC.

And I also take the opportunity to welcome two new members, Doctor Donna Kenski and Doctor Jon Samet. I know Doctor John Samet will be joining us by the phone today, the next two days. And thank you both for being part of CASAC, I appreciate that.

As Angela indicated, this meeting is a public meeting of CASAC. We appreciate comments form the public commenters and thanks in advance for those who would like to submit comments for the panel and CASAC's consideration. I appreciate that.

I'd like to also take this opportunity to thank the Agency representative for this morning. You will hear from Doctor Ila Cote and Doctor Mary Ross

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are responsible for the preparation for the integrated assessment.

And tomorrow you will hear from Mr. Lydia Wegman and Doctor Karen Martin and her team from the Air Office that will speak with you about the risk and exposure methods document that you will give consultation on that report.

Finally I'd like to thank Angela Nugent for stepping in and serving as the DFO.

Some of you have been interacting with Fred Butterfield who has been the CASAC DFO, and he still is. As you all know he now has a lot of work to do given the fact that the Agency now is working on many pollutants. So you will still interact with Fred in a different capacity, but Fred will still be part of the charter of CASAC DFO and Angela will be part of this particular review for the nitrogen oxide panel.

And in December you will be convening again to delivery advice on sulphur dioxide and Holly Stalworth, also a member of my staff, is going to be supporting the DFO for the sulphur oxides issues.

With that I'd like to turn it over to Doctor Rogene Henderson, and once again we would like to thank, sincerely thank Doctor Rogene Henderson who has been Chair for CASAC and continues on this year as

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well.

Thank you so much, Rogene.

DR. HENDERSON: Welcome. It's good to have you all here. I think we are doing something extremely important today.

As I have said to some of you, this is the first ISA document after years and years of suggestions to condense the criteria document into something that's more focused on policy relevant information for setting standards.

Now we're getting the first attempt at doing that.

From all of the comments that I read I think people have been extremely helpful in giving the Agency a very detailed critique of this first ISA, and I expect we'll have lively discussions.

But the product of what we do today will be information to the Agency so that they can revise the ISA, hopefully condense it some more and we will be reviewing the next draft in several months.

But before we move on to the public comment, I would like to pay honor to a member of this panel, Henry Gong, who passed away very suddenly in the last few months. And, you know, Henry was a great panel member. He though well, he was, he had his

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clinical connections but also was very involved in setting regulation, was a member of the CARB, the California Air Resources Board. A very good discusser. We used to say he interacted, played well with others. I mean he always got his point across, but in a very civil fashion.

So I just want to take, you know, just this moment to honor Henry, he meant a lot to me.

And now let's turn it over to Angela who is going to lead the public comment period.

Oh, I'm so sorry, did I miss, I'm very sorry, you have to keep me straight. We're going to turn it over to Ila who is going to give us a review of the draft ISA.

DR. COTE: I was hoping I was going to get out of this.

DR. HENDERSON: No Ila, never.

DR. COTE: (Inaudible).

DR. HENDERSON: We need you to be miked. And the people on the phone really need you to be miked.

DR. COTE: Let's do it again. Can you hear me now?

My name is Ila Cote, I'm currently the Division Director for the National Center for

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Environmental Assessment at the Research Triangle Park Division.

A primary mission for all of NCE is to develop health assessments that are used in the Agency's risk assessments.

RTP tends to focus on air pollutants and Mary Ross, who you'll meet in a moment if you haven't already, is the Branch Chief whose branch is responsible for developing health assessments for the criteria document.

I want to welcome everybody and thank everybody for being here.

In particular I'd like to thank members of the scientific community that have been so helpful to us in the last few months.

As Rogene mentioned, you know, we have a new process and a new product and largely a new staff and largely new management and we just remodeled so we all have new offices, so it's sort of a robust and rampant amount of newness going around the office.

And so it's been very helpful to have the guidance of the scientific community. They're very generous with their time, so I wanted to thank you all for that. Next slide. That's not the right one. Yeah, thank you.

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I briefly want to, I want to give you a quick overview. Many of you will have heard this information before, but I just want to make sure everybody's on the same page, including members of the public that may not have been here before.

So what I'm going to, what I'm going to talk about a bit is the NAAQS process, the current NAQS, NAAQS, I love saying that, the draft IFA is going to be covered by Mary in more detail. Next slide.

So as Rogene had mentioned there had been sort of a long interest in revising the NAAQS process, so a couple of years ago Marcus Peacock who is the Deputy Administrator for the EPA, asked that a work group be formed and those people come up with a new process, which they did. And it is now the accepted Agency process as of maybe last year.

So there are four steps in the new process. Planning, this whole, the whole start to finish NAAQS process is guided by this plan that is developed very early in the process. It's done collaboratively with the Air Office and ORD, essentially OAQPS and CEA.

Some of the key features of the plan are that it contains what is our draft policy relevant questions or the final policy relevant questions so the

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plan is finalized.

One of the major changes that is happening, rather than reviewing all of the science in kind of an equal amount of detail, to really focus on the science that will most make a difference or most heavily impact our regulatory decision making.

The plan also contains a schedule for that particular chemical.

As many of you know we've kind of jumped into this process midstream with NAQS. PM will be the first chemical that goes through the start to finish process so we're doing NAQS, then SOX, then PM.

The science assessment is what, is the subject right now, we're here to talk about integrated science assessment. The concept was that the integrated science assessment would replace the criteria document and present information in a more concise and essentially accessible kind of fashion. It was made more transparent with the key science that the Agency was relying on.

At the same time while it was supposed to be thorough and complete and cover everything, that's kind of a difficult charge and so as with all new processes, implementation has been in the details about exactly what the integrated science assessment

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will look like.

The next step is the risk and exposure assessment which is conducted by the Air Office. The integrated science assessment essentially informs the exposure and risk assessment.

The last step is also done by the Air Office, policy assessment and rule making. The much beloved staff paper has disappeared and has now been replaced with the announcement of the proposed rule making that articulates sort of the broad Agency view as opposed to the staff paper itself. Next slide. Go to the next. Okay, thanks.

This just points out in a little more detail some key steps in the process. You can see the four boxes. This identifies the integrated plan, followed by the integrated science assessment, exposure and risk assessment the draft ANPR.

The bottom half of this slide is predominantly the rule making process. So I'd like you to focus on the top half of the slide.

We will have gone to a kickoff meeting, what we're calling a kickoff meeting in which we bring in scientists who are very knowledgeable about the variety of topics of interest to us, have a workshop about what the key policy relevant questions will be.

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That gets incorporated into the plan.

CASAC has an opportunity as you know to review the plan.

Then at the same time we're beginning, we've done the literature search, we're starting to pull all the information together here and which feeds into what we're calling the science assessment document, but we're simply calling the annexes now.

So at this stage we have a rough summary of all the literature and we've begun to winnow through that to identify the science that most specifically addresses the policy relevant questions.

As this support document or the annexes evolve, what we are moving toward is tabular form summarizing studies so it gives the study and some details for all the studies published since the last review, which is the case of NAQS was in '93.

There was some amount of back and forth about exactly what should be in and what should be out and this rough draft kind of went to press before we had that really nailed down, so as you read it you'll notice there are some older studies that are included that in the next version will essentially be summarized in the, either will be included either by reference or in the annexes that are currently in the main body of

the document.
But in general I think it's a, there aren't too many of those little faux pas.
So then the next step is the integrated science assessment and we begin to really bring together the summary of the information.
The risk and exposure assessment essentially lags the integrated science assessment a tad, but not much, and I'll show you the schedule in a minute.
And again there's opportunity for CASAC and public comment on both of those components. Can I have the next slide.
So in terms of the science assessment itself, as I mentioned the first step is the development of the annexes which are disciplinary specific, so there's an EPI chapter and, you know, an atmospheric chemistry chapter. There was a workshop held in February of '07 for peer review of the initial draft of the annex material and a discussion on how to focus the integration.
The IFA then draws from those annex chapters to evaluate and simplify its evidence, particular with the health outcome focus unless it's one of the eco documents that generally has an eco

focus on it.
One of the things that's really important is to integrate across disciplines which is a kind of tricky business. But there's a lot of, a variety of expertise that's brought to bear for the publication of the integrated science assessment.
And then the last critical part are the recommendations and conclusions that provide support for the future risk assessment, exposure assessment and policy analysis. Could I have the next slide please.
This is the current schedule. In August we completed the first draft of the integrated science assessment. We're sitting right here in October with the CASAC review.
You could see the schedules for the remaining steps of the process, so all of us will probably see each other frequently this year. Next slide.
I'd also like to introduce the NAQS team and I want to particularly recognize Mary Ross and Dennis Kotchmar. I would say the process has, it has been a challenging year and both Mary and Dennis bring this calm presence to the whole process. So Dennis, would you raise your hand back there? Doctor Dennis Kotchmar who led the development of this document,

always a steady and knowledgeable hand.
Jeff Arnold, Jeff, if you would raise your hand back in the back. Jim Brown, I don't know if Jim Brown in the back who does our dosimetry and clinical work. Jeung Kim I don't, oh, Jeumg's back, I can see her, our epidemiologist as is Doctor Ellen Carrain. Tom Long and Tom Rubin are new to our operations. They walked in the door all these new hires have just walked in the door and started being high performance. That's great. Herung Ming who's here, another atmospheric chemist exposure scientist. Joe Pinto, one of our senior scientists, again with much, much experience. And Paul Reinhart who's a toxicologist for that. Lori White who is also a toxicologist is way in the back and William Wilson, an exposure scientist of great, great knowledge.
So at this point I'm going to turn it over to Mary Ross. Can we have the next slide.
DR. HENDERSON: Can we leave it there.
DR. COTE: Which one does it
SPEAKER: Hello, hello.
DR. COTE: Oh, I'm sorry Dave, I really apologize.
SPEAKER: Can you hear us?
DR. COTE: Yes, we can.

SPEAKER: Because we can barely hear you. Can you turn up the microphone?
DR. COTE: We'll be able to in a second.
DR. COTE: So anyway I'd like to turn things over to Mary Ross. Is there anything else I skipped? Dave, I apologize. Okay, Mary.
DR. ROSS: Okay, I'm Mary Ross and I'd actually like to build on that to say that we have some of the experts who have helped us write the document here in the audience with us too.
And purpose of introducing the team is we have resources here available if points need clarification or if for further elaboration on some of the points or a discussion of how we could possibly address things better, they will come up and join us or be able to help answer questions.
Doctor Kathleen Boulanger and Jeanine Gant are epidemiologists from Yale who assisted with the document and they are behind Dennis. And I know Doctor Vic Hasselblad is with us, a statistician who has helped us with understanding epidemiology and Doctor Mark Frampton has helped us with the clinical exposure studies.
SPEAKER: Hello, I don't hear a thing.
DR. ROSS: Okay, I'm moving closer to the

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mike. Can you hear me now?
SPEAKER: Hardly.
DR. ROSS: The AV people are working on that.
SPEAKER: Okay.
DR. ROSS: Okay. And if I could step back one more slide to the schedule, just a point of clarification for any confusion there might be out there.
When I put this set of slides together I neglected to update the schedule to reflect the negotiations we've had with the plaintiffs over the last couple of months, so there's a version that was on the web early and has been replaced I think with this version.
The schedule is now a little bit shorter than it was in the version that I first sent to Angela, but these are the current dates that have been, that are just about done. There still is not a formal consent decree schedule, but these are the dates.
So the final decision is to be completed by the end of 2009 in this agreement.
So this is the schedule we'll be working under unless something else develops.
DR. COTE: Unless it changes.

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DR. ROSS: Yeah, but it does seem to be the way it's going to go.
So the next slide if you'll skip over to the next one after that, just a brief overview of the organization.
As part of the transition from the criteria document to the integrated science assessment we've really struggled with how to present the information in the most policy relevant way.
And I'll just say a couple of words about where we ended up and how we organized it in this way.
At the bottom of that slide there are the annexes and the annexes represent the work that you do at the beginning of science assessment in any form it takes, is gathering the information from the different disciplines. So the annexes are still discipline specific, you know, atmospheric science, toxicology, epidemiology and they involve compiling, summarizing and briefly overviews and details of the studies from the different disciplines.
And then in the integrated science assessment we have a, our Chapter 2 is called, source to dose. And the purpose of that chapter is to pull together information from atmospheric sciences, sources

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of NAQS, the measurements and concentrations and exposure issues that can help inform interpretation of the health evidence.
The third chapter is, integration of health evidence and there we've pulled from the annexes for toxicology, clinical studies, exposure information and epidemiology studies to try to pull it together in a way that we think hopefully will be most relevant to the policy.
The first order of division was by short term exposure and long term exposure, generally grouping the effects, right now we have an annual standard for NAQS but there are a number of studies that have looked at effects with shorter term exposure. So the first discussion is on short term exposures which ranges from the toxicology studies, it could be, you know, a number of hours, a lot of epidemiology studies use 24 hour or one hour of max concentrations.
And long term exposure as you know is in the chronic toxicology studies or the sort of cohort studies that have been done in epidemiology within those, within short term exposure studies for example.
And I'm just going to point that Cas Ito just walked in the door. We've been introducing members of the team. Cas Ito assisted us with the

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epidemiology studies. Sorry, Cas.
Within each exposure window then we looked at sort of the health outcome orientation so we focused on respiratory morbidity first as the type of health outcome that was most strongly associated with NAQS in the past.
We've begun with what we knew before in the 1993 criteria document for NO2 and for nitrogen oxides and we've built on that to the extent we could.
We've then, you now, other morbidity and mortality are discussed and then the health outcomes.
We discussed the basic evidence and then we try to draw in what information we have about the levels at which the effects were seen within the health evidence discussion.
The way we tried to structure this is at the end of a particular section, for example airways inflammation or lung function, we tried to provide a brief summary of the effects for that individual outcome. And then we prepared integration sections at the end of a general group, like respiratory morbidity.
So there should be an integration section where we tried to integrate the evidence from the different outcomes related to respiratory morbidity. And that was the purpose of that structure.

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Chapter 4 includes just some overview of the types of susceptible groups, the evidence we have for susceptible groups and sort of the public health impact information we have available.

The conclusions provide some overarching conclusions about the conclusions that we have in this draft, and we added some table at the end that include the effects seen and the levels at which effects are seen. There's a table for toxicology studies, a table for controlled human exposure studies. And then for epidemiology studies you don't only have a dose, but what we presented is the studies with some points in the air quality distribution there.

And I'll note that there are some blank columns in the table of epidemiology studies that could be, we could get data from the studies and prepare things like 98th and 99th percentiles for the air quality distribution within that study period. That's been useful for the program office in the past in terms of evaluating the distribution across which health effects were seen.

Now I'll skip through the last few, the next set of slides just give you a basic overview of what we did in this first draft assessment.

We grouped charge questions 1 to 3 here

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on this page and the general questions we're seeking input in, is how well have we characterized the atmospheric chemistry and air quality information in mostly Chapter 2 that can help inform the interpretation of the health evidence, are the properties of ambient oxides appropriately characterized? Many of you have specifically addressed these questions which is much appropriate so I won't read them all.

But they generally refer to atmospheric sciences and exposure issues.

The next slide is just a figure that we pulled, slide number 11, is a figure that we pulled from the document that provides a general overview of the fact that oxides of nitrogen is a complex mixture. NO2 is the oxide of nitrogen for which the standard is set, that's the indicator for this current standard right now. And it is the, when you look at the health evidence, the vast majority of information is available on NO2.

Within NAQS, the general NOX that is measure that is considered by chemists, NO2 and N0 and then you have this broader discussion of N0Y or N0Z kind of compounds that are the other oxides of nitrogen that we try to discuss in Chapter 2. And I won't go

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into any detail there.

The next slide just has a few key highlights from the atmospheric science thing. On atmospheric chemistry we discussed the processes involving NO2 and other oxides of nitrogen there. It's part of the photochemical production of ozone and PAN as well as acidic and nitrogen oxides and nitro pH's and there are a whole range of chemicals that we discussed in some detail in the annex and then we bring forward a few highlights in Chapter 2.

And the measurement that was discussed in some length, we measure NO2 at the FRM, the Federal Reference Method, but it's long been known that there is interference of NO2 by other compounds called N0Z, the short of mixture of non and NOX compounds. And nitric acid and PAN are probably the biggest contributors to that.

We discussed measurements of N0Y which is the overall oxides of nitrogen measurement that can be done and it is a more precise measurement of the overall mixture of oxides of nitrogen. I know some of you have commented on that and it's appreciated.

The annual average of concentrations, there's a couple of characterizations or it in Chapter 2 and then more detailed discussion in the annex. The

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annual average is about 15 parts per billion. The standard is 53 parts per billion annual average for the current NAAQS. So generally the levels are below the NAAQS all over the United States. You can have a few peak concentrations in specific areas where a one hour average concentration can exceed 100 parts per billion.

If we flip to the next slide just a couple of highlights from exposure which we think is a really key issue in this interpretation of health evidence, is the relationship between ambient measurements of NO2 or NOX or N0Y or whatever you're measuring and the nitric oxides to which people are exposed.

When we looked at studies that evaluated the relationships between ambient NOX, NO2 and I must say the studies were all on NO2 so I'll stop saying NOX, so we looked at ambient levels of NO2 and personal measurements of NO2. Many of the studies actually found the correlation on a day to day basis was pretty good. Some of them did not.

And we discussed a number of factors that can contribute to that result, such as obviously factors around the house that contribute too. But a number of those are discussed in Chapter 2.

Epidemiologic studies often use

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measurements at central sites. There are very rare studies that use more localized measures.

Measurement error, this has actually been discussed in more detail in ozone and particulate matter and so we relied a lot on evaluations we've done before. But it found that measurement error often results in underestimated risk estimates and increased standard errors as a general conclusion.

And I'll skip ahead to charge questions 4 to 6 which are primarily about, primarily related to the integration of the health evidence. And without reading them all, you know, we're interested in your input on how well we've characterized the health effects, how well we've pulled them together to integrate them for the different health outcome measures, and you know, your comments on our conclusions about the strengths and consistency and the causal nature of associations between NO2 and the different health outcomes.

A couple of key slides, the next two slides, the first one is on short term exposures and these are just our key conclusions. Respiratory morbidity was the outcome that was most strongly associated with NO2 in the last review and it remains the health outcome for which there is the most

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evidence. And we conclude there's a likely causal evidence.

There's a lot of new evidence from epidemiologic studies, emergency department and hospital admissions visits, that was not available previously.

There also are new studies, a couple of multi-city studies on symptoms and further indoor and personal exposure studies related to NO2 in homes or in schools. These gave us a lot of confidence that there was an association between NO2 and respiratory morbidity. Less evidence on cardiovascular morbidity, a few epidemiologic studies have shown associations with things like cardiovascular hospital admissions but the evidence is a lot less conclusive.

And the same with all cause mortalities. There's some evidence from epidemiologic studies that generally shows positive associations, but it's difficult to draw causal conclusions without a lot of mechanistic evidence for that.

The next slide is about long term exposure and this comes from things like the Children's Health Study in California and the other, the related similar studies to that and prospective cohort studies of mortality.

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The studies on respiratory morbidity have given some suggested evidence but they're not always consistent so we refer to that as suggestive evidence for lung function growth in asthma prevalence with long term exposure to NO2.

With lung cancer there is epidemiologic evidence indicating that NO2 may be associated with lung cancer. In a broader perspective the NOX include nitro pH's that are known to be, some of them are known to be carcinogenic. So it's possible but we don't have a lot of evidence linking NOX with lung cancer incidence.

There's a few studies on birth outcomes. We refer to that as limited evidence.

Cardiovascular evidence, there are no studies that we had available to us that looked at long term exposure and things like atherosclerosis, things that have been studied for PM.

And with mortality we consider that inconclusive evidence. Again a few of the prospective cohort studies did indicate some associations with NO2 but it wasn't consistent across all the studies.

And the last two slides I'll quickly wrap up, we asked, the last two questions are, how well did we characterize the public health impact? And your

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views on the adequacy of this draft to inform further risk and exposure assessments.

And we certainly welcome comments on that. I'd say the team that we've had with us has worked really hard to try to pull this information together and we know we have some adjustments to make and we really, we've seen some preliminary comments that we've been reading carefully and we really appreciate them and look forward to your comments.

And I have one more slide that's actually sort of an add on. It's the susceptible groups that we identified in Chapter 4 and the existing respiratory disease in children were identified as susceptible groups in the last review. There's some very limited information on genetic susceptibility, I think one study. And also some discussion about high exposure populations. Not a lot of evidence directly related to NO2 but a little bit of evidence is discussed in there.

So with that I will close. And if there's any questions, we can clarify. Or I don't know, Angela is we have time.

DR. HENDERSON: I would ask the members of the panel if they have any clarifying questions for Ila and Mary. We will be discussing this report all

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day long, but is there anything about their presentations that you would like to have clarified?

Okay, and you all

DR. COTE: Thank you.

DR. HENDERSON: will be around, right?

DR. COTE: We will do that.

DR. HENDERSON: And then we're going to Angela is nudging me here I haven't forgotten, Angela.

We forgot to take role of those who are on the telephone, so I'll let Angela, you do that.

SPEAKER: Can you hear us?

DR. NUGENT: Good morning to those on the phone. I would ask that, this is Angela, I would ask that the members of the panel who are on the line right now identify themselves please.

DR. BALMES: this is John Balmes from UCSF, UC Berkeley. Can you hear me?

DR. HENDERSON: Yes, John.

DR. BALMES: Rogene, when you spoke we could barely hear you.

DR. HENDERSON: Okay, thanks for telling me that.

DR. BALMES: Now it's better.

DR. HENDERSON: Is that better?

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DR. BALMES: Yes.

DR. HENDERSON: I'm kind of eating the microphone now. Okay.

DR. NUGENT: Are there any other

DR. ULTMAN: This is Jim Ultman, Rogene, how are you?

DR. NUGENT: Other than John, are there any other panel members on the line right now?

DR. ULTMAN: This is Jim Ultman, can you hear me?

DR. HENDERSON: Jim Ultman, very faintly.

DR. ULTMAN: Okay, well I'm having the same problem as you. I'm hearing my colleagues that are in California very clearly but you are much closer to me in Pennsylvania and I can hardly hear at all.

DR. HENDERSON: Are you burned up yet in California?

DR. BALMES: Well actually the fires are in Southern California.

DR. HENDERSON: Oh, okay.

DR. BALMES: So I'm fine up here.

DR. HENDERSON: You're northerners, okay.

DR. BALMES: So all our firefighters are down south so if anything starts up here we're in trouble.

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DR. LARSON: This is Tim Larson from Seattle.

DR. NUGENT: Thank you, Tim.

DR. SHEPPARD: And this is Lianne Sheppard, also from the University of Washington in Seattle.

DR. NUGENT: Thank you all for being on the line. Any other panel members on the line?

Please let us know either by email or by an interjection into the discussion if you have problems with audibility and we'll work with the team here to fix it. So thank you.

DR. SHEPHERD: Well anything you can do to make it better, it's awfully faint and difficult to hear. But we're hanging in there.

DR. BALMES: Well said.

DR. HENDERSON: Okay. Now we will go to the public comment period which is headed up by Angela.

DR. NUGENT: Thank you, Rogene. This is the first of our two public comment periods. We've had three individuals requesting the opportunity to provide public comment and I would ask them to step up to the mike at the center of the room.

Vanessa is offering you a seat at the table so please join us.

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Our first commenter is Doctor Christopher Long from Gradient Corporation and he is presenting comments on behalf of the Utility Air Regulatory Group and he provided some slides last night. And do you have this material with you?

DR. LONG: Not yet, I'm working on preparing that right now.

DR. NUGENT: Okay.

DR. LONG: Yeah, I'd first like to thank you for the opportunity to present comments on the NOX ISA.

You know, as Angela mentioned I'm presenting comments on behalf of the Utility Air Regulatory Group.

Since my time is short I'd like to immediately dive into our comments which primarily deal with the Chapter 5 findings and conclusions section of the ISA.

In this section EPA outlines a decision paradigm for, you know, assessing and integrating the overall weight of the scientific evidence within the three lines of health effects evidence, namely epidemiology, clinical toxicology and experimental toxicology. Next slide please.

In this chapter they proposed this

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decision paradigm to draw conclusions regarding the overall strength of the evidence and the extent to which causal inference made be made.

And in doing this they identify several essential characteristics of the scientific data bearing on the health effects of the ambient NOX. These include strength, consistency, coherence and plausibility. Next slide please.

I've taken the liberty of converting EPA's textual description of its paradigm to a table that clearly illustrates the required level of findings within the three lines of evidence necessary to support a given level of inference.

Beginning with the likely causal level of inference EPA essentially requires that all three lines of evidence be strong, consistent, coherent and plausible.

To make a suggestive level of inference either the epidemiology or the clinical toxicology must be strong, consistent, coherent and plausible. And in suggestive the experimental evidence can be limited.

For the inconclusive level of inference all three lines of evidence are generally considered to be limited. Next slide please.

In the application of its paradigm, you

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know, there are several examples where the evidence is described as weak, inconsistent, with no clear pattern, confounded and/or limited. And generally EPA makes the overall determination that the evidence in these cases are inconclusive.

Examples include short term NO2 exposures and cardiovascular effects and long term NO2 exposures and mortality.

However, generally quantitative or even methodical criteria as to what constitutes strong, consistent, coherent and plausible evidence are not clearly outlined in Chapter 5. And in some cases the text doesn't seem to reflect rigorous application of this paradigm. Next slide please.

Some example of what we've identified as inconsistencies in the application of the paradigm can be found in Chapter 5. One of these involves the case, the conclusion where a likely causal relationship between short term NO2 exposures and adverse respiratory effects is made. In this case EPA appears to heavily rely upon strong new epidemiological data of associations between ambient NO2 and increased emergency department visits and hospital admissions for respiratory causes.

However, no where in Chapter 5 is the

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strength, consistency, coherence and plausibility of these EPI data systematically assessed despite, you know, observations in Chapter 5 that these studies typically showed high correlations between a number of co-pollutants and that there remains uncertainty as to whether NO2 is the causal agent or is instead a marker for the effects of another traffic related pollutant or a mix of pollutants.

Another example of an apparent inconsistency involves mortality in short term exposure where the epidemiological associations are described as suggestive, and later in this section both clinical and experimental evidence are characterized as limited.

This would appear to support an overall conclusion of inconclusive, but in the conclusion section, mortality evidence is characterized as suggestive. Next slide please.

Just a few, just to conclude my comments, a few recommendations for EPA.

Overall we feel that the ISA document would be strengthened if the EPA evidence evaluation paradigm was more consistently implemented. That is, strength, consistency, coherence and, you know, plausibility or dose response require a more quantitative definition.

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Often, you know, the positive attributes of data are merely given as significant evidence, numerous studies, new insights, robust effects and high correlations. You know, in addition the supportive or non-supportive role of clinical and experimental studies at the specific ambient concentrations in question is not fully presented in Chapter 5.

So just to reiterate, you know, I'd like to commend EPA for laying the groundwork for this useful decision framework, paradigm, but I'd like to strongly encourage EPA to more rigorously and transparently follow through on the application of the paradigm.

Thank you for your attention.

DR. HENDERSON: Thank you. Are there any questions. Okay, well thank you very much for your comments.

SPEAKER: We can't hear again.

DR. NUGENT: We'll try harder. This is Angela introducing the next public speaker, Doctor Will Ellison from the American Petroleum Institute and he's presenting comments on behalf of API.

MR. FELDMAN: Good morning everyone. Those of you who know me know I'm not Will. Will has effectively delegated upwards and I got to come to the

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meeting.
This is Howard Feldman from API and I do have some handouts, but not to those of you on the phone though.
Okay, as they're going around let me just, let me get started here. And I don't have slides, I'm sorry, so we can just hold off on those for the moment.
Good morning, I'm Howard Feldman, I'm here on behalf of API. API represents almost 400 member companies in all aspects of the oil and gas industry and thank you very much, CASAC, for taking these comments on the ISA.
A preliminary review indicates that there need to be significant changes made to the draft ISA. The ISA conclusion that NO2 concentrations below the current standard are causing health effects is based primarily on observational EPI.
The inherent limitations of these studies do not permit such a conclusion and the reasons for our views will be stated below.
First, we recommend that the draft ISA be revised to conclude that ambient NO2 levels are poorly correlated with personal NO2. I just heard Mary saying some yes, some no, but we think that they are

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poorly correlated with the ambient monitors and also that observational studies reporting effects of NO2 are confounded with ambient PM.
These ISA conclusions contradict those in the final PM criteria document, so we're trying to balance, what are we seeing in one CD and then we're seeing something else here. How does that all come together?
This contradicts what was in the final PM CD and staff paper.
In the PM review EPA concluded that the monitored gaseous ambient concentrations, including NO2 were poorly correlated with personal gaseous exposures and better correlated with the personal PM.
Nor are these conclusions supported by results from recent studies in Baltimore, Boston, Steubenville, that confirm the poor correlation of ambient and personal NO2 exposures.
Furthermore the ISA acknowledges that the Federal Reference Method for NO2 fails to provide reliable measures of NO2, but rather of N0I which is a whole bunch of compounds that varies in response to composition of the ambient mixture and humidity.
Okay, second, I'm going to give you four reasons why we recommend that the draft ISA be revised

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to conclude that there is inconclusive evidence rather than stronger suggestive evidence, that ambient NO2 levels below the current standard are causing decreased lung function, respiratory symptoms and increased emergency department visits or hospital admissions.
We also recommend that the draft ISA be revised to conclude that the multi-city and mechanistic studies providing no convincing evidence, provide no convincing evidence, rather than suggestive evidence that current ambient NO2 levels are causing acute cardiopulmonary mortality.
First, I want to go into four of these, pulmonary function, the ISA cites a number of observational studies as evidence of acute effects. No association of peak exploratory flow rate, PEFR, with NO2 exposure reported in nine of the nine studies using self-reported PEFR measurements.
The ISA discounts these negative results, concluding the PEFR data are notoriously unreliable. And of course this contradicts the use of the PEFR studies in the ozone we're making.
In two of the three NO2 studies performed using spirometry, small associations were reported using single pollutant models. Since similar responses were observed for other highly correlated air

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pollutants, it's not possible to attribute these effects to NO2 alone.
In the third study no association was found using spirometry. So as the ISA proceeds, the ISA then proceeds to go on and to discount results from the human clinical studies, including studies of potentially susceptible groups such as the elderly and those with COPD which fail to report pulmonary function effects at ambient NO2.
Moving on to the respiratory symptoms, Schildkraut, et al in 2006 is cited by the ISA as strong evidence of respiratory symptoms in child asthmatics. We commend EPA for considering this study which was ignored during the ozone review, possibly because they reported no positive associations for ozone. However Schildkraut, et al does not provide clear, much less strong evidence for independent effect of NO2.
In three of the four results the risks attributed to NO2 were not statistically significant when PM 10 was included in the multi-pollutant analysis.
Moving on to emergency department visits. The ISA cites selected observational studies as evidence of independent effects of NO2. However the

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results of these studies are mixed, with some reporting positive statistical significance and others not.

In many of the studies reporting positive associations, only single pollutant models were used. And many studies considered positive, only one of the multi-pollutant results presented was statistically significant. And NO2 risks were not generally robust to the inclusion of other pollutants. Rather, in many of these studies the risks attributed to NO2 were markedly reduced in multi-pollutant models.

Moving on to acute cardiopulmonary mortality, the ISA concludes that multi-city studies, particularly n-maps provides the most useful information for determining whether ambient NO2 is associated with acute mortality. Although this study provided the primary basis of early mortality effects for PM and ozone, the authors reported no association between NO2 and total mortality.

The ISA apparently revised its conclusions to the n-maps authors without performing published or reviewable independent re-analysis. The ISA also reinterprets the Canadian eight city study, assuming little PM confounding, although the authors report that the inclusion of PM 2.5 markedly reduced estimates of NO2 risk, particularly when everyday PM

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data were available.

So that concludes my remarks. We will be submitting comments into the docket.

DR. HENDERSON: Thank you, Howard. Are there questions from the panel? Okay, thank you.

MR. FELDMAN: Thank you.

DR. NUGENT: Our third and last oral public commenter is Mr. John Hice from the Air Improvement Resource, Incorporated, speaking on behalf of the Alliance of Automobile Manufacturers. And I was expecting him to be on the phone. Are you there?

DR. HICE: Yes I am.

DR. NUGENT: Hello, are you there on the line, Mr. Heuse?

DR. HICE: Yes I am.

DR. HENDERSON: You're going to have to speak up a whole lot louder.

DR. BALMES: Now you know what we've been experiencing.

DR. HICE: Can you hear me now?

DR. NUGENT: Better.

DR. HICE: Can you hear me now?

DR. NUGENT: You're on.

DR. HICE: Okay, then I'll start. My name is John Hice with AIR and as indicated I'm

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providing comments for the Alliance of Automobile Manufacturers.

We will be providing detailed written comments next week to the Agency and CASAC.

We appreciate the Agency's efforts to enhance the review process with the ISA as a replacement for the CD.

We believe the following areas can be improved through the continued attention of staff and CASAC.

First, the ISA primarily focuses on EPI studies, gives only limited attention to control studies that can establish cause and effect. Since NO2 occurs in conjunction with other common air pollutants, issues like confounding of surrogacy plague the interpretation of the EPI literature.

Even in the case of indoor NO2 sources such as gas stoves or unvented appliances, it is now know that other gases and particles that are perpetual confounders are also emitted by these sources.

Furthermore, in a recent detailed study of asthmatics in Fresno, California Tegger, et al found that both central monitoring site NO2 and personal exposures to NO2 were associated in concentrations of several bio aerosols, endotoxin, sporia mold and

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agricultural fungi.

Thus NO2 not only is a marker for combustion, but also for bio aerosol components.

Tegger, et al indicate that their analyses highlight the importance of the consideration of effects of bio aerosols in the assessment of health effects and related anthroprogenic leads.

Second, the ISA must consider dose plausibility when integrating the results of controlled studies with the results of observational studies. Biological plausibility involves consideration of both the kinds of effects the agent can cause as well as the dose required to cause the effect.

Third, the ISA focuses on similar model results rather than evaluating the results in the context of a full suite of air pollutants. This can lead to double counting or triple counting of health effects as different pollutants are reviewed.

The tables in Chapter 6 of the annexes and most of the discussion in Chapter 3 focus on single pollutant NO2 results and the multi-pollutant analyses that include NO2.

Although many of the studies evaluated a suite of pollutants support results for many more outcomes. In most cases the authors implicate air

pollution in general rather than NO2 in particular as being associated with a given health endpoint.

Fourth, to ensure scientific credibility ISA must address the issues of publication bias, model selection and uncertain confounding that hinder the interpretation of air pollution EPI studies.

CASAC has pointed out in the ozone review where systematic analyses have been carried out as n-maps by Steeb, et al and also I'd add Ito 2003, similar patterns of associations are reported for many pollutants. This includes the warm season effect. While there are many more studies than available in the prior review for NO2, there's reported to be a wide range of results from positive and negative in systematic analyses.

The full range of mortality and associations in the individual cities is not 0.5% to 3.6% as over the United States, but it's something like -3, 2.5%.

So those are the many issues related to interpreting such wide ranges of associations, especially the knowledge of time space studies as a blunt tool have limited utility in establishing air quality standards.

Fifth, the ISA must not omit key

information and/or key caveats when summarizing and drawing conclusions. For example, the Mortimer, et al 2002 study that was used in the ozone review, there is evidence of respiratory effects in asthmatic children. And now the ISA chooses evidence for NO2 effects. The authors of the study implicate summertime air pollution, not NO2 itself.

ISA also uses the Schildkraut 2006 study as evidence of respiratory effects of NO2. However that study showed no effect of ozone and that finding was not considered by the Agency's proposed ozone rule.

In addition, Schildkraut, et al conclude their findings may represent particulate matter effects.

ISA also relies on Schwartz, et al '94, but that study discounts any NO2 associations with symptoms compared to other pollutants.

And for air pollution associations with respiratory admissions after emergency department visits, there are similar examples where many authors note the inconsistent results.

And as a result of these five issues the ISA conclusions overstate the evidence for NO2 health effects and the certainty of those effects.

Finally, in order to aid in the judging

of the adequacy of the current standard the ISA should clarify the extent of new information since the previous review in each case.

We identify the ISA as the basis for scientifically sound air quality policy. Therefore we strongly urge continued development of that in accordance with our panelists.

Thank you.

DR. HENDERSON: Are there any questions from the panel for Doctor Hice?

DR. BALMES: This is John Balmes. Yes, I do have a question.

DR. HICE: Yes.

DR. BALMES: You quoted the Tegger, et al Fresno study. I'm a co-investigator of that study and I don't think we've published anything as you've described. There must have been a presentation.

DR. HICE: It's the final report for the ARB contract 99322.

DR. BALMES: Okay. Yes, thank you, I just wanted to clarify.

DR. HICE: On page 5.6.

DR. BALMES: Yeah, no, so it's not that's been, it's not a peer reviewed published paper. It's been peer reviewed only by ARB. Just to clarify,

it's not a regular

DR. HICE: Good, good.

DR. BALMES: publication.

DR. HICE: Yes.

DR. HENDERSON: Okay, thank you. Are there any other questions? If not, we thank you very much for your presentation and that ends our public comment period I believe. Is that right, Angela?

DR. NUGENT: Yes.

DR. HENDERSON: Okay. Next we'll turn to the very important part of our meeting where we begin to discuss the answers to these charge questions.

I want to reemphasize that the purpose of our critique is to improve this ISA. This is a very important process we're going through because this is the very first ISA and we want to work with the Agency to develop an ISA that is the very best possible.

So, we are and I remind the people whose names are underlined, that att eh end of our discussion I would like for you to summarize in writing the findings of the committee.

So, Ted Russell and Ellis Cowling are responsible for leading the discussion. Anybody can comment on this, they're just going to be the lead off people for Charge Question Number 1 which is it's on

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the, the first three questions as Mary said, the first three charge questions are really quality, but it's to what extent are the atmospheric chemistry and air quality characterizations clearly communicated, appropriately characterized, and relevant to the review of the primary NOX NAQS?

DR. RUSSELL: Again this is Ted Russell for those on the phone and elsewhere.

First a couple of comments. Having a greatly trimmed down report was great. I really like the idea that we're getting much faster to what is relevant to the task at hand which is reviewing a standard.

But that being said, I think there are a number of things with this chapter, and also again in the summary, that needs some work, if not quite a bit of work.

Just going through it, the first thing was is that, and I write this in my comments, is I still find the chapter somewhat scattered and I think it could use a little bit more structure. And it goes back to a much more traditional structure showing, specifically having a section on sources because one doesn't I think, get an appropriate view of what the sources are that are most important at this, in this

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day and time. And consider the balance between outdoor and indoor sources as well as sources that are local versus those that are more distant, those that are at ground level, those that are at more elevated sources.

You know, I think that that has to be presented right up front just so people can get an idea of what are the sources of oxides of nitrogen that are most important to them and most important to exposure.

You sort of get hints of this in the chapter as you go along, but I don't think it's really presented in a way up front that puts the rest of the chapter in perspective.

And I think as part of this they do talk later about how much time people spend indoors and outdoors. I think that that has to be up front just so one can get a feel.

I thought it would also be very good if a bit more attention was given to quantifying the fraction of NOX indoors that would be from an outdoor or ambient source. Just again so that the reader when they try to assess what are the important processes that are going to impact their exposure, they have that, a much better feel right up front.

So go from sources and then you can talk about atmospheric processing. And I'd do this, indoor,

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outdoor and indoor atmospheric and indoor together again because they're so closely linked.

I found that the one section later on about indoor exposures and processing sort of just didn't work where it was. But again that's my personal take on it and I think it would have been much stronger if one puts it where you're talking about what's happening in the atmosphere and then what's happening indoor at the same time.

Similar chemistry going on, it tends to repeat things now between the two.

And I then go on to measurement methods with ambient indoor concentrations, et cetera. And after that I leave the exposure sections to someone else.

It's not radically different but I think it would add some structure and really focus on what is going to be important in terms of assessing exposure, and to what sources.

The whole, and again, any more information that could be provided on the fraction of ambient NOX that one gets indoors would be good.

In their discussion, in the discussion of sources I thought it was again a bit short and light on detail. I also thought the annex was somewhat light

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on detail, but not going back over it again, probably not as much as thought the first time.

I really think there should be again a table of source emissions with emission estimates to put it all in perspective.

One thing that is really not present in this chapter is looking a the fraction of NOX that's NO2 or other sources where there is a large push or a concern in Europe that some of the new control devices are moving more of the NOX to NO2, thus potentially increasing exposure to NO2.

Even though you might be bringing NOX down you could actually be increasing NO2 exposure. So just looking at the inventory alone for NOX without some attention to the speciation could be misleading if your concern is primarily NO2 exposure.

I would also put not just a current inventory but looking forward to the future, just because we have a number of NOX controls going in right now. But I think it's important to show what future exposures are going to be, given that the standard is going to have a future effect. And if you're shifting it from one source to another, that has implications on how you might want to go about controlling things.

And I thought the section on chemistry

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was sufficient and about the right length. And I would put more emphasis that NOX comes out primarily and N0 and is then transformed to NO2 by ozone and other oxygen species. This has impact on near source exposures, particularly if you are going to start changing the speciation of N0 coming out from the source, from the source itself.

And then also talk more about how the transport and rate at which re-speciation of NOX takes place, both first from N0 to NO2, then nitric acid PAN and the differences between nighttime and daytime I think would be important when you're looking at exposures.

The section on measurement techniques and measurement uncertainty I though came across as very non-quantitative. But it seemed to infer that the current measurements are woefully inadequate and provide tremendous uncertainty.

And they cite, actually in a different part, the Mexico City results to say that there is significant uncertainty and confounding right now. And it's, it is well known that the NOX monitors, there is significant interference form species like nitric acid and peroxyacetyl nitrate.

But at the same time that there's

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limitations to how much that can be confounding just because of how much PAN and nitric acid you have at any one time and in particular, in many of the monitors it's not going to have a very big affect at all, just because of their location.

So I thought it would be very good if one could be more quantitative, and instead of relying on results from an extraordinarily different city to suggest how uncertain the measurements might be, if one actually took typical measurements from a U.S. city or cities where they have done these sorts of measurements and assessed what the interference is, and discuss them in that rite.

It would be good to have a pure NO2 monitor and that actually gets to something in the, later on in the summary.

The question has to be is, how much would that change what we're doing right now?

So, and also, let's see, also in this section when you're talking about measurements it should ask, it should look at how indoor measurements and personal exposure monitoring is also done. I guess it's again bringing a discussion that is later more up front, just so you get an overall sense of how the various monitoring is done, because again right now you

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sort of, it pops around in the various sections back and forth.

As I said, the ambient measurement section should include indoor measurements as well, just to put that in perspective.

And one of the things I found a little bit confusing throughout this was sometimes it seems as though there is a quick focus on NO2 without looking at the other species and I thought some more balance would be useful there.

One thing that I think would be very good is just to put it in perspective, have a figure with observed actually I say in my notes NO2, but actually NOX and NO2 concentrations of all the monitors throughout the U.S. And something like a probability density function or a cumulative density function, just so you get an idea of where the various cities currently reside in comparison to the NAQS.

And if one is looking to have the potential of a short term standard, that should also be given, not just in terms of the long term standard, but also show the distribution in terms of the short term, potential short term standards.

And the other thing that this section really needs is to show how NOX correlates with related

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species. There's a number of locations where you can get, actually throughout the U.S., how N0 and NO2 correlate with related species such as PM 2.5, primary, or not primary but elemental carbon, sulphate, nitrate, et cetera, that have potential health effects.

And I think it's important to put that up front just so one can get a better appreciation for the confounding that will come later.

Looking at the findings and conclusions and how it relates to the atmospheric chemistry, I was actually taken aback when I read the conclusions, the findings and conclusions chapter, because it doesn't seem to actually pick up what was said in the, at least what I was taking as the main points in the, in Chapter 2. And in particular it seemed to overemphasize the monitoring issues. There was something, most of the bullets that came from Chapter 2, the atmospheric chemistry part, really have to do with monitoring. There were multiple bullets there and it didn't seem to make sense, given what the discussions were.

They were saying that maybe we should monitor N0I, but then they criticized that the current measurement sort of was an N0I measurement. I personally would say that let's at least measure what we think we're trying to measure.

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So it would be better to get an NO2 measurement device as opposed to something that measures a collection of things and then we don't know what the species are. But that's just a personal view in terms of I like to know what I'm looking at.

So I would take and re-look at the conclusions section and see what are the truly important pieces from the prior chapters and not try to come up with, I would say in some ways what appear to be personal sort of issues or whatever that and in this case the monitoring seemed to be a real focus at that point, but I don't think was, when at the end of the day it's going to be as big of an issue when it comes reviewing the standard.

Thank you.

DR. HENDERSON: Thank you very much, Ted. Ellis, would you like to add your comments and then we'll open it up for everybody?

DR. COWLING: Okay. Let me ask that everybody who is on the phone who can't here me, speak up because we can try to do better.

And obviously we are all engaged in a new set of processes with a new set of actors. A new set of authors, a substantially new some changes in the statutory membership and we have an entirely new

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process. And we are engaged in something that we think, we all have hope can be made more efficient and I support Ted's motion that a document, well a more modest document maybe would be a better way to describe it.

A more modest document, clearly focused on issues that are pertinent to the need for reexamination of the standard.

The standard in the case of oxides of nitrogen was established in 1971. It has never been changed in the 36 years since 1971.

The standard has four parts. It requires a definition of a letter or air concentration. It requires a definition of the indicator of choice. It requires a statistical form. And it requires an averaging time.

There's only one place in the ISA where all four of those are discussed and that is in the preface.

Another important point is that the indicator chosen in 1971 was NO2. There is no description in the ISA of why EPA chose NO2 when the standard is the oxides of nitrogen.

Now Mary mentions earlier in her comments this morning, that there is a larger body of

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evidence available for NO2 than for the other oxides of nitrogen and if that was, in 1971, the primary basis for the selection of NO2 as the indicator for this large array of very diverse oxides of nitrogen, we ought to say that someplace in this document.

And it seems to me that we ought to focus on the elements that make up the standard.

Chapter 2 contains no reference to the existing standard. Now Chapter 5 does, and I must say I commend the organization of Chapter 5. And Ted mentioned this as well, the summary that are, there are nine summary statements derived from Chapter 2 but all nine of those relate to the method by which oxides of nitrogen are measured.

It does not deal with the questions of indoor or outdoor exposures and other parts of Chapter 2 are not very well summarized by those nine statements.

Now there are 37 statements in the whole of Chapter 5 and I commend the effort that is being made to summarize the distilled essence, the distilled essence of the new insights that have been developed since the last review that are relevant to the question of whether the present standard is quite adequate or whether the evidence should suggest that some

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alternative standards should be considered.

So this is the first ISA. Everyone speaks of it with great hope for its success and I join with Ted and others on this panel in my hope that it can be made a very much more efficient communication device to provide the foundation for a wise choice.

Now, I said in my individual comments that it must have been very wise on the part of the Administrator and the staff of EPA in 1971 to have created this standard that has never required any change in 36 years of additional scientific and public debate about oxides of nitrogen.

Now I think there are some in the health community that would argue that, well, it should have been changed. Well, we'll see at the end of this day whether there is a consensus view about whether the standard is, as written in 1971 and never changed, a suitable basis for exploration of how to manage the oxides of nitrogen exposure in this country.

It's important to remember that this is a national ambient air quality standard that we're discussing as it applies to the nation as a whole and it would be worthwhile though, and I was disappointed not to find a map that would show geographical variability.

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I think it would be very helpful also to have a graph that would show trends in oxides of nitrogen exposure over time, at least as well as it can be inferred from the available evidence, and that it would be not just for NO2, but for each of the oxides of nitrogen for which there is some substantial evidence of health effects.

I was very pleased to find in this, in the preface, a history of all the revisions that have been considered in not changing the nitrogen, the oxides of nitrogen standard. And there are places in the document where it's called the NO2 standard.

Well yes, it is the, that is the indicator but that's not the whole. It's just like ozone is not ozone, it's ozone and other "chemical oxidants" so it's well worth our while in understanding what it is that we're seeking to measure and what it is that has health effects and what it is that we should consider by way of managerial approaches in order to decrease the health effects.

And finally, I'm an ecologist and I worry more about welfare effects than I do about health effects in my personal life, that is, in my professional life. This chapter deals with oxides of nitrogen and it deals with health effects. We will

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have, and Ted will be leading us in a discussion about the welfare effects.

But I would hope that we could at sometime in the course of this discussion, in spite of the fact that this criteria of pollutant is called oxides of nitrogen, and reduced forms of nitrogen certainly are going to be concerning also.

But we don't have a standard for ammonia, we don't have a standard for reduced forms of nitrogen and I was in fact delighted to see that there is at least one place in the introductory chapter where reduced forms are mentioned.

And I would like to encourage awareness on the part of our panel that there is serious debate about whether a standard for nitrogen that emphasizes only oxides of nitrogen is adequate to protect public welfare.

And I'll be interested to see if there is any discussion today about the health effects of reduced forms of nitrogen, particularly ammonia. And I would also mention that the total ammonia emissions of this country, and of the world as a whole are larger than the total emissions of oxides of nitrogen, either in this country or in the world as a whole.

I look forward to comments and

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discussion about these matters.

Thank you.

DR. HENDERSON: Thank you, Ellis. Now are there other people who have comments on this first charge question, the chemistry question?

I would like to ask if Ila and Mary have any response to the critique or any questions for clarification.

DR. WYZGA: I had my hand up.

DR. HENDERSON: Oh, I'm sorry, didn't see you, Ron, go ahead.

DR. WYZGA: Let me say that I'm not an atmospheric chemist and I sort of approached this chapter in a little bit of a naive sense and tried to learn as much as I could.

And I have to say that I agree wholeheartedly with what Ted and Ellis said.

I guess I had a couple of concerns and one is, there is a lot of discussion about the measurement method. And I'm not sure who makes the decisions about what is the appropriate measurement method.

And I guess one question I have for the staff, is any discussion or recommendation from this committee useful in terms of suggesting what an

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appropriate measurement method should be for whatever we're going to measure?

And I think Ellis' comment about what the correct index is, is of some concern.

And when I read the health information, particularly the toxicology, I noticed that there seems to be some evidence for some independent health effects of N0 as opposed to NO2.

And for that reason I would to see to the extent that it's possible, more discussion in Chapter 2 of the split between N0 and NO2. What is it? What is the reaction rate that determines it? If things like ozone influence it as you said, is it different in the summer and in the winter?

And to the extent that we have such measurements in the future we could consider them in epidemiology studies for example to see whether or not something may indeed be going on with N0.

The other thing that I think would be useful is that a lot of the discussion in terms of looking at correlations and measurements and changes over time, are really dependent on where monitors are placed.

And it would useful to have some discussion of the criteria for monitor placement.

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I think, and we're probably getting into the next question a little bit, I felt that, I got a feeling that many of the characterizations of the spatial homogeneity of NO2 is pretty complicated because you basically have some relatively large background levels in an urban area, but also you have point sources.

You know, clearly, you know, people talk about this A-frame effect near roadways. And so you have, so depending on where your monitoring station is located, it can reflect very different things.

And I think it's important to sort of get some understanding of what these monitoring data really represent so that they can be analyzed appropriately.

And I would also ask when we're, you know, looking at some of these near term sources, how important is N0 as opposed to NO2. So I would urge to the extent and let me say that I'm not an atmospheric scientists and maybe we just don't know enough to answer these questions but at least I'd like to see them raised. And that's something that hopefully if they're not, haven't been addressed to date, that the research community would consider them in the future.

DR. HENDERSON: Thank you, Ron. Yes, go

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ahead, Christian.

DR. SEIGNEUR: Okay, yes, I'll just make two comments. The first one is further to a point that Ted made earlier which is that the ratio of NO2 to NOX in the emissions is much more at issue than the restructures.

At some point it says that NO2 is 5% to 10% of NOX which definitely is not true. Some PowerPoints may show 5% of NO2 as to NOX. And as Ted mentioned, in Europe a major concern today is that NO2 from diesel trucks is going to be much more than 10%, it could be 40%, 70%.

And I think this ISA should reflect the fact that this NO2/NOX ratio is unknown and is likely to change in the future. I think that's going to be particularly important when you look at exposure of people living near roadways.

The second point is a figure which I find is very useful in the document and Mary showed that figure earlier which is that summary of the NOX chemistry, NOX/N0I chemistry.

I think there is a need to actually clean up the figure a little bit, some parts are a bit too complicated with points which are not very important. And also the treatment of PM nitrate should

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be revised in that figure. You have an arrow going from ammonium to nitrate. What you should have is an arrow taking ammonium and nitrate together to go to a nitrate.

You also may want to add coarse nitrate formation.

And one thing which is mentioned in the text but is not reflected in the figure is the formation of organic PM nitrate.

Just a point, but since the figure is really a centerpiece of that chapter I think we need to clean that a little bit.

DR. HENDERSON: Thank you, Christian. Was that clear, Mary, do you get what he's

DR. ROSS: Yes.

DR. HENDERSON: his correction, he's got those in his written comments as I recall.

DR. ROSS: Yes, that's helpful. And I think that the advice we've received has been very helpful, but the team that worked on this, Joe and Mung and Tom I don't know we have any questions that we'd like to address to the panel right now, I find the comments generally quite helpful.

Joe, would you like to

DR. PINTO: We were looking for from this

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panel, what should be the appropriate monitoring effect. And what are the implications for, you know, epidemiologic studies.

SPEAKER: Okay, a few points. As I say, I don't know where to start.

You know, it's ironic in that, you know, with the current monitoring technique, you know, the one species which we can measure very well is N0, nitric oxide. Unfortunately none of the states report N0.

So it's not like we can do any we would have loved to have done analyses with N0, NOX and NO2 we just can't, okay? Because that data isn't reported.

A few minor points. Let's see, yeah, it would be useful to include something, you know, about monitor location or criteria, thanks Ron.

Yes, spatial homogeneity I mean is very complicated for NO2, especially since there's a lot of chemistry going on. And unfortunately there's not much known about, you know, the neighborhood point sources, you know, the pizza parlors, you know, you know, et cetera. Wish we had that data.

Let's see, and Ted, okay, a few points just for clarification.

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With regard for associations between NO2 and other species we have six tables in the back, those are Tables 2.5 to 2.

DR. RUSSELL: I was looking for something a little more

SPEAKER: Yeah, that you'll find in the annex. I mean, you know, you know, you know, we haven't, we have, you know, rather serious space constraints on us, so you'll find that in annex 3, okay? And there are long discussions in there, you know, about associations.

We have summary tables for it up front, okay? So there's six or seven summary tables.

Also with regard to this question about the for the fraction of a person's total exposure which is due to exposure to ambient, that's covered briefly on page 2-29. But again I mean, you know, there are rather lengthy sections in annex 3 that deal with, you know, the calculation of, you know, you know, of that quantity.

Okay, what else did I want to talk yeah, the issue about the buses. Yeah, no, no, no, this is something which is very, could potentially be very important. It's shown to be very important in London, okay, where you take buses, you know, that are

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fueled by ordinary diesel engines and then you fit this catalytic trap on them, you know, to remove PM, okay? You know, to oxidize PM, basically you're doing that by oxidizing the N0 and NO2 and you have the NO2 oxidized to PM, okay?

Unfortunately what happens there is that you wind up making an awful lot of NO2, especially at the ratios I think of what, 30% to 60% of NOX comes out as NO2, you know, in that case. Okay, this is something, I mean I think there's only one study I know about in the U.S. It was a study done in New York City, it was a paper by Shorter, dealing with that issue.

And yes, and then found similar results. However, there are programs, you know, by EPA, involved the EPA, CARB and other groups, okay, which are, you know, addressing this issue and, you know, thinking of ways, you know, to work around, you know that problem.

Nothing has come out yet, it's very transient and that's why I haven't included it, okay? That's simply that and waiting for, you know, the program officers to come out with, you know, their reports.

Ted, coming back to your question on let's see, you also mentioned the buses, yeah, Mexico

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City and the artifacts and the measurements, okay, and the NOX boxes for instance, okay?

Yeah, what, I mean how would I put it to you? I mean it's not like those measurements in Mexico City, I mean were measurements of, you know, some of the things which you don't know, you know, what it's composed of, okay. And you're comparing that to the, you know, to the NOX box, no.

What you have there are measurements of individual interference, okay? And in conjunction with laboratory studies, okay, which look at, you know, the efficiency of conversion, you know, of those species. You know, you make an estimate.

So what I had done was actually a few issues here in which I'm involved, okay. So what I had done was we looked at, you know, the levels of the potential interference, that's the PAN, that's the nitric acid in, you know, in Mexico City and indeed, at the time of the measurements, you know, they were fairly typical of what you see in the U.S., okay. However I didn't stop, you don't want to stop there, okay?

I mean it's not like, you know, you're looking at hydrocarbons in Mexico, Mexico City for instance. Yeah, there I mean, you know, you have this

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very, very poorly characterized mix. I mean here you're just looking at a few species.

Okay, also what I've done is I've taken CMAC results, okay, for the Middle Atlantic, okay? And I looked at the ratios, okay, of the NO2 to the more oxidized products and then compared those, okay? You know, I mean to those measurements.

And, yeah, I mean what you find is that, yeah, you know, the ratios are highly variable. NO2 for, you know, so for instance in downtown Baltimore, yeah, I mean we think that maybe you're under overestimating, you know, true NO2 by 20%.

However, I guess as you're well aware, that if you go out, you know, to a relatively unpolluted area, okay, where all the NOX has been oxidized, okay, that here you have the potential from which the larger artifacts are being formed. And those I calculated.

Also, I have a paper in preparation

DR. HENDERSON: I wonder if you could wind this up because I think we

SPEAKER: Okay, several, several

DR. HENDERSON: I mean one possibility is that you consult with Ted during the break which we're going to have to have very quickly here. Is that okay

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with you, Ted.
DR. RUSSELL: Yes.
DR. HENDERSON: Because I think you all could talk. I hear very loudly that the Agency would like advice on how to do the monitoring. Is that something that we are able to give advice on?
DR. LARSON: Rogene, this is Tim Larson. Just one brief point and I think the question is
DR. NUGENT: Excuse me, this is Angela Nugent, the DFO, who is speaking please?
DR. LARSON: This is Tim Larson, can you hear me?
DR. NUGENT: Tim, could you speak more directly into your phone, we're having trouble.
DR. LARSON: All right, can you hear me? Hello?
DR. NUGENT: Barely.
DR. LARSON: Well, I'm almost yelling.
DR. NUGENT: Okay.
DR. LARSON: I just had a question. To what extent is the Agency already measuring N0I at the monitoring sites, versus NOX?
It seems to be an unstated issue that, you know, the recommendation is you should do this, but I think there are sites where this is already going on.

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DR. HENDERSON: Yes, go ahead and tell us and then we'll take a break.
DR. HOYER: My name is Marion Hoyer from the U.S. EPA's Office of Transportation and Air Quality.
And I want to just clarify something so we aren't left with misperceptions about what's happening in the diesel world. Retrofitted diesel engines do emit more NO2 because of these heavily catalyzed traps. However, the Agency has finalized rules that go into effect in 2010 for new engines that will control those NO2 emission.
So when we're talking about this as an issue in the U.S. it's going to be more an issue related to the retrofitted trucks.
DR. HENDERSON: Thank you very much. The next two charge questions are in the same area.
DR. ROSS: Doctor Larson asked a question about whether N0I is measured at some monitors and I believe there are some monitors that can measure N0I but correct Jeff?
DR. ARNOLD: That's correct. Measurements between measured NO2 as in the Federal Reference Method and total N0I are not systematically done anywhere in the network.

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DR. COWLING: Could we get a map, excuse me, a map of where these monitors are that are in existence now and where those that also measure N0I are located?
DR. ARNOLD: Yes, we can provide that.
SPEAKER: You'll find a map of the measurements of NO2, Ellis, in annex 3.
DR. COWLING: In annex 3.
SPEAKER: And annex 2.3, okay.
DR. ARNOLD: These are not the standard monitors.
DR. THURSTON: This is George Thurston and can I ask a quick question related to this, which is having dealt with, you know, the NOX machines they give you N0 and NO2, the data are there, they're just not reported.
Is that something that could be, you know, a recommendation that could come out of this? That they would report N0, and would that be, you know, I don't know, would the committee think that's a good idea if we could do it?
DR. HENDERSON: Everyone's saying no. I think you get, what, N0 and NOX and then you get the NO2 by subtraction?
DR. ARNOLD: That's correct, but

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DR. THURSTON: All right, either way.
DR. ARNOLD: But he's correct that the N0 number is available, it's not reported to AQS so we would welcome recommendations that would help us understand what that measurement could help us with.
DR. HENDERSON: I think we should give some thought to monitoring during the break and I would ask that you only take fifteen minutes if possible.
So be back by 10:30 if you can.
(WHEREUPON, there was a recess).
DR. HENDERSON: If everybody could take their seat, we'll get started.
I tell you, we are into some very important discussions and I'll tell you my game plan.
The next two charge questions are very similar, I mean they're in the same area as Charge Question 1. And I would like to finish those charge questions, 1, 2 and 3 before lunch.
I'm wondering if it wouldn't be good to comment on the other two questions and then have a general discussion of all three charge questions, or at least finish up.
But I want to know if that would, if anybody sees any problems with that. I know we need to finish the discussion on monitoring, but it seems to me

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it would be wise to have the lead discussants on Charge Questions 2 and 3 give their summaries.

And then we can discuss the whole atmospheric chemistry, all three questions. Anybody object to that?

Okay, then I would like to start off with Christian if you would on Charge Question 2.

DR. SEIGNEUR: Okay, I will do that. I will make only three major comments, I won't go into any details.

And the first comment I have relates to discussions which started earlier on the measurement method, N0I versus the M0X, NO2 measurement method.

One related to exposure, my view is that if all the health effects, the epidemiological studies have been derived from measurements using the method which measures NO2 by the difference between NOX and N0, I think it will be dangerous at this point to switch measurement techniques if we come up with national air quality standards, they are from a given technique. And then use another measurement technique which will give different results possibly, because then there will not be consistency between the standard and measurement that we'd use to define it. And I think that consistency will potentially be very

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important.

Also, in the ISA I was a little bit confused in the measurement section, which is Section 2.3 because by reading it I didn't see a conclusion at the end, I just saw a lot of information being presented on different measurement techniques. And at the end I was wondering why are we talking about N0I measurement techniques when all the discussion in the health effects section is on NO2. I don't see how you could define an NO2 standard if you're measuring N0I and that's more coarse too, which is not the case.

Anyway, so that was the major comment I have on Section 2.3 I think.

The other comment I want to make is on the spatial variability of NOX and NO2 concentrations. I didn't see a lot of discussion in the ISA about the strong gradients that you can see near roadways which obviously are going to be a major issue when dealing with exposure, population exposure, either people on the roadways or people living or going to school next to a roadway, because those people will be exposed to much higher concentrations of NO2 than the rest of the population.

There is some discussion of spatial gradients but they are at much large spatial scales.

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So I would recommend to have a much more in depth discussion of that issue of near roadway exposure.

And the last comment I have is actually in an annex of the report which is on the CD, annex 2.7.1 of chemical transport models. And this annex addressed CMAC, which is a fine model. The challenge there though is that NO2 being mostly an issue near sources, CMAC because of its spatial resolution which is several kilometers, is not going to be the major tool that EPA will be using I assume to look at population exposure.

Actually in the report that we'll discuss tomorrow, the methods document, EPA talks about another model or mode, which is to address near source exposure.

So I would recommend that in the ISA the models which will be used by EPA to calculate population exposure be presented and discussed in terms of their present counts.

That's all I have.

DR. HENDERSON: Thank you. Donna, do you have your comments ready?

DR. KENSKI: Yes, and this is sort of adding on to what Christian had to say.

To address the charge question I guess

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is, are properties of oxides of nitrogen, you know, adequately addressed? Including the background concentrations and spatial and temporal distributions.

I found that that was not adequate actually to satisfy me. And a lot of the detail I would like to see was in the annex, but I think it should be pulled into this chapter. In particular, you know, at the very least we needed a map of spatial concentrations across the country.

And also, you know, along those lines of spatial distributions it's also important to look at, you know, to have some visual representation of the spatial gradients within a city. And as Christian said, you know, those very small scale gradients from roadways are going to be very important in determining exposure.

So I think it's imperative to have, you know, a great deal more information on that in this section and not relegate that information, much of which does exist in the annex, not, you know, to pull that into this section.

And not only do we need the spatial concentration patterns but I think it's also important to have a map of the monitors because I think people making exposure assessments need to, and the health

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people, need to understand the very sparse nature of our existing NOX network in the United States.

It's really a bare minimum, and to think that it perhaps is adequately capturing the highest exposures that people could be exposed to I think is really a stretch. You know, when you talk about most of our major urban areas have, you know, three, four, five monitors, I don't think that that's probably adequate to, you know, if we're talking about short term exposures to peak concentrations which are going to occur on a very small scale.

So I think it's important to have that map of monitors available.

I thought the policy relevant background concentration was fine. I thought they adequately established that those concentrations are very small.

And okay, also we talked about spatial patterns but I think temporal, this section could include a great deal more information about temporal variation as well. It just sort of touched on it but here again, you know, and there were temporal, information on temporal distributions in other sections of the report. But that's another aspect of, you know, sort of general NOX behavior that needs to be here.

Again, you know, to help in assessing

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when, you know, when are those high concentrations occurring.

And along with that I guess I'd like to see not just that spatial and temporal distribution of NOX but and the affect of monitor siting, that's, you know, goes along with having so few monitors and, and with these sort of intense spatial gradients that the effect of monitor siting is going to be critical.

So there should be some summary of how the monitors are currently sited. And that varies quite a bit from city to city.

This whole idea of NOX versus N0I versus, you know, N0Z and when do we, and N0 and what do we need to really measure, I guess I'd like to see that, those various species better characterized in terms of their, and to the extent possible, in terms of their temporal distribution.

So when, you know, when NOX goes up, when NOX is peaking, what does that mean in terms of N0 and what does that mean in terms of PAN and nitric acid?

So are those, because, I think that might be useful information and sort of leads into another issue that I think needs to be addressed more comprehensively in the document as a whole, which is

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the, you know, confounding by various species, not just the, you know, the components of N0I but PM 2.5 and ultra fines and all the other associated species.

You know, it's touched on in many, many different places but it's never addressed really comprehensively. So I guess I'd like to see a section and it seemed most appropriate in this particular chapter but I think that could be, I don't know, you know, put in here and tackled up front before we get to the health studies.

And finally I guess I think there was some data about given that traffic exposures are, seem to be very, you know, very important, I think that, those exposures should be addressed in this section as well, rather than it's really not until you get to the section on susceptible populations that that's talked about comprehensively in the document. It's probably more appropriate for this, you know, in talking about sources, that those, you know, vehicles exposure could be addressed here.

DR. HENDERSON: Thank you, Donna. Could the people on the phone hear Donna?

SPEAKER: Yes.

SPEAKER: Yes.

DR. HENDERSON: Good. Okay, because the

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Charge Question 3 is related to Chapter 2 and that it asks, does the information in Chapter 2 provide a sufficient atmospheric science and exposure basis for the evaluation of human health effects presented in the later chapters?

Since it's related I'm going to ask Tim Larson on the phone to go ahead with his comments.

DR. LARSON: Yes, can you hear me?

DR. HENDERSON: Yeah, speak up, just shout as much as you can.

DR. LARSON: Okay, I'll try. Yeah, this is a fairly broad question that I'm sure everybody will have a lot to say about.

I think it, you know, it's broken down into the topics we've already discussed for the most part. And the document, you know, has its strengths and weaknesses, but it covers certainly the issues of what is it we're actually measuring with our monitors, what are the correlations between personal exposure and ambient exposure to and what are the things that determine the strength of those correlations?

What are the other measured pollutants that, and how do they, you know, that come along with NO2 at the various monitoring sites for use in multi-pollutant models subsequently?

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And I think Ted pointed out a good point about sources which are really kind of lacking, which I think would help in a number of ways to address this issue as well.

I come down to a couple of points and I agree on my comments, I also mentioned the fact that the siting criteria for NO2 monitors needs to be discussed a little bit.

It would be nice to see, because the information is there, you know, how far from major roads for instance are these monitors and how does that compare with where people live? It might be an interesting perspective.

I think that the siting of those monitors was basically predicated on an annual average standard with the hope that even though they were away from roads they were capturing a spatial field because they had a long term average.

But in fact as well all know, you know, roads don't move around in time and so people who live nearer to those sources are going to get systematically higher exposures. And I think that's discussed, especially in the approaches to the health assessment later on.

One issue which isn't really discussed

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as much, and other people mentioned this, is this sort of surrogacy issue having to do with NO2 being a surrogate or NOX being a surrogate for other traffic related pollutants or combustion related pollutants more generally.

And I think George pointed this out in his comments, written comments, that especially some of the components of PM which people have just been looking at, that EPA had been looking at quite a lot, have a similar kinds of health endpoint outcomes and associations.

So I think that and there's various sentences in this document in the first couple of chapters mentioning that, but there's not a lot of elaboration on the point.

I mean one could argue a theoretical case that NO2 is merely a surrogate for certain ultra fine particles. And that may not be true but, you know, there's, I mean I there's a plausibility to that argument and I think it deserves some attention because I think there is information that might be, be able to brought into this discussion that could shed light on whether that's true or not.

So my two major, I think, two points I think are sort of the way the discussion needs

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elaboration, you know, we can argue about the conclusions of it, but at least we should discuss it as relevant to this question, would be sort of this spatial distribution issue and the surrogacy issue.

One of the spatial distribution points which I'll repeat again when we do the health assessment, is that proximity to a road is only really one dimension of the spatial distribution problem.

And another one, which there's been a lot more work done in Europe because of the configuration geometries of the cities, has to do with the confined roadways and streets. And you get a spatially stationary feel determined by the buildings, basically this sort of classic street, so called street canyon effects.

And those correlations over space, we've been doing some studies in New York City and other places, have little to do actually with proximity, the classic sort of proximity to a roadway, that has to do with the sort of classic gradients that are in the literature.

Those fields are stationary in the sense that the buildings don't move as well as the roads.

And so it's not clear to me anyway at this point, that the even in a long term average the

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currently sited monitors reflect that longer term or chronic exposure distribution within the cities.

And it's mentioned also I think briefly in the chapter about the vertical distributions. A lot of attention was paid to sort of the height of the inlet monitors. But really, more importantly with people living in dense areas, you know, what's the vertical distribution relative to where you live and what floor you live on or where the inlet to the building is?

These are very complicated issues and I'm not saying that we have all the answers but I think it deserves some discussion and we really don't have any of that.

One possible way to do this is, a number of European cities have basically as you know, their NO2 monitors are really sited next to the roads or in the canyons they do have sort of urban background sites that are additionally required. And that might be an interesting comparison to see, because those urban background sites are much more similar in spirit to our, you know, NOX, NO2 monitoring sites in this country.

Finally the issue of surrogacy, I think boy, that's a tough one. I think it's generally

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concluded and fairly concluded later on, although not a lot of discussion of it in the earlier chapters, that there can be surrogate confounding in the, for traffic related pollutants for the NO2 interpretations.

But you know, one thing that, there's a, reading the thread of the later chapters there's some emphasis on some of the indoor intervention studies, the Palato studies in which basically the unvented gas heaters were removed from homes and the difference in the, the improvement in health was noted.

And that's sort of a qualitatively different and more powerful study design and a natural experiment.

And so there's an opportunity there it seems which it must, you know, I don't know the role of in the first chapter or two, but there's an opportunity to explore whether or not the same surrogacy issues confound that type of study as are potentially confounding the outdoor measurements.

Because it's an important study in the sense that it, the argument is that the NO2 levels were high and they went down independent of these other pollutants and it's the real life exposure to NO2, albeit in a longer term, that we can't get in the clinical environment. And it, you know, points the

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finger at NO2.

And it may be right, I'd just like to be able to see a bit better support for that.

There are the Canadian studies I mentioned in my comments by Vick, et al recently in 2007, the Canadian survey, it's admittedly limited to eastern Canada where they were looking at ultra fine source indoors. And I think in a different set of sources than the classic NO2 combustion sources indoors.

So there may be some basis for arguing that, you know, inside homes there are independent sources of these potential confounders.

And again I think it goes back to Ted's initial comment about talking a little bit about sources. I think it would help the framework of this discussion because when you come down to it, those indoor sources are really one of the strengths of the argument for saying that NO2 actually is doing this.

And I think that's so my comments in general are, we can all argue about the finer points of these various issues, the ambient versus personal correlations, the correlations with other pollutants, the measurements, artifacts of the instruments, the spatial variability and the indoor relatives, the

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importance of various source, other combustion sources.

But I think at least those two, the spatial variability issue and the surrogacy issue deserve a little more expansion, either in these chapters or refer to the annexes and give it more space there. I realize people are pressed for space and I appreciate that. I think this is a, you know, I'm an old guy and I used to read these giant tomes of the criteria documents and when I was doing it in the past my kids were at such an age that I used them to put on their highchairs so they could sit at the table.

And so at least we've gotten to the point where that's no longer useful.

Anyway, those are my comments.

DR. HENDERSON: Thank you very much, Tim. You're not the only one who's used it for the highchair or for the doorstop or whatever. But it's also gotten some students through graduate school, I've heard that they've based their thesis on it.

DR. LARSON: That's true.

DR. HENDERSON: Well let's finally hear from Jim Ultman, the final one that's on this list. But of course we'll have many more speak. Jim.

DR. ULTMAN: Is the volume okay?

DR. HENDERSON: Can you get a little

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closer to your mike, or to your phone?

DR. ULTMAN: I can try. Let me switch on the handset. Is that a little better?

DR. HENDERSON: Yeah, that's good.

DR. ULTMAN: Okay, good, good. Okay. Some other people have already stolen my thunder, but I'll press on.

The first point I have is kind of general and I think it impacts on the Charge Question 3 as well as just the document in general.

And that is that I think that there's a lack of context in this document as to the, how the information is presented relates to the current standard. You know, it's not, it's not entirely clear, you know, whether a study is showing effects because it's, you know, under the current standard or because it's over the current standard.

So it's not clear if we were to change the current standard for example, whether it would have changed those studies or not. Maybe not because maybe those areas were out of compliance.

So I think that the, I think that the document needs to put more context and I think Ellis stated that very eloquently previously.

More context with respect to the

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exposure condition relative to the current standard.
Okay, now more specifically in Chapter 2 there are a set of equations that are given which quantify personal exposure. And even though my background is in engineering, I don't get anything out of the equation. They're algebraic equations, they're very complex. They are referred to later on in the chapter. I think these are equations 2.1 to 2.5.
So they're referred to once or twice later in the chapter, but even when they're referred to there's only a couple of parameters that are referred to and then you have to kind of dig out their meaning on your own from the equations. And it gets to be I think counterproductive.
So I think that the information is, it's bad, it's really critical in that chapter that the information people understand let's say how in a physical sense, you know, the various micro environments and people's activities and movements between micro environments, how that affects their personal exposures.
And it's also critical to understand how the various micro environments themselves interplay with each other to affect the ambient conditions in the different environments. You know, things like

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infiltration of outdoor air into indoor environments for example.
So there's a lot of physical associations here which are really not clearly explained. And so you have to get it by implication in the chapter, and I find it very hard to dig out.
Some of this can be, I think can be solved by organization. But I think that the most important and the most useful thing I would say that could be done, was to have one or two figures instead of equations, which you know, basically block diagrams which introduce the factors which influence personal exposure and show how they interplay with each other as people move around and as they involve different kinds of activity and how the various micro environments themselves interplay with each other.
So I think that would be a big help in terms of understand the chapter and it might also help in terms of formulating a conclusion in the document.
I found it very interesting on page 221, that there were some calculations made in the annex, the annexes, to see what the effect of expired NO from people would be on the surrounding environment.
In other words, endogenous NO, NO is produced endogenously and it has a physiological role.

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It's a mediator, it's a very important mediator, a signal transducer which affects things like smooth muscle tension in the circulatory system.
In fact I think most of, some of you or maybe most of you realize that in order to treat certain lung diseases, NO, at least experimentally has been administered thinking that it will, exogenous NO will make up for deficiencies in the body and will cause pulmonary artery relaxation and improve circulation. So it's even used as a therapeutic tool.
So I thought it was interesting that the authors of the document actually did an analysis of how much the environmental level of NO would be increased if there were a group of people in a closed space, in a room where the ventilation, you know, was at some, in different conditions. And what they found was that, you know, if there was a low enough ventilation and if you pack in the elevator enough, that you could actually build up NO concentrations in the atmosphere.
So I thought that was very interesting.
But I think it was even more relevant as the reverse question. And that is, if there is NO present in the environment, what affect will it have on physiological functions?
And this plays out into the

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cardiovascular effect I think of NOI. You know, they will have a cardiovascular effect if there's sufficient NO present. That we know from some of these therapeutic studies, particularly on, I should say not particularly, but probably only on people that have some preexisting disease, circulatory disease.
At any rate, the biology of these processes I don't think are explained in the appendix. They're certainly not explained in the document itself.
So I think there needs to be some explanation of the biology of NO. And possibly some exploration of the studies that are quoted to see if there's any conditions where the NO might rise to a level which would create some physiological changes. And that would help I think with some of the plausibility arguments later on in the document.
Okay, so that's that point.
Okay, the dosimetry section which is really my background, I don't really have a lot to say about it. Although I found it peculiar that the title of this chapter let's see if I can dig out the exact it was called, Source to Tissue Dose, was the title.
So if you count words, dose occupies 25% of the title and yet if you look at the amount that's allocated to dose, there's only two pages in the

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document.
So I think I either have to advocate for, you know, for fairness and we ought to expand the section on dose, or we ought to recognize the fact that there really been much new work in the dosimetry area since the last review and we should change the title to something else.
But I think it's inappropriate to have the word dose in the title and have so little really devoted to dose.
So I would recommend changing the title.
DR. HENDERSON: Jim, do you have a specific alternative?
DR. ULTMAN: Well it could be, I guess it could be, Human Exposure or something like, Human Exposure to, you know, to Nitric Oxide, something like that.
I mean it's basically, I think it's basically an exposure chapter.
DR. HENDERSON: Okay, I was thinking maybe, Atmospheric Chemistry.
DR. ULTMAN: Oh, the other's Atmospheric Chemistry.
DR. HENDERSON: In Human Exposure.
DR. RUSSELL: If I might, that's a page

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and a half more than it has on sources. And actually I like the title that this is Ted Russell by the way
DR. ULTMAN: Yeah.
DR. RUSSELL: if it goes, it was for the beginning and the end and so it captures everything that's not mentioned is in the middle.
DR. HENDERSON: Yeah.
DR. ULTMAN: Okay, well I just, I bring it up because it just seems, it seems a little bit strange.
DR. HENDERSON: I thought it was pretty catchy myself but
DR. ULTMAN: Yeah.
DR. HENDERSON: I don't know if I like it as well as Jim.
DR. ULTMAN: You're going to have deflated expectations when people read the title and then go on to read the chapter.
But anyway, but I, something else though may be more substantial that maybe could be added to that section. Because it only, because so little has been done since the last review, I mean what's in the section now is basically some of the biochemistry that's been done recently and a little bit about uptake, you know, kind of global uptake.

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But there's nothing really in the chapter about the distribution of dose and there's nothing about animal to human extrapolation.
And these, it's understandable because nothing much new has been done.
Nevertheless, when you look at the rest of the document there's really nothing about, it doesn't, nothing else in the document ties into does, I mean there's this one little section.
And I think part of the reason for this was the mentality that, or the philosophy, I mean mentality has a bad connotation with the philosophy that animal experiments speak only to the toxicology of the substance or the plausibility of particular mechanisms. But they don't really help you in arriving at a standard.
I think that's why it was omitted, because it really doesn't seem to have any practical purpose.
And I think if you start thinking in terms of animal to human extrapolation it might change the philosophy a little bit. So that if there was some of that material, the older material, that was put into the dosimetry chapter, there were some things that Fred Miller had done in the past looking at extrapolation

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between laboratory animals and humans, both, well primarily from a modeling, from a modeling point of view.
And that kind of material then starts stimulating your imagine in terms of, well, maybe some of these studies, even the newer ones that looked at the effect of exposure on hyperreactivity of the airwave or the effect of exposure on the immune system, et cetera, maybe some of those studies could be extrapolated, the exposure conditions that were used in the animals could be extrapolated to humans. And, you know, it might turn out that those conditions are closer to realistic human exposures than we think.
Now I don't know that that's the case and, you know, it's pretty likely that it might not be the case, but
DR. BALMES: Jim
DR. ULTMAN: by putting that material in it really helps as I said, look in that direction.
DR. BALMES: Jim?
DR. ULTMAN: Yeah.
DR. BALMES: This is John Balmes. Sorry to interrupt but I wanted to make a comment directly pertinent to that last point.
In several places in Chapter 3 it would

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be very helpful to have that kind of context about how the animal doses compared to human doses. You know, we had that for ozone with the ozone CD.

And even if we don't feel we have good enough data to be able to extrapolate, just to put it into context, some of the toxicology sections would read better because it's really hard to figure out, you know, what a five part per million dose is to a rat, you know, versus a human.

So I think that's an important point. I just wanted to echo it.

DR. ULTMAN: Okay, thank you. Well that was about it. I think otherwise I think that, you know, other people have already mentioned some very useful things. And I think that basically the material, a lot of the material except for this source material I think and some of the things we've been saying about the dosimetry, a lot of the materials there, it could do possibly with some reorganization, as I said, putting things in context a little bit with the current standard.

But I think the material needs to be there.

DR. HENDERSON: Okay, thank you, Jim. We'll all be up for more discussion of all three of the

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first charge questions.

I would just like to note, in my reading of Chapter 2, that there's a great health effects section at the very end of it on this Australian study that looks at the indoor air where

DR. ULTMAN: Yeah.

DR. HENDERSON: it's mainly NO2 that they were looking at. And I thought it was a great description of health effects, but I wasn't quite sure why it was

DR. ULTMAN: Yeah.

DR. HENDERSON: in Chapter 2 and not Chapter 3.

DR. ULTMAN: Yeah, I had the same comment, Rogene.

DR. HENDERSON: Okay.

DR. ULTMAN: It seemed out of place. My feeling was that there was a little of a, there was a little bit both there because the kinds of exposure they were getting were a little bit out of the ordinary and very useful, because they were getting, the idea is they were getting these exposures, you know, they were getting the indoor exposures that were, for short periods, relatively short periods of time overlaid on their other expose you know, on kind of a background.

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So it was kind of an interesting exposure scenario. And I think, you know, for that point of view it was, it's useful to be in Chapter 2, but because mostly it's about the health effects, it also seems like it should be in Chapter 3.

So I was kind of torn. I mean I have a comment that said it might be moved. But I don't know if it's possible to somehow split it up to minimize redundancy but capture some of the exposure scenario in Chapter 2.

DR. HENDERSON: Okay, now James Crapo has a comment.

DR. CRAPO: One of the issues that I think is going to come up as we go more into health effects is the issue of what kind of a standard we ought to have.

I remember when we talked about it earlier some time ago, we had a very detailed discussion of the short term or the 24 hour standard, a long term standard at peak levels and how they interface with it.

And that's really not been very effectively addressed in the NO2 document or the literature. All of this is starting to build a fairly good body of literature that suggests that the short

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term effects are strong and that there are likely peak effects as well.

And while we're on the exposure chapter we're going to talk about that because I think ultimately we're going to talk about whether the standard or the recommended change in the standard, what type of a standard it ought to be, what the form ought to be.

And as we have this discussion of form here and the data that would underlie that, which I think is going to become a profound question at the end of the day.

So I think from the point of view of exposure we ought to see the data expressed in a form that tells me more about the excursions and the shortened effect, the difference between cities in terms of the for example if you have an average annual level which we talked about at the beginning which is about fifteen parts per billion, if you lowered the national standard to that level, how many cities would be out of conformance with it and what would be the peaks and would that have an effect on all the adverse health effects we're starting to see?

I'm sitting her wondering if the exposure data is going to really support us looking at

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the form of the standards.
DR. HENDERSON: And that's the kind of information we need for this to tell us, to support the standard setting process.
I'd like to did the Air Office want to say something?
DR. ROSS: One of the things we really aren't directly in the ISA trying to choose a standard or a form. The form is actually less influenced by science. It's sort of a hybrid of science and policy.
What we're trying to is develop the evidence that can inform, like what are the effects of exposure to short term exposures and what are these exposure, 24 hour, a one hour peak, what information is available that we can summarize for the Program Office.
I'm not sure, I think we're getting some helpful feedback from people in the audience. I think some of the recommendations, some of reasons we didn't some of the things that are discussed is it was just lack of data.
So we would welcome any input from CASAC about data that are available to further expand on these issues like extrapolation from animals to humans for example.
Just a follow up statement is that much

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of the exposure analysis that we're talking about, you probably will see that it'll be in the risk and exposure assessment that comes from the Air Office.
DR. HENDERSON: Okay. Go ahead, Terry.
DR. GORDON: Yeah, even though I'm a non-chemist I wanted to emphasize a couple of points that were stated earlier.
Given that NO is so biologically potent and given the fact that all the health effects appear to be on NO2 and that's what's discussed, I'm just wondering if it's the cart or the horse, and that maybe we should really and seriously encourage the EPA to include NO and other temporal species in the routine monitoring.
Otherwise we're going to drive it and continue to drive it to NO2 which may or not be appropriate, but we don't know until we have more data NO in particular.
DR. HENDERSON: Okay, Ed.
DR. POSTLETHWAIT: I'm a little concerned about the use of the word potent.
In most clinical situations therapeutically delivered NO is administered in the range of 5 to 10 parts per million and it's given to premature infants on respirators with high

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concentrations of oxygen for literally weeks and weeks and weeks at a time.
Now, the pediatric community considers that to be "safe". One can make arguments about that but you're still talking 5 parts per million.
What are the environmental NO exposures relative to what it requires on a therapeutic basis to induce peripheral vasodilation?

So I think some context along those lines if you're going to go down that road I think that that context needs to be included in terms of this dose issue.
DR. GORDON: Oh, I agree, it's just we're including some NO2 studies that are private and the relative NO to NO2 emissions could be brought into play in your concept. I agree.
DR. HENDERSON: When you monitor, you monitor both NO2 and NO, correct?
DR. PINTO: Yeah, but the NO isn't deposited into the air quality system, you know, that's been available to the public. That's the problem.
DR. GORDON: The data was required in the report.
DR. HENDERSON: Well that could be

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changed, right, if it was deemed necessary. I'm just saying, could it be made available?
DR. PINTO: I don't know, what's the regulation for it? Mary, do you have that?
DR. ROSS: We're not the right people to speak to the monitoring network. Out colleagues in OAQPS I'm sure could find out.
DR. PINTO: It might be a better question for tomorrow. Seriously.
DR. HENDERSON: Okay.
DR. LARSON: Back to the point about the relationship between the short term and the long term averages. This is Tim Larson again.
I think you would find that that might be different depending on proximity to source, in this case the most ubiquitous sources being near major roads. And as you know some of those monitors are sited as far away from major roads as possible, but still fairly close in these urban areas.
So if you're going to be looking at that later on, you probably already have, but it's useful to try to qualitatively separate out those monitors in that regard because they get very different temporal patterns.
DR. WYZGA: I think one simple thing

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SPEAKER: We can't hear you.
DR. WYZGA: Oh, I think one simple thing that can be done to reorganize some of the material in the tables to the extent it's available, is that what I think in terms of trying to sort out the epidemiology, I think that the big issue is the whole issue of surrogacy and so it's very important to look at correlations between NO2 and some of the other pollutants.
And it's going to be very dependent upon where the monitor is. I suspect that if the monitor is sort of source neutral, you're going to get a different set of correlations than if your monitor is near a roadway.
And to the extent that that can be separated out I think would be useful. And I think also temporally too. I think that annual average correlations could be very different from some of the peak average, peak correlations.
So to the extent that we can separate these out I think it would be particularly informative and help us in understanding the epidemiology studies.
Because one of the problems we face about it is we don't know who is responding. Is it the people who are near the roadways or people who aren't?

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We just don't know from a lot of these studies.
So it's useful to have both in mind.
DR. HENDERSON: Oh, George, do you have something?
DR. THURSTON: I'd like to take a moment just to talk about the question of indoor and outdoor exposure and I think that we need clarification in the document about the exposure, the personal exposures to outdoor NO2, because EPA is regulating outdoor NO2. It's not going to regulate indoor NO2.
I think indoor NO2 is important vis-a-vis, especially vis-a-vis studies that have been done of it. I think the point was made earlier that some of the most instructive studies about the effects of NO2 have been indoor studies.
But in terms of the epidemiology and standard setting processes that I think are largely relying on epidemiology, backed up by the other, or not backed up, you know, by the other disciplines, you really need to differentiate the exposures and distinguish in the discussion between NO2 of outdoor origins, personal exposures to NO2 of outdoor origins versus personal exposures to NO2 of indoor origins.
And I think that was done in the PM document and I think it was a very helpful discussion

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and clarification, because I think, you know, it gets confusing when people start seeing that the personal exposures may not correlate with the central site.
But what we're looking at is, does the central site correlate with people's personal exposure to out you know, to NO2 or not, I should say, of outdoor origins.
So I don't know if I said that clearly enough, but I think we need to make those distinctions in the document to make it more useful.
And then a second comment. Really I wanted to pick up on Doctor Crapo's argument just in general I think, that throughout the document, starting right at the beginning, the thought has to be, well, how is this useful, you know, what is presented? How will this be needed for the standard setting process?
And a lot of the information is very interesting, but it might not be what is needed at the end.
So, you know, throughout the document I get the feel that each and you know, I'm sure it's true each section was written independently but I think we need to do another iteration where everybody says, okay, this is what we really need, this is the endpoint we've got to get to and you need to give me

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the information that's most relevant to this end, you know, the endpoint of the process that we're involved in. And make it most directly relevant, you know, the things like the exposures, who is getting them and what are the various levels of exposures, source of background. I know that example, that'll be covered later in the next document.
But I think throughout that theme has to be there. How is this useful to the end goal?
DR. HENDERSON: Okay. Thank you. And Ed has been wanting to talk and I haven't seen him, so Ed.
DR. AVOL: Yeah, thank you, this is Ed Avol. Just one comment on Ron Wyzga's sort of claim that we don't know who is responsive in terms of NO2 and whether it has to do with roadways. I mean there are studies coming out and in fact the studies in Southern California for example, have shown pretty clearly that it's the kids that are closer to the roadways that we see increased incidence of a number of things, symptoms, low lung function, asthma, et cetera.
So I think that information is starting to become available. So it's not quite I agree the jury is still out, but there is information becoming available.
DR. HENDERSON: Thanks Ed. Now, are

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there other comments regarding the first three charge questions? I haven't heard oh Dale, hi.
DR. HATTIS: Hi, hello. Yeah, I think the vertical gradient in NO2 exposures and therefore being where you have exposure to the higher up are less than the exposures at ground level, and that people have to be located more close to the ground level than the monitors do, I think that's a terrific problem for the interpretation of the epidemiological data in the context of this Australian study which is based upon actually personal measurements, or at least areas, measurements indoors.
So in order to translate between these two we have to have an idea of how, of what that vertical gradient is, how often, and how many monitors are located how high.
So, you know, the interpretation of the EPI studies in particular is going to be greatly modified by what your analysis is of that business and the distribution of those differences in the people that have been studied. And I think that reinforces a point that I think you were making, Donna.
And so I think that that's really the central issue for the interpretation of how distorted the epidemiological studies are, because you have both

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systematic error from the differences, the overall differences between the outdoor related exposures to the people relative to the monitoring measurements.
And likely quite a bit of random error introduced by the fact that there's some correlation but by far, a far from perfect correlation between what's being measured in the monitors and what's being experienced at least for the outdoor exposure, related exposure of the people.
So I think that, you know, that is, because of that difference, the different pollutants in particular, you have a really good chance of distorting, you know, the attribution of effects between pollutants of different kinds.
So I think in order to do an quantitative analysis you at least have to have that feature pretty thoroughly quantitatively analyzed, even though the data may well be very sparse to do such an analysis at the moment.
DR. HENDERSON: Thank you, Dale. I would like to hear someone summarize what our advice is on monitoring. I think I heard you say, Christian, that since the past monitoring has been with this chemiluminescent technique, that to switch would cause problems.

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Did I hear you right?
DR. SEIGNEUR: Yes. Well, maybe I can take a quick example or an extreme example. Let's say that the existing technique will estimate by a factor of two, then you do an epidemiological study to really understand that based on that measurement technique.
Then if you introduce a new technique, which then would give you values which would be higher for what you had before, you may have areas which would be in non-attainment with the old technique which suddenly would turn into attainment.
The EPI study would tell you that you would have problems, you know, on the health effects analysis.
So I think it's important to be consistent between the EPI studies and the measurement techniques.
DR. HENDERSON: Yes, Ted.
DR. RUSSELL: If I might, I think it comes down to more not necessarily changing the measurement, but understanding it better.
And my advice certainly would be to provide a more thorough assessment of what the uncertainties are with the various measurement metrics of NO2. Not necessarily saying go and start changing

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our measurement method, though it would be nice if we had one that was truly specific to NO2 in the long run, but right now saying, this is the current measurement technology, this is the level of NO2 we usually get, at which time and which season, and this is the likely level of interference and bias that we have in it.
Not necessarily throw out the whole thing but really understand what it's trying to tell us at this point. And I think that information is available.
DR. HENDERSON: That sounds like very wise advice. Are we answering the questions that you wanted to have answered and is there anything we haven't discussed that you were hoping we would discuss?
DR. ROSS: Yeah, I think it's been very helpful and it should help us improve on the document for the second draft.
DR. HENDERSON: Okay, I'm sorry, go ahead, Ellis.
DR. COWLING: I wanted to be sure, is there a consensus among this group that NO2 is the indicator of choice for oxides of nitrogen?
We're talking about alternative methods of getting to NO2, but that involves the original

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assumption that the wisest choice, the most adequate way for this country to understand exposure to oxides of nitrogen, is to get accurate measurements of NO2.

DR. RUSSELL: If I might?

DR. HENDERSON: Yes, go ahead.

DR. RUSSELL: Actually Ellis, I think your question is not as looking at exposure to oxides of nitrogen, but looking at the relevant health effects. That's what we're trying to assess.

So I think that has to come from the people who can tell us which oxides of nitrogen is likely to be given the ambient concentrations one's exposed to.

DR. COWLING: No, this isn't just a chemical question. It is fundamentally a public health question.

And I accept your comment, but we have a number of people who are very skilled in health research here.

Do you who are skilled in understanding what America ought to do about management of oxides of nitrogen, do you who understand the health effects as thoroughly as possible, just as Ted is suggesting, do you believe that NO2 is the indicator of choice to protect people from oxides of nitrogen?

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DR. COTE: One of the I'm about to step into quicksand because this is not my area of expertise at all, but there was a lot of discussion in house that in fact what is really monitored is NOX and what people are really exposed to are NOX and that, you know, we might be better served by simply it that as opposed to NO2.

DR. FRAMES: Can I make a comment? Mark Frames, I'm from the University of Rochester.

I mean my understanding certainly of NO2 is the regulated pollutant in the NAQS and not NO. And I think most of that comes from a fairly extensive body of literature, both in vitro and in animal studies and some studies in humans of sort of direct cellular effects but also respiratory and irritant effects of NO2 are much stronger than NO at a given concentration.

For example I think Ed made the point that, you know, we're using NO therapeutically at ranges of 5 to 8 and sometimes higher ppm and those kinds of concentrations of NO2 are definitely irritating and cause symptoms and cause lung function changes in some people and cause inflammatory effects as well. And NO does not.

The thing that hasn't been examined are the cardiovascular effects and this was mentioned. And

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NO is a pulmonary vasodilator, it's a pulmonary vasodilator in healthy people as well as sick people, it's just a, it's a smooth muscle relaxant. Just that it doesn't seem to have any adverse effects when you inhale it over the short term. But that really hasn't been examined in clinical studies or in long term studies, neither NO2 or NO.

But in terms of its irritant inflammatory effects, NO2 has a much stronger action than NO.

And I would make the comment that I think the more important thing to be monitoring or considering as a confounder, and this has been mentioned previously, is not NO per se but its particle member, or ultra fine particle counts, because I think many of the indoor studies which look at effects of NO2, the things that produce NO2 indoors are the things that produce ultra fine particles as well, including natural gas combustion.

And it's very possible that many of the symptom effects that have been associated with NO2 in indoor studies are in fact studies of particle exposure where it wasn't counted.

So I think looking for confounding with PM 2.5 really does not address the issue of whether

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what we're seeing with NO2 effects is in fact ultra fine particle effects.

DR. COWLING: Can we infer from your comments that you think well, let's ask the question directly. If you were Administrator of EPA, would you endorse the idea that has been with us for 36 years, that the most useful indicator of exposure to oxides of nitrogen is in fact NO2? And do you think that the present system that we've devised is reasonable?

After all, that's why we're here, is to examine the scientific evidence for a decision about whether to keep the standard we've had for all these years, or to alter it in some way. And I mentioned these four important indicators, the averaging time, the concentration, and what's the fourth one, I can't remember form, right.

If you were Administrator, what would you recommend?

DR. FRAMES: You're all fortunate that I'm not the Administrator.

DR. COWLING: I know.

DR. FRAMES: And I am too I think.

DR. ULTMAN: I don't know about that actually.

DR. FRAMES: I'm sorry?

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DR. ULTMAN: I don't know about that, I think I'd rather have you.
DR. FRAMES: Thanks, but I'm not ready to pronounce my opinion on whether the standard ought to be changed.
But your questions about whether NO2 is the appropriate indicator, I'm not aware, at least from the evidence that I'm aware of, I don't think we have evidence to change whether NO2 versus NO is the indicator.
I don't have, I don't see any evidence that pushes us to say NO ought to be one of the regulated criteria of pollutants.
On the other hand, you know, how do we know unless we have data to look at? And if there's going to be some additional studies of cardiovascular effects in the future, particularly epidemiology and panel studies, it would be very helpful to have NO concentrations in order to gather that information.
DR. COWLING: NO of course is only one of the many different oxides of nitrogen and I appreciate what you've just said, and you're demurring from taking the responsibility if you were Administrator.
But I think this question, what is the indicator of choice and how should we measure whatever

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it is that we will measure in order to administer a standard for the nation, that is a fundamental issue that we ought to try to wrestle with.
DR. BALMES: This is John Balmes. May I say something?
DR. HENDERSON: John Balmes, are you, is that you on the
DR. BALMES: Yes.
DR. HENDERSON: Okay.
DR. BALMES: Can you hear me?
DR. HENDERSON: Yeah.
DR. BALMES: So I'm glad that Ellis raised the basic question, not so much because I want to get into a discussion about NO2 versus other ways to measure oxides of nitrogen per se, but to get the larger issue of the fact that we currently are regulating pollutant at a time.
I don't have a ready suggestion about how to change that, but I do recall from the ozone discussion and it's actually even in our letter to the Administrator, we've written a letter, that we can, the Agency should consider ways to deal with oxidant pollutants in total and not pollutant by pollutant, because it's really probably the burden of oxidant pollutants that are responsible for at least some of

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the health effects.
And I think again the issue that kept coming up in my mind as I read the document, is the fact that there is often good correlation with other pollutants related to combustion sources. And I think it would behoove us, even we don't have a specific way to, a specific recommendation about a new approach, to say that a new approach needs to be considered, because I really think that we somehow spend a lot of time, waste a lot of time, trying to pin health effects down to a specific group when it's really the pollutant mixture causing the health effects.
And so that regulating the pollutant mix should be a goal for the future.
DR. HENDERSON: Thank you, John, I think that's a goal of many, many people. Ed?
DR. POSTLETHWAIT: It's Ed Postlethwait. I think there's been various speakers that have touched on this, but we have to remember that as Mark pointed out, the standard is for NO2 yet what we're measuring really is non-NO/NOX.
And so the exposure estimates based on that for NO2 are probably only going to overestimate the exposure, not underestimate the exposure.
So as long as the catalytic reductants

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continue to be used, you're actually measuring by and large the entire population of NOX. You're just not getting recordings of NO reported.
DR. AVOL: This is Ed Avol. I think there are two other issues echoing this part of John Balmes' comments about the mix.
And that is that you remember at the earlier workshop there was a lot of discussion about whether NO2 standard setting was useful in the context of separating it from particulate NOX or nitrates and going at the health effects and even control strategies.
And so in terms of thinking about the mix it's not the NO2. It may or may not be the NO2 and in fact from the community of epidemiology, you know, many times that's what's pointed out, the correlations and the association of the combustion exhaust involves both particles and the gases, so it's often difficult to separate those out.
So it really is a more complicated issue that even just talking about NO/NO2.
From the epidemiological sense I would also, or the standpoint, I would also point out that in terms of understanding public health and looking at trends in public health, it may or may not be the case

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that we want to go forward with NO, or pick up NO and continue with NO2. I think if we do go forward with NO, we don't, because of the fact that it hasn't been reported all these years, we don't know much about NO nationally.

DR. HENDERSON: That's true. Perhaps, you know, this idea of the multi pollutant is something we may want to address in our letter because it's such an important point. It's not an answer to a charge question but it's a very important point.

So I have noted that we've mentioned that. George?

DR. THURSTON: Well, a couple of comments. George Thurston.

One is I think a start for that would be something that I've mentioned in my written comments and something I mentioned at our last meeting, and other people have alluded to, and that is to start with the interaction of NOX and PM and particulate matter.

And start with that, you know, I think that would be a big step forward and it's doable within the context of this document.

Parts of it are already in the document here and there, but it's just a matter of organizing it and trying to see that as a theme throughout the

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document.

There was one other thing. Oh, and that was with the exposures. Is there a place here to look at the exposures of susceptible populations? As we get to the end of the document we're focusing on susceptible populations, people with asthma, children, people who live near traffic, actually those are all three pretty much the same people, because a lot of children with asthma live near traffic in the United States.

So what are their exposures and how are they you know, we can characterize exposures throughout the United States in the general population, but this is a very large group of people that will end up I think being a focus of the evaluation at the endpoint, protecting public health. Are we protecting the health of children with asthma in inner city locations?

And so I think we might want to have information about their exposures in the exposure section or just in general exposures of susceptible populations to outdoor air pollutants, outdoor NOX.

DR. HENDERSON: Okay. Can I ask, Mary, do we have data to do this?

DR. ROSS: Well I believe there are no

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published studies of exposure. There aren't any studies that have used children in exposure studies. There are panels for other specific groups that I think we've discussed.

One of the things I will mention though is tomorrow we'll be discussing the exposure assessment and we'll be some models and available data to try to estimate exposure to children and other groups like that possibly. There's data that we'll be commenting on tomorrow.

So we can look at what studies and what data are available and I'm not sure that there were any data available on children.

DR. KIM: When you use the specific term, susceptible population, in Chapter 2, but if you look at table, especially Table 2.5 or a, a lot of studies are focused on the children and senior groups.

DR. COTE: The other thing I'm sure everybody is aware of is HEI has this large effort ongoing that they are hopeful they can share with us before the final draft that's focused more on roadways and transportation issues.

DR. HENDERSON: You're concentrating on the exposures near roadways, is that what you're saying?

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DR. COTE: I think that's right.

DR. HENDERSON: Yes, I think so. Ed?

DR. AVOL: I'd just ask for one clarification from Mary coming from the children's health study in California.

Did you say there are no children's studies?

DR. ROSS: There are children's studies. But I was commenting on the personal exposures and ambient concentrations.

DR. HENDERSON: The Australian studies have too. I thought those were very impressive.

Are thee other questions? Yeah, Dale?

DR. HATTIS: Yeah, I've been taking a quick look at the data that are in one of the annex tables, AX 3.1, and I think in the context of looking at the relationship of the existing data to the standard, I think there are some facts in that table that are helpful.

First is that, off all of the monitors in CMSA in urban areas there aren't any that get even close to the current .053 annual average, okay? That I think might be a fact that's more prominent. So if in fact you think that the current epidemiological studies are detecting effects, then you must believe there are

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effects below the current standard, okay?
The second is that, you know, one of the things that I've been doing just sort of on the side here is to try to look at the difference in the variations between averaging times. And so I've got a figure that does that but maybe this isn't the right time to show you that. But basically the shorter averaging times that you expect have more variability than the longer averaging times.
And we can know how much that is and that seems to me one of the things that could go into the decision as to how to structure the standard. But of course, even more important is, okay, what is the averaging for the actual causation of the biological effects.
And I don't have a clear idea of the existing discussions of the health effects yet, what that is.
DR. COTE: Rogene, I have two quick questions.
DR. HENDERSON: Okay.
DR. COTE: I thought I heard in answer to Doctor Cowling's question, that there wasn't a substantial argument for moving away from NO2 as an indicator. I think that's what I heard as a consensus.

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DR. HENDERSON: I thought I heard that there is not now good evidence to move away from NO2, though there is concern about the multi pollutant effects and how you handle that, which probably goes way beyond the scope of this panel.
DR. COTE: We're concerned about that too. We've been discussing that a lot.
DR. HENDERSON: Yeah.
DR. COTE: I don't want to get into a long discussion but the second question I had, I just wanted a little feedback on is, you know, a number of people have said, have mentioned looking at the uncertainties around a number of these factors.
And my questions is there's, you know, I'm sort of of the school of uncertainty analysis, but there is a deep seated feeling in the organization that CASAC in the past has not particularly looked favorable on uncertainty analysis.
Now maybe that has more to do with how the uncertainty analysis was done versus a general dislike of it. But maybe Mary can shed a little more light on that.
Meta-analysis, Mary says it was meta-analysis, not
DR. HENDERSON: I think I've heard very

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favorable things about doing uncertainty analysis.
DR. COTE: Yeah, I think that's okay, Mary has clarified that that was really meta-analysis rather than uncertainty analysis.
DR. ULTMAN: Those are two different things.
DR. HENDERSON: No, I think uncertainty analysis is favorably
DR. ULTMAN: Is Lianne on the phone, because that's one of her areas of special expertise?
DR. SHEPHERD: Yeah, I am on the phone. I don't know that I have anything to add to that now. It'll probably come up a lot more tomorrow.
DR. HENDERSON: Okay, is that Lianne?
DR. SHEPHERD: Yes.
DR. HENDERSON: Okay, I thought we needed a comment.
DR. SHEPHERD: I don't have anything to add right now.
DR. HENDERSON: Okay, she said she --
DR. ULTMAN: More later.
DR. HENDERSON: would have more later, yeah.
DR. SHEPHERD: Right.
DR. COTE: Okay, that was all that I

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wanted to know.
DR. SHEPHERD: I do have a comment though about
DR. HENDERSON: Okay.
DR. SHEPHERD: Chapter 2 with respect to this comparison and discussion of correlation coefficients.
I just couldn't make sense out of it, there are so many different correlations being compared and they weren't clearly defined and there were so many factors that would make them different, like seasonal restriction and so on.
And that was tried, attempted to be addressed, but that whole piece needs to be reworked because I didn't think that we could draw any conclusions from the data as presented.
DR. HENDERSON: Thank you, Lianne. Ron?
DR. WYZGA: Just one thing. I think this is in response to the issue about what's the appropriate indexing method, you know, NO2 is thought to be appropriate.
But I would still urge that to the extent the Agency can update the report NO data, it would be particularly for people with a deeper analysis.

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So I think that's something we don't want to let go of.

DR. HENDERSON: Okay, thanks, Ron. Ted, you look like you're about to say something.

DR. RUSSELL: Yes. I was going to ask Ellis, I actually got the feeling you were pushing maybe the Agency looking at something like the nitric acid or something like that. And I'm not sure if that's

DR. COWLING: No, I have biases of course over the two, but I have no special bias towards the nitric acid simply raising the question, what is the appropriate measurement technique and what is the appropriate monitoring design and what is it, as you pointed out yourself, what is it that worries the health people in terms of their experience in dealing with humans that suffer from asthma and all the other difficulties that observed?

The Academy of Sciences has urged that, in its most recent management of air quality in the United States report, urged consideration of multiple pollutant, multi effects ways of approaching the air quality management.

And this discussion about what about the connection with ozone, what about the connection with

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PM, emphasizes exactly why that committee strongly urged, and why Europe is in the process of accepting that recommendation.

We have a bias in this country to doing one thing at a time and we're biased also to not do anything until there's a crisis.

I presume they were interested in the crisis in 1971 relating to oxides of nitrogen and that that's where we got the standard that we now have and have continued to use for 36 years.

So we should take a wiser choice, a wiser, make a wiser series of recommendations. And certainly as Rogene said a few moments ago, we'll probably have to deal with that multiple pollutant, but Amen.

So I'm asking in the most general way, what is it that CASAC ought to recommend to the Administrator with regards to management of oxides of nitrogen? And if that means what they ought to do about ozone and PM at the same time by all means.

That is a bias, I am biased toward the notion that managing air quality is a much bigger job than managing one pollutant at a time.

DR. HENDERSON: Well as far as consuming time it certainly takes more time to do it one

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pollutant at a time. So I think we will eventually go to the multi pollutant system.

DR. ARNOLD: I just want to say just one thing, this is Jeff Arnold.

DR. HENDERSON: Can you speak into the mike so we can hear you?

DR. ARNOLD: I just want to say that one of things we are trying to do with the discussion about the monitoring of NO2 in itself, and this bears directly on both of Ellis' points, is that we were talking generally about the uncertainty in the NO2 measurement and whether or not NO2 is the indicator chosen to go forward, because we thought it was important to have that information available to people who are working on health effects.

The other side of this whole thing, we were talking about the more general measurement in trying to get to a characterization of the mix is the reason that we were looking at and talking about the measurement of NOI together because it's a fairly simple transformation to make mechanically. And some measurements are actually in place in the network now and we can understand what those relationships look like.

And that NOI then captures more of the

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actual oxides of nitrogen mix than we do with the NO2 measurement which has got an unknown and varying amount of interference. It varies both spatially and temporally at all the measurements that are in there.

And so as part of the point of getting to a multi pollutant strategy, which I'm not recommending that we try to do at this point in this meeting, but that was part of the idea of looking at NOI because it characterizes more of the oxides of nitrogen.

DR. HENDERSON: Thank you. Now, we're going to be breaking for lunch.

Before we do as we discussed earlier, we have a little new process at the end, so Angela is going to try to summarize what we want to say to the Administrator, the key points.

And so those of you who have, your name is underlined, I'm hoping that you will be able to get a written summary of our, the panel's answer to those charge questions to Angela by email.

There's two important things, monitoring Ted, will you put that in, and you had I think a good summary of you and Christian together, be sure that monitoring is in there.

And then Ellis, could you write up a

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little sentence on that we need to start addressing multi pollutants?
DR. COWLING: I would be happy to.
DR. HENDERSON: Thank you. And send these snippets to Tim Larson, are you on the phone?
DR. LARSON: Yeah.
DR. HENDERSON: You may not realize you're supposed to be writing something up.
DR. LARSON: Yes. So you'd like me to, would you like me to try to summarize some of these points about the sufficiency for evaluation?
DR. HENDERSON: Okay, I could barely hear you but if you would send us that email, to Angela, she's going to collate them.
DR. LARSON: Okay, can you hear me?
DR. HENDERSON: Yeah, when you speak up I can hear you.
DR. LARSON: Okay, I don't know what the phone is but I'm sort of yelling into it.
DR. NUGENT: Rogene is asking for this by tonight.
DR. HENDERSON: Oh yeah, this is not in the future, this is today. Today.
DR. NUGENT: Today.
DR. HENDERSON: And tomorrow morning

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we're going to pass this around and we're going to decide whether this is something that we can agree on as far as the letter to the Administrator and how we think this document needs to be changed to improve it or whether we can't.
If we can't we have a conference call later on.
DR. LARSON: Rogene, what would you like me to emphasize and what part of the discussion?
DR. HENDERSON: What did you say?
DR. RUSSELL: What would you like him to emphasize.
DR. HENDERSON: Oh.
DR. LARSON: What part of the discussion do you want me to try to summarize?
DR. HENDERSON: Well, Charge Question 3 but that's, I know what you mean, that's kind of, it involves everything under, in Chapter 3.
The indoor/outdoor or maybe NO as the surrogate for, I mean NOX, NO2 as the surrogate for nitrogen oxide. That's something we want to have in there.
DR. LARSON: Okay, okay.
DR. HENDERSON: Just a paragraph, short, short and sweet because the letter, we don't want the

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letter to be 50 pages long, but you know.
DR. THURSTON: And Angela said she wanted it at the latest by 10:00 p.m. eastern time, is that daylight I guess, we're still on daylight, right?
DR. HENDERSON: And I really thank Angela for being willing to pull this all together for us.
Okay, let's have lunch. The restaurant is what are we going to do?
SPEAKER: Vanessa knows.
DR. VU: Lunch for CASAC members is where you meet for breakfast, the Raleigh Room.
DR. HENDERSON: So we will convene at 1:00 and there are people here who are going to be on the phone, so let's be back.
(WHEREUPON, the morning session was concluded at 12:03 p.m.)
DR. HENDERSON: The next three charge questions are all related to health, the Charge Questions 4, 5 and 6.
So I think, and we have many health experts here to comment on this. This is a very important section, quite critical and I hope everybody has read the bottom line that was on the last paragraph of Chapter 5, because it tells you that the Agency considers that there's sufficient evidence to, that the

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standard should be strengthened as I understand what's written up there.
But we need to put this in context as we go through these different charge questions.
We'll see how it goes, we may want to combine some of these discussions. I think they will combine themselves almost automatically but we'll start out with Charge Question 4, which is really at the heart of the whole thing.
To what extent is the discussion and integration of evidence when the animal toxicology in controlled exposure human experimental studies and epidemiologic studies technically sound, appropriately balanced and clearly communicated?
So that's going to be headed by Terry Gordon.
The man who is writing down what we are saying would like for us to identify ourselves before we start talking, and particularly those who are on the telephone. So if you don't mind doing that, that would be helpful.
And Terry Gordon is speaking first.
SPEAKER: Rogene, I can't hear anything.
DR. HENDERSON: Well nobody's talking right now. That's good.

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SPEAKER: That's good, okay.
DR. HENDERSON: We have to speak up into the mike.
SPEAKER: Okay, all right.
DR. GORDON: There's a great deal of good work here in this Chapter 3 and 4 and I feel that the health relevant studies have been presented. This is really loud to me.
Obviously this long, long chapter was a multi author effort and the inconsistencies in integration across the different sections is what I feel is the main problem with this chapter, this Chapter 3, in terms of answering the Charge Question number 4.
So the proper degree of integration and study discussion in terms of relevance to our task of reviewing the science of NOX health effects, it's presented in a few places, mostly in the descriptions of the clinical studies. But adequate integration is most absent in the animal tox descriptions and sometimes I feel the EPI studies were not integrated, they just tend to wander.
So part of me was thinking that a single or maybe two at the most authors should be charged with the next step of condensing and integrating this

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chapter.
And for example there are several redundancies in these studies, things repeated two pages later.
So in general I just have four short bullets and I feel it's important that only the key studies that support or refute the NAQS should be included. And unlike Chapter 2 comments we heard earlier where they wanted to bring some of the annex information into Chapter 2, I think a good bit of information in Chapter 3 should go back to the annex, and more integration and discussion devoted to the key health relevant studies.
And then because it's such a large chapter, and I don't know if anybody is going to suggest splitting it up, it seems it should have a summary at the end of each section that discusses the relevance of that section as it relates to adverse effects with concentrations, something that was brought up before and something that's missing.
And in this latter point it's key across all the study types, especially the EPI studies which I think are driving the NAQS review.
And therefore if the EPI studies, if it's decided the EPI studies drive the NAQS, I think it

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might be easier to give a full interpretation and integration of the EPI studies and then mention briefly in each one of those sections afterwards, how the clinical and animal tox data supports or refutes the EPI data, rather than how it is now. It's a little bit separate.
Then, and this is just out in left field, I was wondering is Chapter 4 necessary, the susceptible sub-populations, even though it's something I actually do research on a lot. It seems it's partly duplicative of what's going on in 3.
Why would you pull out the most sensitive sub-population effects into a separate chapter? Shouldn't that be in the Chapter 3?
And in summary I think is like a key if not the key chapter and it's needs better balance between providing the details of the central studies and the overall integration with health effects.
And as Ellis said this morning, it needs to be made a much more efficient communication device. And it's most important to have an integrated analysis that draws the key conclusions from the available data sets, and I stole this from Dale, and include the magnitude of the concentration response for the different health endpoints.

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And that's probably the key to this whole chapter and it's only there as I said in a few places.
And to reemphasize what Jim Ultman said earlier, that the exposure concentration in studies, the EPI ones of course, should be put in context throughout during the summary at the end of the chapter in the context of the current standard with respect to reviewing is it appropriate or not.
DR. HENDERSON: Thank you, Terry. John, are you ready to give your comments?
DR. SAMET: Yes, it's Jon Samet or John Balmes?
DR. HENDERSON: Oh, I'm sorry, it's Jon Samet
DR. SAMET: Okay.
DR. HENDERSON: and not John Balmes, I'm sorry.
DR. SAMET: Just checking.
DR. HENDERSON: I was thinking J-O-N, but you can't tell the difference.
DR. SAMET: Yes, so I wrote fairly lengthy general comments that I think speak largely to this charge question.
So my general comments were that I did

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not see this document succeeding in meeting what it was called, integrated. And that this problem really reflects sort of a failure of process which I think sort of comes through in the last comment and some of the other comments.

There are models for doing systematic, integrated reviews and I don't really feel that this document looked to those models, the authors looked to those models, the Agency looked to those models in setting out on a process.

And then I think that comes through because the methodology is rather opaque for me in sort of achieving the integration. Terms like coherence, plausibility, consistency pop up but they're not really clear as to the intent of those terms as they're reviewed. They're sort of convenient to use. The word is integration is used without integration taking place.

So I will say that as a general model for how to proceed to do integrated summaries, I'm concerned about this as a starting point.

And then that reflects back of course on question 4, on Charge Question 4 because that is the one where the integration is supposed to come in. And I just don't see that the methodology was set out. I

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mean there's sort of these little mini reviews of that, the mini reviews of some tox that might be viewed as relevant. But it's not really brought together.

I was concerned, and I think I saw some of this in George Thurston's comments as well about sort of the underlying framework and ideas. And I think the interpretation of effects attributable to NO2 and NOX is very difficult because of the links back to common sources of other pollutants, the contributions of NOX and PM, the role in ozone generation.

And these sort of simple underlying causal models that seem to play throughout the document may not be correct. And again in my comments I sort of outlined some of the different models and there's some little figures there that are the kind of thinking that I think ought to come up front in the document.

Because again, the document has to make clear that NO2 is the right indicator itself, that reduction of NO2 could be reasonably expected to have benefits, which is the causal model and potentially some of the other models.

But again if we're working to lower PM, and that is one way that NOX is in fact mediated, we're sort of going after the same sources twice obviously and I think that that could be acknowledged.

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So I saw problems and the problems don't relate to necessarily these were picked out in how they were represented, but really whether they were integrated or not. And as I say right now my view is that the integration and synthesis that was needed here has not been accomplished.

And so much of this sort of reads I'm sorry to say this but sort of like a mini criteria document with sort of recitations of studies with, you know, paragraphs starting of with, you know, Schwatz, et al shows and so on, so that it's, I just don't think the model's integration has been met.

So that means that the answer for the charge question is that this has not yet been done adequately.

DR. HENDERSON: Okay Jon, was that all you had for this charge question?

DR. SAMET: Yeah, and I think again I've laid out a lot of general thoughts in my comments.

DR. HENDERSON: Yes, you sent extensive comments. Well now let's go to John Balmes.

DR. BALMES: Okay. So first of all I apologize for not submitting written comments yet. I've been working on a grant and that's had to take priority. But I will submit those by the end of

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tomorrow.

I didn't hear the start of Terry's comments but I heard the end and I heard of Jon's.

And, you know, the question for charge 4 has four, excuse me, three specific components, is the discussion integration of the evidence from different types of studies technically sound, appropriately balanced and clearly communicated?

So on the technically sound part I would say that my major concern was just articulated by Jon and also George Thurston in his written comments, that I think there need to be clearly communicated criteria about how steady the epidemiologic studies in particular were selected. And then how the results are evaluated.

I thought Jon and George both articulated that well. So that's on the technically sound thing.

With regard to appropriate balance, I guess I was a little concerned that two negative studies that I've coauthored didn't appear in the discussion. And I think while neither one of these studies is earthshattering, given the relative dearth of information with regard to nitric acid vapor, our 1993 study which I think is one of the very few studies

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to compare filtered air and nitric acid vapor, the controlled human exposure study, the fact that's not even mentioned, and it has been published since the last criteria document, should be mentioned.

Again it's a negative study. There's also a study that was published in 2005 by my group which was a negative study about NO2's affect on allergic inflammation using induced sputum rather than bronchoalveolar lavage. There's a brochoalveolar lavage study mentioned.

I only point out these two studies because those are ones I knew about because I'm the coauthor. I am a little bit concerned that even though we need a shorter document than the old criteria document, that there may have been some cherry picking in terms of studies to the exclu you know, which, to the exclusion of some relevant information.

I don't know that for a fact but I'm concerned about it.

And, you know, in terms of the clear communication, I don't think it cuts it. The chapter is repetitive about mechanisms for sure. I don't think the mechanistic information is well integrated with the epidemiologic information.

You know, an example would be when the

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long term exposure and morbidity sort of integrated summary of that piece is done, the first paragraph is about, it mentions respiratory illness and growth of lung function, and then there's like three or four paragraphs about respiratory illness, potential mechanisms by which respiratory illness in kids might be increase by NO2 exposure.

And then there's a little, there's very little about possible mechanisms for the observed effect on growth of lung function from the Children's Health Study.

And I just think you could do a much better job of integrating the toxicologic information with the, in support of various epidemiologic results.

So I would have to agree with Jon that the 150 pages or whatever it is that are there are, while better than a criteria document, it's kind of a mini criteria document, it's not really an integrative summary that I think can inform policy makers with clear communication.

And the one final sort of picky thing that I think would make it easier for or two things in terms of policy makers reading this. It goes back and forth between micrograms per meter cubed and parts per billion and parts per million. I realize that

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they're taking, that the authors are taking what the original studies probably used, but it would be nice to have a common metric when you're going back and forth between studies.

And I also think that the tables and figures, which I like, at times need better labels or legends because they really should sort of stand on their own so you don't have to go back into the text and figure out what's there.

So those are two picky things.

I guess one more, sorry, there is a section on the effects of NO2 on allergic responses in synthesized individuals which I think is an important set of, it's an important section, but that important section in my mind doesn't make it into the integration with a focus on asthma. And I think it should because that may be an important way by which asthma is exacerbated by NO2.

That's all I have to say --

DR. HENDERSON: Thanks, John.

DR. BALMES: at this point.

DR. HENDERSON: Thank you very much, those are very helpful comments. And Ron?

DR. WYZGA: Let me first of all apologize, I've been in the office two days in the past

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six weeks due to personal and professional activities. So I have not had a chance, had access to all of my files and all of my data, but I depended very heavily on what I know and sort of grabbing a couple of things when I was in the office.

And it's difficult, we don't want a criteria document but we really want to include what's relevant and it's sort of hard to decided what the dividing line is.

But the first issue I asked myself is, what's here, is it comprehensive? And the idea is we don't to be as comprehensive as a criteria document, but where do we stop? I don't know.

But I'll say that I was very disappointed that it's not comprehensive. Thinking about studies that I've been involved in, there are some very key studies that have been published that are not listed.

They were negative studies that looked at a whole range of pollutants, including NO2, the findings were negative and the studies aren't referred to at all, including one looking at physician visits for childhood asthma.

I grabbed a couple of papers as I was leaving the office that had NO2 in them and I looked at

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them on the airplane. They weren't referenced either. And one of the studies was a study in Southern California that looked at VOCs and NO2 and basically when the two are looked at together they show nothing for NO2 and it's very hard to discern on both of them.

So I felt that it wasn't comprehensive.

And the second thing is, again thinking about the studies that I know well, I didn't feel that they were accurately reported and there were just parts of them reported.

An example, as part of the area study, Peel, et al looked very extensively at respiratory endpoints. And when they looked, she looked at single pollutant models she found association with NO2 and respiratory, hospital admissions for respiratory diseases.

When she looked at multi pollutant models she found that NO2 went away and the ozone seemed to dominate everything.

Now, there are problems with multi pollutant models and you have to wave your hands a little bit and explain them, but I felt at least the document should have presented the multi pollutant results and not only the single pollutant results.

The same is true of the area study by

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Metzger which looked at cardiovascular disease and admissions. You know, NO2 is reported in an earlier data set, NO2 was reported and then they spoke about results of NO2 and CO together where NO2 was still important. But in a later data period where we had much more extensive data, NO2 went away, EC and carbon particles were much more important as was CO.

Again, these results were not reported. I was involved in a long term study with mortality with Lipford where we found associations with NO2. And again when we looked a multi pollutant context it was dominated by ozone and it went away.

And the study that's in here reports the single pollutant results and does not report some of these multi pollutant results.

Now there are caveats in dealing with them and I think they can be handled and discussion, but I think it's fair to get them.

I think the major problem we have to ask ourselves with NO2 is clearly in single pollutant models we see a lot of evidence of association with health effects. And the really big question is, is NO2 serving as a surrogate for something? And that's something we really have to, you know, dig into and think about it.

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And for that reason I think that multi pollutant studies are particularly important. How robust is that association if you look at other pollutants?

And I think this document needs to look at it more systematically and sort of talk about what are the co-pollutants under different circumstances? If you're near a roadway in general.

And I think more weight should be given to those studies that tend to look at co-pollutants rather than studies that look at a single pollutant. And this is why I think it's also important to tie it in with the clinical studies and the toxicology studies because in the controlled exposures we know exactly what people and animals were exposed to and tie them together.

So I would ask that one go back and see, are you missing other important studies? Are you treating them fairly when they deal with co-pollutants? Are you emphasizing that? And then ask yourself other

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questions too.

In looking at some studies, in looking at results, you know, people looked at different lags and I found, you know, it wasn't always consistent. In some cases it was a very short lag that's important. In other cases the lag was several days out.

Is that meaningful or not? I don't know but I think it's something that needs to be entertained.

Those are my major comments and I'm happy to answer further questions and I'll send you those specific references as soon as I get back to the office.

DR. HENDERSON: Thank was my first thing, I wanted to be sure that we will have those copies of the reports you're talking about.

Can you off the top of your head say why some of these negative studies were not included?

DR. ROSS: Well I've been looking in the document because cheery picking is obviously something we take very seriously. And all I can say is we did a systematic literature search using source terms that we worked out with the librarian and worked over. And I think we tried to gather information.

For Peel and Metzger I'm looking at the

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multi pollutant figure we put together and as I recall the results were in figures and not quantitative results that we could pull into to a figure ourselves.

So I think we tried to look at those studies as much as we can.

I don't have any reason, I don't know all the specific studies people are mentioning, but we certainly tried to include as many as we can and we welcome any we will look very seriously and do another literature search and make sure we didn't miss something.

But please, you know, submit references that you think we missed.

DR. SAMET: Rogene, this is Jon. Can I make two follow up comments?

DR. HENDERSON: Sure.

DR. SAMET: Yeah, just one on the literature search strategy, I think it has to be more transparent than it is. And I think, I'm sympathetic to trying to have a list, but when it's not clear and replicable how studies are being selected you'll always be subject to enquiries like, why wasn't whatever study included?

And I think that that's a problem with the document.

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I just want to have a caution, and this comes in light of the little figure, that interpretation of the multi variant models here is very complicated, because of the possibility of direct pathways, indirect pathways and confounding.

And I think that this issue needs very careful intellectual attention up front. And how you do interpret these models and when effects come and go depending on what variables are included, the interpretations are not so simple as either the document portrays them or very often how authors interpret them.

So I would urge some real thinking about how to interpret these multi pollutant models. And of course if in fact NOX is acting through other pollutants and you put those pollutants in a model and the NO2 goes away, that does not mean it's not having a causal effect. Just as one example.

So I think you need to build a better framework up front for interpreting the evidence you're going to present.

DR. HENDERSON: Thank you, Jon. Yeah, Ed?

DR. POSTLETHWAIT: Yeah, this is Ed Postlethwait. In Chapter 3 and Chapter 4, although it

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was very briefly mentioned about endogenous NO production, I thought in terms of trying to put the experimental results, both in toxicology and epidemiology into a biological plausibility context, that the endogenous production of reactive nitrogen species was pretty absent from the discussion.

In the field of free radical biology it's been recognized now for many years, that NO2 is produced endogenously anytime you have an inflammatory response.

How you put that into context relative to the low ppb NO2 inhalation exposures we're talking about, especially in the epidemiology studies, I don't have an answer to. But to equate causality to something that is 10, 20 parts per billion relative to the exact same molecule that's produced from a peroxidase reaction and uses nitrite and hydrogen peroxide, I think somewhere in this document that whole issue has to be addressed.

Now as I said, putting that in terms of quantifiable amounts of NO2 is an extraordinarily challenging thing to do. But I think on a relative term at least, that should appear.

Likewise when in the document when we're talking about some of the co-pollutant stuff, nothing

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was said about the endogenous production of carbon monoxide and CO now is recognized as a second, and in fact it's being used in preclinical trials. And so they're delivering CO to people that ten years ago we would have thought was just nuts to do. And now it's shown to have some anti-inflammatory and other types of efficacies.

And so the connection between the known mechanisms of action and biological plausibility, et cetera and the outcomes that were reported in the document, I think could really be tightened up.

DR. HENDERSON: Okay. Ed, those are some important points and I thank you for bringing it up.

Ed Avol has a comment and then I want Kent Pinkerton to come in because Kent at one time was not going to be here and so he inadvertently got left off this list, so he's going to speak after Ed Avol.

DR. AVOL: Thank you. So I just have a couple of comments to get at the charge question related to clear communication.

And it seemed to me the heart of the issue in this document is the understanding and relating in terms of the public health context. And there are threads throughout the different chapters, this one included, that get at how we interpret what we

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do.
But clearly because NO2 and NOX is so closely associated with combustion exhaust and other pollutants, for example ultra fine particles that Mark Frampton measured and mentioned earlier.
I think we need to sort of think about how this is communicated and the context really in which it's reported throughout the document. So it goes back to what Ted Russell had said earlier about sources, because I think if there is an overriding writer that sort of integrated many of the chapters because there were many different writers and contributors to this document, understandably, but there's sort of a theme that underlies all of these facets that goes from the sources and the fact that we need to identify it, its multi pollutant nature I guess and then look at the pollutants and health effects and understand that in fact we have these potentially confounding issues that might be able to be uncoupled by multi pollutant models by some of these studies and to what extent we believe that the studies have successfully demonstrated that.
And then finally to conclusions later on that say, that talk about this rather than just a sentence here or there that sort of says, allows it as

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a possibility. I think that would help the overall document and make it clearer to the user of this document as to what it means and how the document itself is integrated.
DR. HENDERSON: Thank you, Ed. And now Kent, it's your turn.
DR. PINKERTON: Thank you. What I'm about to say will echo much of what has already been stated.
But as an animal toxicologist I think that it's very important to me to better understand how we integrate animal toxicology to human clinical experimental studies as well as epidemiological studies.
And I think that with the document, although it's really been a great effort to pull together a lot of the literature and perhaps there are other sources of literature that still need to be considered, but a concern is the fact that in order to produce toxic effects in animals we're usually dealing with an order, the two orders of magnitude, higher concentrations of nitrogen dioxide than we need to use in the human clinical studies.
And then even with the human clinical studies they tend to be usually an order of magnitude

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higher than the epidemiological studies that are beginning to show effects, especially in children with asthma.
And so I think that kind of integration and interpretation of how do we use the animal tox studies, if at all in the creation of the next rendition of this criteria document. Is there a place for that in the document?
I think it's also really important, since this criteria that has been established for NOX is on the order of 36 years that I thought I heard earlier today, you know, where do we go with that? Because it seems as though with the current standard as it is, there is very rare exceedances of the standard as it exists today. Yet how do we take into account that there are health effects in children exposed to incremental levels that are on the range of 10 to 20 ppb levels?
So those are things that I think are really critical for the integration for this document.
And really, before Ron mentioned anything and as well as John Balmes, I thought the review of the literature seemed to be really good and that it was, you know, with new literature and things that are there, but again it sounds like it would be

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good to take advantage of the things that we're learning today about other literature, other studies that may be pertinent to helping us with this criteria document.
And finally I would like to think that, you know, there really is a lot of pressing issues here from the perspective of whether this document needs to be changed or not in terms of a new standard.
And so again these discussions and the way you put together the document will be critical.
And I would just like to also emphasize the fact that it is very important because it seems to be a recurring theme throughout the document, that the health effect that are attributed to NO2 may always be confounded by the association of other co-pollutants or it may be that NO2 is just serving as a surrogate for other pollutants.
So again that's another point again that I would emphasize that needs to be really clearly defined in this document.
DR. BALMES: This is John Balmes again. I wanted to thank Kent for bringing up a point that I had meant to bring up but I forgot to and that's a key point.
With regard to ozone we have good

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experimental data, both from clinical human studies and animal toxicologic studies to support inflammatory effects at levels at least close to ambient. But we don't have that with NO2.

So that it makes the integration of the epidemiologic literature with the toxicologic literature, both human and animal, you know, very important.

And I think that insufficient attention has been paid to that as Kent pointed out. I think there has to be an acknowledgment that both the animal and human studies that show acute effects are at higher levels than ambient.

So that sort of brings up again the issue of how NO2 is acting to, in its association in the epidemiologic studies with health effects. Is it direct NO2 effect or not? Or is NO2 a surrogate? You know, the various models that Jon Samet included in his written comments.

But I'm repeating Kent because I want to underscore, think that's very important and I think one of the public comments this morning already brought up the relative lack of support from the toxicologic studies for the epidemiologic evidence. And so I think we have to sort of, I think the Agency needs to deal

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with that head on.

DR. HENDERSON: James Crapo.

DR. CRAPO: I'd like to sort of partially weigh in, I think the major issue that we need to provide advice on as a committee, and that is if you read this document the way it's written right now there's a very persuasive argument that there's a profound effect of NOX exposures on many tests of mortality, ER admissions or asthma admissions, cancer, lung growth and development and, you know, a lot of studies that support it with a lot of consistency and coherence.

But I think we need to give advice and I'm not sure what the advice ought to be as to whether or not in fact we're looking at a confounding issue and it's surrogate for something else that's doing this or whether the NO2 is doing it directly.

And so we need to have some real depth in our knowledge to put those two things together that Kent and John have just talked about.

But I think we need to be very concrete in our recommendations to the Agency about conclusions that can be drawn from this and the power that relates to it.

It's, I'm a little concerned by some of

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these comments that are brought up that indicate that we may not have been thorough in picking up all the negative studies. And so if there's a positive, it's not a publication bias but a positive bias for finding the positive studies is in there, so it's also very important for us consider in coming to that conclusion.

And then I wanted in particular to draw your attention to a section that hasn't been talked about yet, it's on page 3-126 on cancer incidence. I've been puzzling over this since I read this section since I really hadn't watched these two articles real closely when they came out.

But one from Sweden and one from Norway in which they looked at incidence of cancer and correlated it with air pollution. In this case it's translated all the way down to NO2 being the driving agent to it.

But they, because they actually, if this is correct and I convert the micrograms per cubic meter, basically divide it by two to get parts per billion, you're talking about exposure levels that they say is, by Nyberg's article in 2000, exposure a the 98th percentile to an ambient level of NO2 was associated with a odds ratio of 1.44 for cancer, for lung cancer. And the other study came up with an

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incidence of 1.36.

So you're talking about a possibility if you then extrapolate this backwards, if you were able to reduce the, you know, if you attributed this all to NO2 and then reduced it by 20 parts per billion I guess is what they're standardizing this to, it's kind of hard to reduce from 15 to, by 20, but nevertheless it raises the point that if you could make a profound decrease in NO2 you could have a profound impact on the incidence of lung cancer, and on other cancers as well which is also part of the study.

My instincts are this is not correct. It's probably a substantial bias in it to create such a profound effect because I've not seen anything that could reduce lung cancer by that kind of a magnitude.

And I wonder if this kind of well, I'd like other people's comments on this data. But if this were correct it would mandate that we have to do something abut the NO2 levels.

But my interpretation of this is that it's probably a surrogate for air pollutants and I'm not sure what the pollutant is in that area. Although these are two good countries where you should expect good epidemiology and good data.

But the only correlation is to where the

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people live and to a correlation of air pollutants.
Anyway, this kind of correlation is what's, what we're talking about throughout the whole study. And we need to come to this conclusion concreted, before we can start making conclusions about the overall study and where it ought to go and what ought to happen with it when it goes up to the Administrator for a decision.
DR. HENDERSON: Yeah, go ahead Steve.
DR. KLEEBERGER: This is Steve Kleeberger. I'd like to follow up on James' comments, I think those were outstanding. And actually I was going to save this for when it was time for me to speak but I think I'll start now.
What I got from reading Chapters 3 and 4 is that while there are a number of interesting observations, there are very few that substantiate initial observations and that it's very difficult to make any concrete conclusions based on the very few studies addressing questions related to susceptibility for instance.
And it made me think about what our charge is here. And that is, are we charged only with evaluating what is there in order to make recommendations? Or can we as a group also make

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recommendations for future studies to address these kinds of questions, these gaps in the literature if you will, that will help us or inform us in actually making some concrete conclusions about the literature that's already there?
DR. HENDERSON: Well I think we should feel free to make recommendations for future studies to fill data gaps. However, the regulation has to be set of what's available now.
But I'm trying to think of an example where we've recommended future studies, but there's nothing wrong with making recommendations for future studies.
Our main charge is to say, is this document, is the science in this document sound enough to be used in the standard setting process based on what's available now?
I am very curious about these studies too but I'm kind of like James, intuitively, gosh, I can't believe that NO2 is causing that much cancer around the country.
But I don't know, John Samet, did you look at the, are you familiar with those studies? He's probably muted. Has anybody read those studies that could critique them and will add

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DR. SAMET: Oh Rogene, this is Jon, let me comment.
DR. HENDERSON: Yeah.
DR. SAMET: The Nyberg study I know well and I mean I think the author's intent on that study was that the NO, the model of the NO variable, the NO2 variable was a surrogate for air pollution as I think perhaps James suggested.
And there are many epidemiological studies that point to air pollution in general as contributing to the burden of lung cancer, the Six Cities Study and the American Cancer Society's study most notably.
So I don't think this is new news, I don't think anyone though has felt that there's a way to do anything other than to point toward the general combustion mix as contributing to the causation of cancer.
And again I, you know, I think in looking at the evolution of the epidemiological literature on NO2, if you look back, a long time ago there was emphasis given to just a very few outdoor studies where there was the thought that there was a pure NO2 exposure that was higher for some people. That was the same as the Chattanooga study that Carl

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Shie did back in the '70s.
And then there was the emphasis on the indoor studies because that was NO2 independent of the rest of the outdoor combustion mixture.
And I think what is new in this review, and again I think this goes back to the problems I highlighted of interpretation, is that people are now turning to times series studies or some other studies where multi variable models have been used to try and tease out NO2 as a mixture component.
And to me the heart of the interpretive argument lies in how well you can, how well you can do that. And I think again, just to reiterate, this is something the document needs to deal with.
And this is where the integration with the toxicology becomes so important in my mind.
DR. CRAPO: But can I add further on that. Jon, if you look at the Table 3. no 5.5-3 at the very end of Section 5, it is the table in which I thought that they really made a strong and I think a laudable effort to try to correlate, put it all together and come up with an integration of the various risks.
And what they do on the right side of that table is calculate the standardized excess risk at

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the 95% confidence interval for various functions, which go through a whole lot of different functions over this whole table.

And it's defined, that function is defined as I think an excess risk attributable to NO2 at a, in 20 parts per billion increments.

Another question on this table, but I'm wondering if in fact we've gone too far with this table and started to draw conclusions where we're actually concluding here that a 20 because when they say standardized risk, and if you look at the lung cancer one, which is on page and of course they're all like this, but the lung cancer one is on

DR. ROSS: James, can I speak to that point about the 20 parts per billion?

DR. CRAPO: Sure, go ahead.

DR. ROSS: It's not actually intended to say anything about 20 parts per billion. What you get from the epidemiology study is a relative risk, it's essentially a slope and what we're doing is standardizing it, because the studies presented for different increments in NO2 and what we've done is standardize to an increment that's sort of high to low range in the ambient air.

But it's, that's the way that you could,

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it's just intended so that if we put them in figures you could see them on a sort of a same scale.

DR. CRAPO: Right, I understand that. And I'm feeling ambivalent about what I'm saying because for the last several years I've been sitting in this chair saying, be concrete, give me, take hard stands, interpret this data, put your neck out and we'll, so we can talk about it. And you've done it, and I'm really proud of you for that, and I like it.

But now I'm wondering if we've stretched the statement on NO2 to the point where it's saying something that we probably can't say. Because when I start translating this down to an absolute risk, in fact I, the lung cancer example is one where I agree with Jon, I think it's related, it's a correlation with air pollution and we don't know what it is, it's a surrogate.

And I have real doubts that you can express this as an odds ratio or as a standardized risk relative to parts per billion of NO2.

And I'm, so I'm concerned as to whether we can do this for many of these studies. And the lung cancer is an example that I think is pretty obvious that we probably can't do it.

But maybe that same logic applies

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throughout this table or through many of the other problems and it's part of the problem we're talking about.

So I particularly wanted Jon's comment about this table. If this is an appropriate to analyze it? Does it compare to all these variable studies? Because I like the idea, I'm curious if I can really use it in this context to create an integration across all these very different study designs.

DR. SAMET: Well to me the major issue is whether you trust the model and I mean that's really the key to this.

And I think that comes in light of what the models can tell you in the sense of how these variables may be correlated and what the potential paths for NO2 to have effects are.

So you could estimate these effects but these may be coming under the wrong model and I think that's where the decision has to made about what are the right model or models. And these are sort of, I mean in a sense these tables apply to causal interpretation.

DR. HATTIS: This is Dale Hattis. Notice that there are distortions that are likely in both directions.

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Just because it goes away, the core of the association might go away if you put it in a multi pollutant model, if the NO2 is poorly measured and some other thing is better measured and correlated with whatever the causal agent is, then, you know, the causal agent still could be NO2 and have this affect of going away with the, in the multi pollutant model analysis.

So that's partly why you need to do what was suggested earlier, is to have a background intellectual discussion of, okay, what are the distortions? How quantitatively important could they be with the amount of distortion of the measurements that we know happens for NO2 from the verticality problem and the other problems of assuming that central state monitors are well predictive of the outdoor contribution to personal exposures?

So I think that's sort of we know there are distortions in both directions that need to be to some extent fairly assessed.

DR. HENDERSON: Okay, I think we'll let George Thurston talk about Charge Question 5, it's also a health question. And maybe we're beginning to get into that area a little anyway.

DR. THURSTON: Okay, yeah. The question

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is, to what extent does the integration of the health evidence focus on the most policy relevant studies or health findings?

And I find when I look at what I wrote down here, a lot of it overlaps with what we've just discussed because I do think these are related questions, very closely.

I mean one of the first points is one that Jon Samet brought up. Well first of all, I guess the answer to the question that I come up with is that, yes, but not well enough. Okay, so, you know, the obvious answer, right?

But the need for a framework of the document, and I'd just reiterate that. It's been said before, I wrote something along those lines in my written comments, but page 5-7 talks about the strength of evidence categories, good, the, you know, those are good. But we need a foundation for that.

And that was also brought up in some of the public comments before we started, you know, that we need to better say what the meaning of these are and their foundation.

And we need to set that out at the front of the document. And I think the best way to do this of course is to start with A.B. Hill's criteria and

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figure them into these categories, the strength of evidence categories and say what we expect for the various levels of certainty.

So that really is something that needs to be done up front and then carried throughout the document, that each time someone writes a section of evaluates a section they'll say, okay, how does this fit into those criteria and, you know, the coherence questions and so on?

And we need to look across disciplined evidence, something we've been discussing about coherence. You know, are the effects, when we look at the toxicology studies and the exposure studies, are the effects on clearance and immune function that are documented, are they consistent with the epidemiology?

And I think that there is some evidence that it is. In other words, who are we seeing affected? The children with asthma. So there is a coherence and I think that needs to be brought out and there needs to be a thematic approach to that where each section is not standing alone, but looking across the document.

And, you know, another point was the susceptibility section that's not well linked to the previous chapter. So someone mentioned maybe we should

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move that in, you know, combine them. But again, the susceptibility question is one that should be thought of all the way through the document and from the beginning to end.

Who is most exposed and what are the effects that might make people susceptible? And then what do the studies indicate who are the susceptible people? And do we see a coherent picture?

We need to look at the results, you know, in terms of the policy relevant studies and using it for policy. We need to look at the results as a function of concentration to be more useful for standard setting.

I mean we have this long table and there's a lot of missing information unfortunately, and maybe there are ways to fill this in in terms of and then rank them and put them in groups, you know, across outcomes in certain categories of concentrations.

You know, instead of doing one category, then the next category by health outcome, maybe we could group them by concentration and of exposures and then look across there.

Now, you know, the 98th percentile, the 99th percentile is, you know, sometimes we've got the maximum, we've got the mean, we have the standard

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deviation, I think they could probably estimate what these things are from the data or we could go to the original authors and ask them if they have that information. Or a lot of these studies use ambient data, most of them.

And so that data, you know, are available so that you could look at the start at the beginning of the study and look at the NOX data and come up with those numbers.

So that could be done to fill that in more so we could better categorize these studies by concentration range, which I think would be more useful for standard setting.

So, you know, as we've said before, we need to focus the results on results for the especially susceptible populations and try and work on that, because ultimately those are the groups that you're trying to protect.

I mentioned before about the PM and NOX interactions so I won't go into that again and others have brought this up, that NOX may be acting by making, you know, by knocking down the defense of the body, let's say clearance of particles and then enhancing particle effects, so there may be a pathway that way.

So that needs to be discussed, how these

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pollutants might be interacting in the body and causing greater effects than they would if there was only one of them.

And just sort of lastly to comment, since I've got the microphone, the discussion about the lack of animal and human exposure, exposures at ambient levels like we have for ozone, well I think it's wonderful we have those studies for ozone, that they've been able to be done and we have them.

But I don't think that's absolutely required. And for example we don't have them for PM, ambient exposures where we can replicate health outcomes in human exposure studies. You know, there's near ambient and there's, you know, the concentrator studies and that kind of thing, but we don't have the direct at ambient concentrations for PM.

So I don't think we should set a higher standard for this than we do for PM and other pollutants.

I do think that they're very important, those studies, to learn about the biological plausibility. And again, if you're doing A.B. Hill's criteria you're going to look and say, okay, we've got this association in epidemiology. Is it biologically plausible? Then we turn to the studies we have

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available.

And I think some of the most important studies that were noted in here in that regard, not in terms of setting the standard, but in terms of deciding whether this is a causal relationship, are the intervention study that was mentioned, the indoor studies are very, I thought informative of that question.

So we don't have the controlled studies and animal studies that everybody loves. We do have those indoor studies and an intervention study that wass mentioned. So I think that's very powerful evidence that needs to be considered.

DR. BALMES: So George?

DR. THURSTON: Yes.

DR. BALMES: It's John Balmes again. I agree with you that we don't have to have a toxicologic study supporting the EPI findings, but you're correct about PM.

But I just think we should acknowledge that up front. You know, I think it's sort of a little bit obfuscated in the document the way it currently is.

So I want' trying to say that before the Agency or before CASAC recommends to the Agency that we have a different standard for NO2 that's based on

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primarily epidemiologic data, that that's wrong to do. That's for us to discuss.

But I do think the acknowledgment that the study, the toxicologic studies are at levels higher than ambient needs to be in the document sort of more clearly.

That's two different things.

DR. HENDERSON: Ed Avol has something to say.

DR. AVOL: Just to follow up on a comment that George made with regard to susceptible sub-populations.

I mean I think it's important for the document to look at and identify susceptible populations and that's fine. But I think we don't want to lose sight of the fact that there's, there are ranges of susceptibility. I mean there are certainly asthmatic children that we're interested in, but for example in lung growth function from the Children's Health Study we don't have any evidence that asthmatic children are losing function any faster than healthy children.

In fact healthy children are losing function, have depressed function as well. And so I think in that sense children are a susceptible

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population.

Similarly there is some talk in the document about genetic susceptibility and if you look at the penetration of GSTM presence or absence in the population, I mean there are significant numbers of people, which may be a different way of saying the same things with regard to normal or healthy or asthmatic sub-populations, there are large portions that are at increased risk.

And so I think that's the issue that needs some gradation or some description and discussion needs to come across in there as well.

DR. HENDERSON: I would like to say I agree with you, George, that the EPI studies that were most impressive for me were those intervention studies in Australia as I recall, where they did them indoors and they had, you know, the stoves were taken in and out and he saw changes in the health effects in the children as I recall.

Those were very impressive because you have less confounding by the other air pollutants.

But I have a question for you. What is the level in animal studies of, the level of NO2 that's required to cause problems with particle clearance? I can't remember, I'm asking because I can't remember

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what those were.
DR. THURSTON: Well that's not my area of research. Terry Gordon, can we put you on the spot here?
DR. GORDON: Yeah, Steve, I'll put you on the spot.
DR. THURSTON: Yeah, this is his question.
DR. KLEEBERGER: You know, I think this gets back to part of the problems with what's out there, is these kinds of studies have not been addressed, or these kinds of questions have not been addressed systematically well enough to answer, or come to a conclusion about that.
DR. HENDERSON: Okay.
DR. KLEEBERGER: I mean if you would ask me that question in mice, I would say well you need to set up a strain screen, so you start looking across of battery of inbred strains in mice until you actually find that there are, and you almost certainly will find that there are differences across a particular species.
DR. LARSON: Rogene, this is Tim Larson again. Can you hear me?
DR. KLEEBERGER: Yep, yep.
DR. HENDERSON: Yep.

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DR. LARSON: I had a question about your statement that there was less confounding in the indoor studies.
I thought a lot about that and when you really get down to the question of what's confounding about the outdoor studies, you know, the other pollutants may have a, I mean may have confounding effects, but they're not that strongly correlated with NO2 to begin with.
Other pollutants which we don't measure outdoors, perhaps are. And the question really is, are those other pollutants, the black carbon, the ultra fines, are they similarly confounded indoors?
I mean I think we might be able to address the question. We don't discuss it in the document, but I agree that's an important set of studies that seem to be key to isolating the NO2 effects in epidemiology. But we're not addressing that particular question of confounding.
DR. CRAPO: I think in terms of the animal studies, my memory is that the animal effects require, for all the various effects require parts per million.
DR. HENDERSON: That's right.
DR. CRAPO: And not parts per billion.

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DR. KLEEBERGER: Yes.
DR. CRAPO: So you're dealing within almost two, three orders of magnitude at higher levels to get acute animal effects that we can measure in small numbers of animals.
DR. KLEEBERGER: If there's a generic animal.
DR. CRAPO: Yeah, but I mean if it's a generic animal but various ones are reported at 1, 2, 3, 4, 5, 10
DR. KLEEBERGER: Right.
DR. CRAPO: at 15 parts per million you are causing acute severe injury in an hour of exposure
DR. HENDERSON: Oh.
DR. CRAPO: with ARDS following that. But then you, but if you get down to one part per million you're starting to lose all your effects that you can measure acutely.
That's what I've read.
DR. HENDERSON: That's what my memory tells me and so I think that lessens our concern about ambient levels of NO2 causing
DR. GORDON: But this is ignoring all short term, one hour max values which

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DR. HENDERSON: Oh sure.
DR. GORDON: can get up to 100
DR. HENDERSON: That's right, yeah.
DR. GORDON: or more ppb in talking about those where the verticality issue or whatever the word is, you know, it could be even higher than 100.
DR. HENDERSON: That's right, it could be higher. If somebody yeah, Mary, what
DR. ROSS: Could I draw your attention to the table on page 5-18, it's a table of toxicology where we tried to draw what appeared to be the lowest concentrations at which some effects were seen. And they're in the order of .2 to .8 parts per million.
So I just welcome any feedback you have on that. It's table 5.5-2. And similarly the page before, 5-17 is a human health studies.
DR. HATTIS: I didn't hear that last
DR. GORDON: Another variable that's important here is the duration of the exposure. Some things can have effects over a longer averaging time than others, depending upon the details of the mechanisms.
DR. CRAPO: One more number when we are thinking about those, I looked it up online to find a couple of papers to get, the exhaled breath NO for all

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us normals today, is usually about, a means of about 6 to 7 parts per billion.

DR. HATTIS: Of NO2?

DR. CRAPO: Of NO, NO, in an asthmatic the exhaled breath NO was about 30.

So you're saying that the I'm not sure that NO is a good surrogate for NO2 because NO is a, in my mind a very good molecule except when it interacts with an oxidant like ozone or a super oxide and becomes converted to another species.

But clearly you have biological productions of NO in your body that are very close to ambient, airborne levels.

DR. HENDERSON: Yeah. Thank you for looking that up. And someone was saying today, was it you, George, that the peroxide who was saying that this could go to NO2?

DR. LARSON: You have to scrub the outdoor air before you exhale just to get a legitimate reading.

DR. POSTLETHWAIT: Of course the problem with NO2 is it's so reactive once formed endogenously. You're likelihood of finding it in expired air is almost zero to none.

But in expired breath condensate they do

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find nitrite which is the first, one electron reduction product of NO2. And in all the studies in AODS and inflammation, et cetera, when you find proteins being nitrated, NO2 is the nitrating species.

And so as James brought up, any of these issues with NO reacting with super oxide, the ultimate oxidant that's formed is NO2. In some cases there's also a thing called a carbonate radical that's also formed.

And so you wonder in asthmatics with underlying inflammation if they've got 30 ppb of NO in expired breath, you know, and they've got resident pnn's with peroxidase activity, I have no clue how much NO2 they're making.

But if they inhale a little NO2 on top of that, is it really going to tip the balance into sort of a new realm of health effect, or would it be sort of like a smoker who is exposing himself to a ton of NO2 and give him a few ppb and expect to see something?

DR. CRAPO: I don't know that, but I've heard that these patients all have enhanced labeling of their lungs of nitrotyrosine

DR. POSTLETHWAIT: Right.

DR. CRAPO: so there's a lot of

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nitrated proteins in the lungs of people with inflammation.

DR. POSTLETHWAIT: Absolutely.

DR. HENDERSON: Well you can argue that two ways and I've heard it argued both ways.

If there's an endogenous source, some people will say, well, a little bit more won't hurt. And others will say, oh, but it does, it's building on an already, you know, bad situation.

And so you have to think of it both ways I think.

James, you oh no, Steve Kleeberger, you haven't had a chance. Steve, do you have some comments you'd like to make?

DR. KLEEBERGER: I was just actually doing a pub med search on something here, but hand on a second.

So I will echo comments from George in that I think the integration in terms of reflecting health effects is there, but it's probably not very good at this point. And certainly greater, at least in reading the document, I think greater attention made to efforts regarding the integration are going to be necessary and helpful.

I focused mostly on the susceptibility

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of the chapter, Chapter 4, largely because that's what I'm most comfortable with.

And my feeling is that the document I think actually discussed the existing literature, but as I had mentioned earlier I think what is a critical issue is the darth (sic) of, or the dearth of information to help us make any meaningful sense of the data that are actually out there in terms of reproducibility and systematically looking at specific susceptibility facts that could be considered in terms of our recommendations.

And so it made it a little bit difficult for me to make any real conclusions about the effects of genetic background for instance as Ed brought up, and gender which I don't think was addressed, and preexisting disease.

One point that I also wanted to raise about the document per se is that, I think it was on page 4-12 where there was an estimation of the number of asthmatics and the number of I forget what the other population was oh, heart disease, I'm not sure how meaningful that particular section of Chapter 4 is. And I'm not entirely sure what it relates to.

In fact what they're saying is that, you know, we have a large and growing population of

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asthmatics, we have a large and growing population of individuals with heart disease, but that doesn't necessarily mean that these people are all going to be susceptible to the effects of air pollution, let alone NO or NO2.

In fact there is considerable variability among asthmatics in terms of their response to air pollutants like ozone. And to make a blanket statement that asthmatics as a whole are going to be susceptible or more susceptible than a healthy individual is probably not true.

And so I think we have to be careful in terms of describing or categorizing individuals with preexisting disease as extraordinarily susceptible.

DR. COTE: Just a point of clarification on the table. The implication wasn't that all those people would be affected. It was just trying to get a handle on the potential at risk population.

If you're following up on what George was saying, I think that these kind of disease states would put people at some potential increased risk.

DR. KLEEBERGER: Well they could, they could be. But I'm just saying it has to be

DR. COTE: I think the language that needs to be clear.

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DR. KLEEBERGER: more clear, yeah, yeah. And I have a number of other minor comments but I can, I'll have that in my written, it's in my written document.

DR. HENDERSON: Okay. Thank you. Let's look at Charge Question 6, which is really what we've been discussing.

What are the views of the panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of NO2 related health effects?

And I had asked James to talk about that.

DR. CRAPO: Yeah, and I've already said a lot of what I think on this and I'm trying to I'm really on the fence, do I really go on the bandwagon to lower the NOX level dramatically? Or do we say this needs to be revised in terms of what we've said?

But the way this document's written it scientifically mandates that we do everything we can to lower the NO levels and the NOX levels in the United States.

And so I'm on the fence trying to have my own recommendation on that on which way to go.

But let's assume that I accept, I want

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to start, let's assume that I accept the fundamental conclusions here, because I do see a lot of coherence of findings when you analyze them in the way that they're done, a lot of coherence from human epidemiology studies, field studies or multiple groups all around the world looking at multiple endpoint, hospital admissions, ER admissions, asthma, COPD, exacerbations of a cough, of other asthma symptoms, of decreased lung growth and development and cancer as we've mentioned, all with powerful correlations in the form in which they're analyzed today.

And I've already said that I have concerns that we have a confounding issue going on and we might be, I don't know whether to lower the PM level or lower the NOX level.

But I think we're talking about a very real effect. Better epidemiology and better analyses of all these various groups are finding that there is a profound effect. And I'm on the fence as to whether I attribute this to NOX or not, I want to put that on the table. Maybe by the end of this two days I'll have a strong opinion on that one.

The, but if we assume that this is correct, then I have several concerns about the document that I think need to be done, because my

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question would be, how should I lower the standard? And how should I affect the standard? What should the form of the standard be?

And I find that the document doesn't inform me adequately to start to make the next decision.

If I assume that the conclusion is correct, then I want to know, I want to have a dose response that tells me about what's going on at the ambient level when I know that I can't drop the levels 20 ppb since I'm starting out at 15, and it looks to me like we really, we don't have a very good discussion of the threshold. And again I think your answer is going to be, we don't have good data on threshold and we can't, we can detect effects that appear to be going towards zero.

But we really need a discussion of that because if you, as soon as you accept any of the fundamental conclusions of this document, the one that you mentioned, the last sentences on page, on Section 5, of our conclusion that if it stands will man to me, would mandate action on it.

So I think I'd to see the document worked again about to tell me how to do that action and I'd like to analyze the threshold, I'd like to analyze

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the lower limits to it, I'd like to look at the peak effects and I'd like to have some data that helps me to analyze that.

I mean can I get the benefit by just decreasing the peaks and excursions? And should it be a and then I need to begin to ask whether it should be a daily standard or an annual standard and should it have a certain number of excursions in it and does it make a difference on what those are?

So those are all the kinds of questions that were discussed in detail on ozone and PM that are not here.

And I think that's the in fact that needs to be looked, even if we decide that this is a surrogate for something else. We need to begin to understand that set of data to go with it.

The and I think I've said everything else already.

DR. HENDERSON: Okay. I'm wondering, when can expect, I mean several people have mentioned that we're missing any discussion of the form and averaging time, et cetera.

Is that something that will come tomorrow in the exposure risk assessment document? Or are we expecting too much of the ISA?

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DR. ROSS: The science assistant has never been in the past intended to answer those questions, to say this is what the form should be.

We are attempting to organize the information about short term exposures and long term exposures, that then could be interpreted by others and, you know, and we look at ways we could do that better. To better characterize the 24 hour, one hour and the tox studies with all kinds of exposure levels.

But we'll try to organize that as well as we can. And we'll discuss the levels at which effects are seen and to the extent possible in our EPI studies it's often a range of air at the distribution of air quality and not a level.

But we have not, we were not striving for the integrated assessment, science assessment to have a specific recommendation. That is usually targeted for the ANPR, the Advance Notice of Proposed Rule Making, where the Agency would be looking at the science assessment and the risk and exposure assessment and then making those recommendations.

But we would like to organize the information in a way that can inform those decisions.

DR. CRAPO: Yeah, that's what I was looking for because I was sitting here saying, well,

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let me accept this data, what should I do with it now?

And I discovered that I really couldn't, I couldn't find the information I needed to sit here and say, I'd recommend you drop it to .1, or no, 10 ppb, and these are the reasons why.

And I would need a scientific reason for doing that and I couldn't find it. I also asked myself if there's any evidence of a lower threshold and I so those are the kinds of things that I don't think you ought to make the conclusion, but I would like to see the data organized so it could tell me there is or there is not data to help me make that decision.

DR. COTE: Maybe this section needs to be expanded, but I think there's only a few studies that specifically tried to look for a threshold. You know, that's generally not a very successful kind of approach with EPI.

So I think you would have to rely on something like modeling. You know, the LOTUS extrapolation modeling, my understanding is if you're adding to some sort of background process it's generally considered to be linear.

DR. CRAPO: Well I wouldn't be surprised if your answer was, we looked at all these factors and we can't do it. I would accept that, but I want to

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hear you tried.

DR. COTE: Okay. Yeah, in fact I think we went through that thought process in house but we probably haven't articulated it in the document as clearly as we need to.

If it makes you feel any better, we had those same discussions about, is it yes, is it no, is it yes, is it no? And decided because it was easier for you to respond to that we would present the information kind of going out on a limb, but I guess

DR. CRAPO: And I want to, I really like the way you've presented it because you reached out and took a position and that's, I compliment you, this is a very much more productive discussion than the kinds we were having before where we were struggling with what to do with the data.

DR. HENDERSON: So that's good. Now Ed, you were on the same charge question. Did you have something to add?

DR. AVOL: Yeah, I do but Jon Samet is --

DR. HENDERSON: Well I was letting him, I was going to bring him in at the end --

DR. AVOL: Okay.

DR. HENDERSON: so he could give the final word.

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DR. AVOL: Okay, that's fine.
DR. HENDERSON: So Jon, prepare yourself, after Ed it's
DR. SAMET: Yes, okay.
DR. HENDERSON: your turn.
DR. SAMET: Okay.
DR. AVOL: Okay, that's fine. Well I also, I mean I think a lot of this we've already talked about in the context of the earlier discussion and questions.
Looking at this I did sort of get the sense as Jim Crapo did, that sure, this preponderance of evidence is there that sort of makes you lean in one direction.
But I think it is a fair comment that was brought up earlier this morning in public comment, that we need to, in the document we need to be sort of more an objective discussion and layout of what the decision tree is for getting to why something is convincing or suggestive or not. So that by the time you get to the conclusion section there's a clear and transparent process and it doesn't just sort of come at you from nowhere.
I mean I think if we were to do that, some of these, there may well be some readjustment of

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the words that have been used in some of the earlier chapters.
I think I gave a number of specific comments about form and substance in the written comments so I won't go through those now. You can read those.
I think again though in terms of the strength, consistency, coherence and plausibility, I think the information is there and the information is there but it hasn't, it hasn't been so compelling that I'm convinced that all those four pieces are there yet.
DR. COTE: I think some definitions would be very useful. We actually went through I have on my desk a sheet of paper that has the Rosetta Stones and all of that and we tried to, we tried to read the document to make sure it was consistent, but we can be more explicit about
DR. AVOL: Okay. That would help. And again I think, you know, a big issue throughout all this is this notion of multi pollutants and confounding the inter-correlation and the relationship of NOX with other species, particularly, or especially particulates.
And so I think it's something that, it's sort of the elephant in the room that we sort of, it's

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not brought out in broad discussion here but it really is a big issue in terms of being able to tease out and uncouple how important is, or will the public's health be protected by a NOX reduction as opposed to identifying it and relating it to something else.
DR. HENDERSON: Thank you, Ed. Jon Samet.
DR. SAMET: Yeah, I'll make a couple of comments. So I guess I'll interpret this charge question in two ways.
So one is, does the draft ISA established strength, consistency, coherence and plausibility as a document?
And there I think my answer is, no. And I will say that just looking at Chapter 5 which should be really, I think where that final bringing it together should be accomplished and I think it's just really weak in doing so.
And, you know, just for example at the bottom of page 5-15 there is a sentence that basically says, integrating across all the data, there is plausibility, consistency and so on. But it's not, the document is not really does the job let's the way that a Surgeon General's report or other kinds of public health related reviews would do.

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So I mean I think as a document I don't think that those four features of the evidence are established. And that is regardless of what the evidence shows. As a document itself this is a failing of the way the information is brought together and discussed.
And again I would urge the office to consider the kinds of discussions that are in other models.
So then it comes back to the question of, you know, what do I or we think the evidence shows? And I think when I look at it I go through some of the same sort of agonizing that you've heard already from James and others.
And I think that I don't have a personal bottom line yet on whether the sort of strength, consistency, coherence and plausibility are met. I think if strength means strength of associations and that's the usual way that word is used, I would not really expect there to be particularly strong associations at ambient or near ambient levels. I would actually look to rather weak associations as far more plausible than strong associations.
So I'm not strength, what is even meant by the strength criteria here. I would not

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characterize the epidemiological associations as strong either for NOX or for PM for that matter. They're statistically significant and they're plausible.

And there is consistency in let's say among studies.

Coherence and plausibility are pretty close cousins so I'm not sure exactly what the distinction is.

And so when you look at the body of evidence, and again how the discussion should line up is, in terms of plausibility, what do we have from the toxicologic studies? And I think here the dose question just has to come in. And again most of the toxicology is showing effects at exposures, you know, at the some hundreds of ppb and up.

There is the question of I think what is the signal from the indoor studies where there's not NO2 as present in a different mixture from what you see outdoors, so I think that's a very useful body of evidence.

And I think again there, there is some indication of effects in some of the studies, but not all and I think there is I think more convincing evidence in the experimental study.

And then the outdoor work is just very,

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very difficult to interpret. And I think, and this is a major problem beyond these sort of technical concerns I've raised about model interpretation, I think the issue of publication bias has to be considered here because there are, for example in the time series studies there have just been so many done.

And I think there's been such an emphasis on PM in '03 that we've only seen perhaps a tendency to report the more positive effects for NO2, and not all. And that's where the multi city studies, which are emphasized are most important.

So I think there's two issues that need to get sorted out.

One is the document's handling of these points where I think it's failed right now.

And then there's, actually what does the evidence, what does the evidence show?

And I think strength probably comes off the table in interpreting the epidemiological studies I believe.

So those are my comments.

DR. HENDERSON: Thank you, Jon, and thank you for calling in.

Are there other comments now about the health charge questions, that's Charge Questions 4, 5

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and 6, about any of them that we haven't discussed that people want to bring up?

If not I well I see one, Donna.

DR. KENSKI: Well this is not exactly a question but an observation I guess, and it's built on what Steven had to say about, you know, suggestions for, you know, studies that we need to see.

But what would be helpful I think in this document is some kind of sort of assessment of what we're missing. You know, sort of limitations of the current data would be really helpful.

DR. HENDERSON: It sounds like a good idea. Mary, do you usually do that, have limitations? I think you have in the past had limitations of current data.

DR. ROSS: We have often followed a criteria document with a research needs document, which was a formal process involving a workshop that followed the production of a criteria document.

So research needs to be identified in a process through meetings like this and then it would be a separate document.

We haven't always had, we, I don't think we've usually had separate sections on research needs. At times in a particular issue a limitation will be

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it wasn't a comprehensive search for a research needs but it might be identified on a case by case basis in a specific area.

DR. KENSKI: So is that something we should make reference to in our comments so that you could, you know, incorporate that?

DR. HENDERSON: I think you need to talk into your mike, Donna

MR. DOLAN: Oh.

DR. HENDERSON: because I couldn't hear what you were saying.

DR. KENSKI: Oh, sorry, I was just saying, is that something we should incorporate in our comments then?

DR. HENDERSON: Sure, we could

DR. KENSKI: Rather than asking you to do it.

DR. HENDERSON: we can incorporate those ideas in our letter.

I suggest if there are no more questions, I want to remind people that if your name is underlined, I'm expecting you to summarize the group's thoughts on these charge questions so that and to get that summary to Angela who is going to combine it so that hopefully we can agree or agree not to agree on

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what we want to send to, what message we want to send to the Administrator.

But let's take a fifteen minute break. What time is it? 2:30, so 2:45, come back and we'll finish up Charge Questions 7 and 8 and discuss our, try to summarize what the main issues are.

(WHEREUPON, there was a recess).

DR. HENDERSON: During the break I have asked Karen Martin who is from the Air Office and responsible for the next part of this review process, that is pulling together the endpoint of the exposure risk assessment document and then the what is that horrible acronym, ANPR.

And I thought it would be really helpful if she just spent a few minutes reviewing where we are in the process and the decisions that we need to make today and the advice that the Air Office really needs to help them in how they write their document.

And so I've asked Karen where is Karen?

DR. MARTIN: Okay.

DR. HENDERSON: Okay, you can use that mike. Go ahead.

DR. MARTIN: Since your conversation did clearly stray into the, let's get to the end game of

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what the standards ought to be, it seemed appropriate just to take a step back and revisit the question about the purpose of this document, the purpose of other documents, and how we in the end pull this all together.

And for some of you I'm sure we've been through this before, but for others perhaps not and it seemed worth saying a few words on this point.

The discussion of the Integrative Science Assessment, I think we all recognize that science and the interpretation of the science and getting that interpretation clear and correct is absolutely central and critical to reviewing the standards.

But I think we also all know that it is not definitive of the standard, it doesn't define a standard in and of itself.

The science will never tell us alone exactly what the standards ought to be, and that's why we do other things. That's why we do quantitative exposure and risk assessments and why we do what we generally refer to as a policy assessment, which is bringing in broader policy considerations like what does it mean to protect public health with an adequate margin of safety? How do we give meaning to those

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words? How do we assess the importance of difference choices for elements of the standard when there is no clear cut one way that's the right way?

You know, different forms of a standard matched up with different levels may get you the same degree of health protection.

And all those considerations are part of the broader policy assessment that we've historically pulled together in the staff papers that we used to produce.

And now that we have a new process that isn't going to have a staff paper in it, you all are going to have to wait a little bit longer before seeing how the Agency will pull together the science in the Integrative Science Assessment and the quantitative results from exposure and risk assessments and these broader policy considerations, how the Agency thinks it's appropriate to pull those together to array a range of standards that are appropriate to consider for reaching final decisions here.

And I think it's important to recognize that just as Mary was saying earlier, while the Integrative Science Assessment can go a long way to help informing those judgements, it can't and doesn't, attempt to in the end, try to array the science

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information in a way that creates the bottom line answer to the question of what should the standard be.

And so I think that it's important that we not try to get ahead of where we are. Where we are right is one, trying to get the science document, you know, to strengthen it as much as it needs to be. But also in this early stage, to try to get advice from you as to how we can take the next steps, which is to do the quantitative exposure and risk assessment.

And that's of course going to be the discussion that we have tomorrow. But even tomorrow's discussion isn't going to be about, and therefore what is the right standard? It's still going to be just one of the building blocks that it takes to get there.

But in your discussion today in terms of the information in the science assessment, to the extent that you can help identify, even if you don't have clear bottom line conclusions about the strength of the evidence for different health effects, the where you come out with regard to likely causality or in that spectrum of conclusions or inferences that you might reach, having some initial feedback from you will be helpful because as you well know our next steps are going to be to make judgements about how to structure and conduct quantitative exposure and risk assessments.

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We don't want to be about the business of estimating risks for non-causal relationships. And yet we also realize that we have to start doing that work before there are, you know, bottom line conclusions from the final Integrative Science Assessment.

So to the extent that you can share your initial thinking at this point of information in the first draft Integrative Science Assessment and preliminary inferences you might draw from that that would help us, both in the discussion tomorrow and in the days following tomorrow when we need to go back and start doing those assessments, that would be very useful.

But I think we all, it would behoove us all to be patient in terms of trying to jump ahead to bottom line judgements about elements of the standard, because in the end of course that's going to be informed by, centrally by the science, but also by a lot more information than just the science.

DR. HENDERSON: Does anybody have questions for Karen? Are there any questions?

DR. HATTIS: I imagine it still would be helpful for you if we were to be able to come to conclusions about what the relevant averaging time

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would be for the causal processes.

DR. MARTIN: It would be, it's

DR. HATTIS: If there were some causal process.

DR. MARTIN: extremely useful to understand what exposure durations are linked with what health endpoints.

DR. HATTIS: Right.

DR. MARTIN: In the end of course the averaging time for a standard might not necessarily be exactly the same as any one of those averaging times.

DR. HATTIS: Sure.

DR. MARTIN: But, yeah.

DR. HENDERSON: Another thing that Karen said was, you know, it's helpful to her and to the Air Office, for us to discuss whether we, what we think about for instance this cancer study.

Is that something that, you know, that we think NO2 is causing cancer? Which, you know, we've already discussed that, but that's the sort of thing that would be helpful for Karen.

Thank you so much, Karen.

Okay, so we don't really have to decide everything today which is a relief you might say.

But let's go on to Charge Questions 7

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and 8. I know we've already talked some about Charge Question 7, but Ed Postlethwait, do you want to begin?

DR. POSTLETHWAIT: Sure. Let me preface my comments by saying that I actually struggled somewhat with this because I thought that listening to the discussions preceding this would be helpful for us to try to focus in on a specific issue of identifying susceptible populations.

One of the things I noticed in reading specific, in Chapter 4 specifically, was that at least the impression I derived was that many of the identified populations were almost more intuitive relative to being sort of quantifiable.

I mean we all think of kids, people with asthma, preexisting cardiovascular disease, et cetera, as being susceptible to whatever kind of environment insult you want. And so those were primarily the folks that were identified in this.

What I thought was somewhat lacking in here relative to the charge was whether or not we needed to quantify the specific public health impacts. And I mean, you know, the charge is to come to a consensus on the appropriateness of the public health impacts and characterizations of groups likely to be susceptible. But I mean is a public impact an NOI or

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an NO, whatever?

And so again I thought that was potentially up for discussion.

I liked the inclusion of the ATS criteria for defining what a health effect was. And I really thought that it would be useful to put that portion of the chapter up front to then be able to sort of flow from there across the various groups and then define back to them as has been done to some extent, where they fall in that spectrum of those criteria.

There were a couple of the table at the end about what would be moderate, severe, et cetera, the way it was presented I didn't find those particularly useful because there was no specificity to outcomes from either experimental or population based studies.

There was an interesting component written up front, it's on page 4-8, about the genetic factors. And I point this out, I'm actually going to read from here because it's very clearly defined. The document reads, first the product of the candidate gene must be specifically involved in the pathogenesis of the adverse affect of interest, often a complex trade with one of determinants. Second, polymorphisms in the gene must produce a functional change in either the

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protein product or in another expression of the protein. Third, in epidemiological studies the issue of confounding by other environmental exposures must be carefully considered.

Those are pretty well defined criteria that one subset of the aspect of this whole document that I didn't see anything anywhere near as robust as that applied to analysis of the other studies across the document.

Now that may be a reflection of our understanding of genetics and polymorphisms and potential effects, but that was pretty hardcore biology if you will, relative to let's take some measurements and see what happens kind of thing.

And so whether you want to set the bar at something like that or you want to remove that bar, that's sort of not for me to say.

But the other thing I found about the issue of susceptible populations was the and this got brought up early in the issue of dosimetry was whether or not the intrapulmonary distribution of NO2 relative to the anatomic site of disease should have been included as part of the analysis.

And then I guess my last sort of general comment was, as throughout the document there were no,

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there was no integration among the disease states, measured outcomes, exposure and importantly, the potential mechanisms of action that would relate NO2 exposure to why this group would be a susceptible population.

It was pretty open ended. And maybe that information doesn't exist, but I think even potential mechanisms would help strengthen it.

Other than that, you know, the information, it was essentially presented before in other aspects of the chapter and so I guess I'll withhold any other comments until I hear the rest.

DR. HENDERSON: Okay. Jim Ultman, are you on?

DR. ULTMAN: Yes, can you hear me okay?

DR. HENDERSON: Yeah, but we always could do better if you'd talk a little louder.

DR. ULTMAN: All right, I'll give it a shot. I agree with the comments that Ed made. This is a fairly qualitative chapter. And it includes useful information on asthmatic elderly and children as the subgroups which I think have traditionally been the ones that EPA has focused on with NO2 and for which there is new information available since the last review.

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I guess the main thing that I've focused on or I noticed was the new lung growth studies that have come out in the California Children's Health Study.

And that was probably the, for me at least was the biggest red flag that went up in terms of protecting susceptible populations.

What's not present in the chapter though, at least that I can dig out, was at what level these kinds of effects can be seen, what was the exposure history of these children? And how did that compare to the current standard?

But I think in terms of the risk assessment document that's definitely I think a group that should be focused on. Asthmatics too, there's been new information that has come out having to do with hyperre enhanced hyperreactivity by NO2 and infection, more susceptibility to infection.

So I think that's also a group, a subgroup to be focused on. Probably in my way of thinking though I would put more weight on the children.

The elderly, I think the results on the effect of age, elderly versus say middle aged or young adults, that's kind of mixed and I'm not, it appears as

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if that's not a sub-population. It really would require much more emphasis.

So I think that the, basically the information is here in terms of pointing out the new information that's available to perform the risk assessment. But the same comment I made in one of the other chapters was that there's not any real context for this in terms of the current standard.

So I still can't tell whether the effects that are being seen in children and asthmatics are at or below or above the current standard. So that perspective is still missing from the chapter. It would be nice if that could be put in somewhere. And of course we also measure it.

We mentioned before, and Ed brought it up again, the question of dosimetry and whether an equivalent dose of NO2 in children at a given exposure concentration would be the same as in adults. And I know there is some information that's come out on ozone in that regard recently. I'm not sure if there's anything on NO2, but presumably the authors have looked at the literature for that. If they haven't they should, you know, go back and see if they can put some information in this particular chapter on the affect of these, the differences in the sub-populations,

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particularly the children because of their size, on the affect of the dose that they're getting relative to an adult.

And that's it.

DR. HENDERSON: Okay, thanks, Jim. Are there any other people who want to make comments. There's Ed.

DR. AVOL: Yes, this is Ed Avol. I've thought a little bit about the susceptibility issue and have a suggestion that may be worth considering for the staff.

And that is the following. Does it make any sense, does this idea have some merit to consider susceptibility in the context of the following categories?

You might think about biological susceptibility which would include the sorts of things we've been talking about, either disease or age or children or these sorts of things.

You might think about socioeconomic susceptibility which would have things like a lower SES, stress, violence. I know there's been a little bit of work in that area and some of which is reported here.

And then you might think about

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locational susceptibility which is also talked about here to some extent. And these are things like in-vehicle exposures, living close to roadways.

And wether thinking about it in those sort of terms helps to clarify and identify in some logical framework, who and how large those susceptible sub-populations might be.

DR. HENDERSON: Thank you, Ed. And Steve, I know you made comments on this chapter before. Did you have anything you wanted to add?

DR. KLEEBERGER: No, not really. I think in terms of what Ed has just suggested I think is a great idea. I know I remember reading I think in this document, attempts to sort of subdivide into perhaps intrinsic and extrinsic or internal and external factors of susceptibility.

But I think helping to categorize or in some way compartmentalize the different ways we might look at susceptibility might be an appropriate move.

The, I guess I would also like to make a, maybe this is a plug, but a statement that in terms of susceptibility and genetics, I think the section in the document in Chapter 4 was actually very nicely written and indicates there is great potential in terms of genetics and genomics for helping us understand

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susceptibility, biologic susceptibility if you will, to NO and NOX.

And that the studies up to this point are really a little bit like sort of looking under a light post. You know, we're taking those genes that we think are going to be important without actually the question about what genes should be important or taking a much more systematic sort of evaluation of genetic susceptibility and what it means in terms of the criteria document and setting the standards.

I guess that gets more into the recommendations that I was suggesting before.

DR. HENDERSON: Ed.

DR. AVOL: It's Ed Avol, just one more comment in answer to Jim Ultman's question about the levels of exposure in the Children's Health Study with regard to NO2 and lung function and whether those are above or below the standards.

In fact those are below the current standard.

DR. HENDERSON: Okay, that's important to know. Yes, Terry.

DR. GORDON: I still want to bring my earlier point and wonder what's the justification for having a separate chapter?

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Are you going to leave out the children or the aged from the earlier chapter on the health effects and just include them here? Or are you going to repeat it?

I'm just not sure.

DR. HENDERSON: We can ask well

DR. COTE: The actual intent of that was to bring it out and highlight it as being more important. It doesn't exactly sound like that was a successful strategy. So we might consider integrating it back into Chapter 3.

DR. GORDON: Well having it separate and bringing it out sounds okay too. It just would need more of it.

DR. HENDERSON: Yeah, I interpreted it as trying to emphasize.

DR. COTE: Is it worth a different chapter to do it that way or does it achieve the desired effect to have a separate chapter?

DR. POSTLETHWAIT: To follow Ed's suggestion about the level of categorization, and I think it is useful because it puts into context the various aspects of the genesis of susceptibility, whether it's geographic locale or underlying genetic polymorphisms or whatever, that the broad spectrum of

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sort of the 30,000 foot view in Chapter 3 won't address.

So a tweak and tighten up and I think actually it is useful as a standalone.

DR. KLEEBERGER: I do too. I think there's a danger if we include it.

I appreciate your point, I think it's a difficult separation. But if you don't separate it I think you run the risk or the danger of having it covered or embedded so far in that it's not going to be, the point isn't going to be made that susceptibility is an important issue to consider.

DR. GORDON: Overall I agree that it should be separate showing special emphasis. I guess part of, I tend to think that susceptibility as I assume you do, is physiologic or genetic.

And so I'm sort of surprised that susceptible to me doesn't necessarily mean those who live in traffic areas. It's just one part of the continuum or exposure.

And I guess that's the part that I really thought was an odd choice for susceptibility.

DR. POSTLETHWAIT: It's a high exposure category.

DR. HENDERSON: Yeah, it's higher

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exposure.

DR. ULTMAN: Yeah, I forgot to mention when I was speaking, I agree with that, that section on high exposure groups belongs in the exposure chapter, not here.

It's really just a question of exposure, not a question of

DR. POSTLETHWAIT: And Jim, would you say that again and try to scream it into your cell phone.

DR. COTE: I think he's on the other line. I think what he said was that the high exposure assessment belonged in the exposure chapter.

And it's kind of one of those discussions, if that belongs in the exposure chapter, then the health stuff may belong in the health chapter.

So it's six of one and a half dozen of the other.

DR. HENDERSON: Yeah, there was some in the Chapter 2 that was health.

DR. COTE: You know, I put that in because I was, I thought the traffic related things that were raised there, I was afraid if you waited until the end of several chapters later that it at that point wouldn't be clear.

I took that section and moved it back

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and forth to figure out where I liked it and then finally left it in 2.

DR. HENDERSON: Well some of that is, I thought was the best causal data you had for NO2 because it was indoors and through a controlled study, et cetera.

From my viewpoint it would beef up the health chapter to have it in there, but we're talking editorial things here.

George?

DR. THURSTON: Yeah, George Thurston. Yeah, I think looking at it I like the idea of having a separate chapter. But I think also the point that Ed was making was, at least as I took it, about the lung function is you see the effects in the kids with asthma. You also see it in the kids not having asthma, so we shouldn't forget those.

I think it's important when you're talking susceptible populations to make sure people don't suddenly think, oh, well then everybody else is not susceptible, which would be wrong.

And so I think we have to make sure to always sort of I think maybe an introductory discussion, well you know, a sentence or two or a paragraph saying that everyone is affected, it's a

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question of the degree to which those affects have health implications.

I would say that a child who has asthma, if they're getting the same lung function reduction as a healthy child, it likely has more of a health implication because they're starting out with reduced lung function and then they're going to have an asthma attack or, you know, on top of that.

So they have the same lung function effect perhaps, but the health implications of those effects are greater and I think that's true with many susceptible populations, that they just can't cope with the effect, as well with the effects that we all get.

So we don't want to forget that we're sort of all in this together and these are just the especially susceptible that we're focusing on. And, because you might be left with the impression that this is a very small number of people that we're talking about, you know.

And I don't know what the number is, you're going to probably come up with some estimates.

DR. COTE: Well that was why I had actually put that table in there about the number of

DR. THURSTON: Yeah.

DR. COTE: asthmatics.

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DR. THURSTON: Right.
DR. COTE: It's not that they're all susceptible. Were you speaking about air pollution in general, George, or NOX specifically when you were
DR. THURSTON: Well I would say, you know, probably air pollution in general but
DR. COTE: I just wanted to pin you down.
DR. THURSTON: But I think that it applies across the board. You know, the concept of that the effects, you know, how we define susceptible and especially, oh, I would say especially susceptible populations, rather than just susceptible.
And a couple of other comments on it was I liked to, I would think about using attributable risks in the discussion, because if you just compare relative risks, sometimes you can take different populations and they can have fairly similar relative risks, but one has such a much higher baseline that you're talking about many more adverse health outcomes.
DR. COTE: Yes.
DR. THURSTON: If you have twice the number of hospital admissions let's say in one group versus another, and you have the same percentage increase, that's many more per 100,000.
And so maybe it's worthwhile trying to

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work in that concept when you're looking at these susceptible populations. And, you know, ultimately you're going to look at counts of effects and that attributable or absolute attributable risk is a concept that I think helps clarify. Because you can look at relative risks and say, gee, these aren't that, you know, let's say, you know, if you have a certain percentage death increase in older people which, older adults which I prefer to, versus elderly, I'm getting too close, I don't like that elderly term, but anyway that's semantics, then if you look at it that way, you know, you could say, well, you know, a 10% increase. But there's a lot of older adults who are dying, and that's a much bigger number than younger adults.
And then lastly, also, each of these is looked at independently, these susceptible populations as you go through. You know, children, people with asthma, people living in and I alluded to this earlier but I'll just repeat it, that I think you have to look, what's the intersection of these? Because I do think there's a population that is a big chunk of these especially susceptible people that have all of these.
In other words they belong to more than one category. And I think that's worth looking at.

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Just not looking at them independently, but also saying, you know, is there overlap and is that population and, you know, I think you'll end up with saying that kids with asthma in inner cities are going to be an extremely susceptible population when you're done with that.
DR. HENDERSON: Okay, thank you, George. I'd like to go on to the final charge question which is the be all and end all. I mean it really covers the whole question and while we have two lead discussants, everyone should chime in after they're through.
The question is, what are the panel's views on the adequacy of this first external review draft ISA to provide support for future risk exposure and policy assessments?
In other words, is this document going to help Karen Martin and her group go to the next level?
And so I have asked Doug Crawford-Brown to lead off.
DR. CRAWFORD-BROWN: Well there are a lot of issues with this chapter. I'll sort of summarize them relatively quickly.
I was looking for the analogy here on this and it's sort of like going into a car dealership

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to buy a car and the dealer gives you a pile of ore and a bolt of cloth. And I sort of felt, well, could you assemble it a little?
It gets you a pretty good Deux Chevaux by the way, but that's not anything you'll drive outside of France. And I say that as a former Deux Chevaux owner. A lover of Deux Chevaux.
I think I mean part of the issue that gets raised here is sort of the working of the charge which is, on this first external review draft, can this first external review draft provide support for future risk and so forth?
And, well, if you ask, can the whole report provide the support? That's a different question than, does Chapter 5 take all of the material from the earlier chapters, abstract it, summarize it and make it ready for consumption as a vehicle?
And on that latter question I would say, no, I don't think so right now. I find a lot more in the report as a whole than I find in Chapter 5.
And now I know that Karen is right about the fact that we aren't drawing conclusions here about specific risk estimates or what the form should be and so forth, but it is an integrated assessment. And I don't know what the word integrated means outside of

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specific questions that you're trying to address.
And it seems to me that those questions are, eventually, not in this document but eventually are, what is the incidence of disease in the population of the United States at different levels? What should be the form? What should be the level in the statute and so on?
And I just don't think Chapter 5 gets you there yet. I think if you tore Chapter 5 loose from the rest of the document you just couldn't use what's in Chapter 5 to answer any questions that I think lie at the heart of what we mean by an integrated assessment.
Now, part of the problem arises from the fact that I don't think Chapter 5, the bullets in Chapter 5, are in fact that most relevant bullets that you would get from the earlier chapters. I'm not sure if the people who wrote the earlier chapters got to be the nominators for the bullets that go into Chapter 5. Of if somebody who wrote Chapter 5 just went in and decided what they thought, you know, Chapter 2's major points were and so forth.
I didn't get a sense of the latter very much. I mean I got a sense more of the latter than of the former here.

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So you have the problem that I'm not sure the bullets in Chapter 5 reflect the most important parts of the earlier chapters. And then I'm not sure how you bring the bullets together in Chapter 5 to be able to address any of these questions that I think ultimately someone using the chapter is going to want to address.
Having said that I like the way in which the sort of strength of evidence was at least discussed in there. I like the categorization scheme and that's exactly the kind of integration that you would want to see in something like this. I'm not sure it was applied very formally, I'm not sure how anybody who made the judgement that it's suggestive or strongly causal or something like this, made that judgement because thee is no architecture of thought in here. There's no, there's no sort of framework that's given.
But I think the main issue, and I'll let Dale really touch on some more concrete points here, I think the main issue has to do with the fact that Chapter 5 doesn't point the reader towards any specific questions that are going to eventually have to be addressed by the risk assessment side and by our CASAC at some point in time here.
So Dale, do you want to hit some more

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concrete points?
DR. HATTIS: I tend to agree with that, that essentially, you know, Chapter 5 and to some extent the earlier chapters bring together like data of, data of particular study types and give a survey of them.
And they tend not to do an overall uncertainty weighted inference from the data of particular types.
And in particular what would be needed for the next step is to make some inference of, you know, not only is there likely a causal connection here, but what do the data say about concentration response relationships?
And I'm going to pick on one in particular where, just so that no good deed goes unpunished, is the data from the Von Strem study which is a study of indoor exposures to NO2, measured on time in one year olds or in babies within the first year of life, usually between the second and fourth month of life, and asking the parents repeatedly independent of knowing what the exposure was, whether they had persistent, how often they had persistent cough and wheeze and a couple of other respiratory symptoms.
And basically then they went on to

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divide the group into four quartiles and the figure 2.7-3 shows a plot of these quartile data. And I had a very detailed suggestion to re-plot the data according to basically the, as is usual the exposures of the individual subjects were lognormal approximately.
And so that when you plot quartiles as if they are equidistant from each other, you're essentially plotting things on a log x axis, and that's know to create distortions of a particular kind in ways that tend to make you see thresholds when they aren't there. When even if you had a nice linear relationship, it would appear to be an upward turning curve.
You don't in fact see that in the quartile, they're there, but I felt it would still be more revealing to re-plot the data, estimating means within, mean exposures within the quartiles and see what the concentration response looks like from the existing data which are pretty noisy.
And in my comments you'll see the plots and essentially they look a little bit saturating in their types, okay? And these are indoor exposures.
This does not get rid of the problem of possible confounding with other pollutants that are all, that are correlated with indoor exposures to NO2,

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but it does I think provide another piece of evidence that goes together with the intervention study, which I agree is some of the strongest kind of evidence.

But still, we have this problem of the potential confounding with effects of other correlated pollutants.

Anyhow, this type of plot still does better at getting you an indication of concentration response. It still has its distortion in that they only measured each person's, each one year old, or each four month old's exposure once, okay?

And because they only measured it once you're not quite sure that this is representative of their long term average concentrations. In fact the people who you, who they, who they think are relatively high in this highest quartile, probably tend to be, to have average exposures less than that because of regression to the mean effects.

Had they measured them ten times they would have had, they would probably have had, tended to have lower average exposures than the average that I calculated from the, for the highest quartile. And conversely, the people who they think, or they classified tentatively in the lowest quartile probably tend to have higher average quartiles than you would

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expect just because, for the same kind of phenomenon that if you have a baseball team and you look at their batting aver the distribution of their batting averages after the first ten weeks of the season, you'd find you have lots and lots of 400 hitters.

And by the end of the season you don't have any 400 hitters because of the increased sample size for the hitting performance.

And so in order to get a real feel for what the indicated concentrations times time, concentration versus effect incidence should be from this, these data, what you would want to do is to take into account this, the effect of measurement uncertainty on the slope of the dose response relationship.

So that would be the way I would try to process the very best few data sets, okay, that you have to try to get whatever insights they can provide about concentration response.

DR. COTE: Just to be clear, what you're suggesting is picking the best data sets we have and looking at those in detail?

DR. HATTIS: Yeah, I mean because to some extent you can have, you know, data sets that are, you know, there is also a place for taking into account all

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of the data in some fair combined sense, but that's a, you know, that meta-analytic type of exercise is slightly different than this, although it should probably benefit from the same kinds of considerations because you don't want to bias your overall conclusions by cherry picking as you said

DR. COTE: No me.

DR. HATTIS: only the ones who happen to be positive. So essentially what you do need to go to the next step is in fact to analyze well, you know, any concentration response, you know, some of the studies where you happen to have unusually good information. Not necessarily only the positive ones, but unusually good information.

DR. HENDERSON: Thank you, Dale. Do any of you want to add to this discussion of Charge Question 8, which I interpreted to include more than Chapter 5, but any other general comments on how well the document supports the future risk exposure and policy assessment?

And I will ask did someone raise their hand? Ah, Ellis, yes.

DR. COWLING: It seems to me that the question that Doug raised, how were the authors of Chapter 2 related to the authors of Chapter 5?

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I think that's a very important procedural question and it seems to me it's ideal if the author of any of the chapters was the principal architect of the candidate as you called or the nominator of the statements that would go in Chapter 5.

If you look at the question of how many of the bulletized statements that are in Chapter 5 are relevant to the question of whether we have a satisfactory or unsatisfactory standard, there are only 6 out of those 47 that are directly relevant to the question of the adequacy of the present standard.

So George made a suggestion earlier today that there should be a scan of the content of chapter, or whatever summary chapter we have to be sure that there is an adequate emphasis on things that are directly relevant to what should be done.

And I understand the caution about going too far with that because you're to turn this thing up to an Integrated Science Assessment, but rather into a policy document.

So there needs to be an excellent summary it seems to me of the information that is essential for making judgements about whether the general tenor of this document is favorable to the idea the we ought to make some adjustment in the standard,

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or not make an adjustment to the standard.
So, I would hope that very careful attention would be given in the next integrated assessment document that we see, to the very careful formulation of summary statements from all of the things that are covered in each of the chapters, and that those become the candidates for the summary.
And I would agree with George Thurston's recommendation that a scan of those statements of findings, maybe preliminary statements of findings, are evaluated in a coherent set of policy relevant statements is being presented as the foundation for the decision making process.
And on page 5 of my individual comments you'll find an outline, a guideline for a series of questions that were suggested by the Oversight Review Board for the NAPAP Program, the National Acid Precipitation Assessment Program. And the group of people that put those, that checklist series of questions together is how to evaluate a statement that tells the truth about some phenomenon that is relevant to the decisions that are being made.
And I would encourage, and I said in my statement I hope that you might look at those guidelines for the formulation of those kinds of very

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carefully crafted statements of scientific findings which could be used for policy purposes, and that that be done in the next assessment, number two, external review draft.
That's all that I wish to say.
DR. HENDERSON: Thank you, Ellis. And of course your comments as well as everyone's comments will be attached to the letter that goes to the Administrator.
I'd like to, before we go into the summary section, ask the NCEA folk if you have any questions or any more advice that you would like from us that we have not given?
DR. ROSS: Well, as Karen said, I think we'd like to invite you to also comment on even the conclusions. On slides 15 and 16 I summarized the real brief points we had.
You know, you've been talking about some of the evidence, but whether or not you agree with us that the science, the evidence for respiratory morbidity would be likely causal or such, where we have suggestive, inconclusive or limited evidence for the other health outcomes discussed on those two slides.
So we're inviting discussions of the science too, how well we've pulled this together and

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our conclusions from the science if you can offer any feedback to us.
DR. HENDERSON: So we could put it up there. Everyone should have a copy of the it's slides 15 and 16.
So that's a good idea, Mary. We can discuss these individually.
The key conclusions are for short term and long term exposures. These are the short term. Respiratory morbidity is deemed likely causal. Then there's four points given under that which, rather than me reading it, you can just read it off of there.
And I'd like to hear if anybody considers this not likely causal. I mean if you have any problems with this conclusion.
DR. POSTLETHWAIT: Considering all the uncertainties we've heard today, is everyone comfortable with the likely causal related to NO2?
DR. AVOL: This is Ed Avol. Again I think we've talked about some of this through the day that there's sort of been, I get the general sense that there's consensus that there's been a, either, not a transparent or an inconsistent determination of what goes into the equally likely causal inconclusive suggestion, and that if in the document if there was a

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clear tabulation or algorithm or something for how one gets to this, then these might flow more smoothly.
It's not clear from what has been presented that these are consistent with what's been shown.
DR. CRAWFORD-BROWN: Yeah, I think that's the direction I was going to say too, is that there's a big difference between asking the CASAC what their opinion is on these things, and asking the CASAC whether this document makes the case for these things.
And I've really been assuming it's sort of the latter issue.
When I look at Chapter 5 for example, I'm not sure I would necessarily disagree with those things. I'm not sure that if I did a close reading of the text of Chapter 5 the case is made coherently for those particular claims right there.
DR. COTE: I guess what would be useful is, you know, I think a number of things that need to be changed in the document to clarify the case have been identified, and that's been very useful.
But when we come back again, you know, to the extent you have a sense of the underlying scientific data, are we headed in the right direction with these conclusions?

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And the supporting evidence, I mean like one of the things I heard is, even if everyone agreed upon this, one would want to see another statement about mode of action and the clinical and animal data.

So I think what Mary was more asking was not so much did the document lay out the case, but what's people's feeling about the science?

DR. HENDERSON: I will go out on a limb and say, though I think it could be presented much better, I don't have any problem with the likely causal respiratory morbidity effects based mainly on the Australian studies in the homes, indoors.

I mean that was a convincing study for me. But others should say what they think.

Yeah, George?

DR. THURSTON: This is George Thurston. What I would say is that I would, that there is sort of the rankings of these I would agree with.

In other words the case is strongest for respiratory morbidity and so forth. And I'm still, you know, whether I would use exactly likely causal or not, you know, could go up or down in terms of causality for me once I see the revised report in terms of, you know, looking at Hill's criteria and then looking at the evidence for each across all the outcomes and the

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information.

But I think that certainly the direction of this and where you're putting the most reliance, I agree with based on what I've seen.

DR. HENDERSON: Do other people wish to commit or say anything?

DR. LARSON: This is Tim Larson. I've been putting in the qualifier about the surrogate exposures for especially those indoor studies.

But I think what puts this in that category are the clinical studies. Even though the symptoms are not, you know, necessarily the same as, you don't get the same effect, clearly those are several hour exposures and it's difficult to tease that out.

If the clinical study shows no inflammatory effects, hyperresponsive effects, then I would probably lean on the other side, but I think I'm persuaded that this is reasonable, given that, as well as those indoor exposures as well the somewhat confounded EPI work, the outdoor EPI work.

DR. HENDERSON: Anybody else have comments?

DR. THURSTON: I have a question.

DR. HENDERSON: Okay.

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DR. THURSTON: And this is sort of a basic question, this is George Thurston.

But, you know, is, let's, I mean if you get right to the endpoint and say, well, if we control, set a lower standard for NO2, will these health benefits be achieved, is a slightly different question than, will the reductions of NO2 themselves, and alone, cause those benefits?

Because I believe that if we were to set a more stringent, or set a short term standard, that if you controlled NO2 you would also control co-pollutants, there would be co-benefits associated with this, such that, you know, the do you see what I'm getting at?

You know, the real question I think is, if we control, if we set a more stringent standard, will health benefits be accrued?

And, you know

DR. ULTMAN: George, I would defer to the, you know, the affected industry to, especially the automobile industry, but I don't know that that's always going to be the case. I mean especially the ultra fine NO2 connection. It's not clear to me that if you go after NO2 in these latest control strategies, that you're going to also by definition go after ultra

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fine.

DR. THURSTON: Right. Well, I mean but couldn't that assessment, part of a, maybe I'm getting into tomorrow.

DR. ULTMAN: Yeah.

DR. THURSTON: But couldn't you make that assessment as part of it? In other words

DR. ULTMAN: Sure, sure.

DR. THURSTON: not just do a benefit analysis, or impact analysis or whatever we want to call it

DR. ULTMAN: Right.

DR. THURSTON: looking only at NO2, but saying, okay, if we could, if a standard were set here, what changes would there be in NO2 and PM?

I would actually think that if you included those two and then, you know, you could use epidemiology where they've used PM and NO2 together, I, you know, then I would, on just those two pollutants then together they're, I don't like using individual

DR. ULTMAN: I would agree with you, George.

DR. THURSTON: things, but you know, if you used them both together then the net impact is correct.

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So, you know, along, I'm thinking along those lines.
DR. ULTMAN: It's better anyway.
DR. THURSTON: What?
DR. ULTMAN: It's better anyway, a meta-analysis of proof.
DR. HENDERSON: Ted.
DR. RUSSELL: I would definitely with what Tim is saying on that is, I'd be very cautious about even thinking in that direction, by decreasing the NO2 necessarily you are decreasing ultra fine particulate and vice versa.
And that some of these control strategies are the ones that are going to decrease particulate but possibly increase NO2.
DR. COTE: The other thing is I'd rather like just settle that we have the right words here before we
DR. RUSSELL: Sorry, maybe we'll worry about that tomorrow.
DR. COTE: I understand the need to protect the public health of America though.
DR. RUSSELL: Well yeah.
DR. HENDERSON: Yeah, what's really being asked is, is there a likely causal effect of NO2

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exposure on respiratory morbidity? And it may be based on non-environmental studies like was mentioned, the human clinical studies and the indoor studies. And we've based it on that because we can pin it down to NO2 itself more readily than if we do outdoor studies.
So to me we oughtn't to get off into the environmental thing right now because we're only asking, is there a likely causal effect of NO2 on respiratory morbidity? And are there studies that would suggest that?
Okay, Terry.
DR. GORDON: Well I'm not going to speak necessarily for the other toxicologists, but I'm confused, I haven't heard this group come to a conclusion yet on exactly that issue, likely causal.
Is there confounding or not? And I just would like some guidance from the epidemiologists. I've heard both sides, I heard skirting around and some saying absolutely and some saying no.
And I feel like maybe are we ignoring that by just saying likely?
DR. HENDERSON: I'm not really understanding your question, Terry. Because this is a qualitative, this likely causal.
DR. GORDON: But it depends on how we

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interpret the EPI studies and the Australian studies, is there confounding or not?
When Samet spoke earlier he I think sort of blew them away, saying that it was very little relevance, didn't he?
DR. HENDERSON: No, I thought he liked the Australian study.
DR. GORDON: Well someone spoke and said that they thought this was a
DR. SAMET: This is Jon, I'm on actually.
DR. HENDERSON: Terry, there's Jon now.
DR. SAMET: Could I make one comment? I mean I think the Australian study I think is very useful. I think the dilemma and I think George's question or comment speaks to this, is what inference about NO2 based on the indoor may not be informative as to what will happen with reduction of outdoor NO2 where, I mean, that's where the need for integration comes.
Because, you know, obviously all the chemistry, the transformation and what is happening outdoors is substantially different from indoors.
So they are distinct questions. One is, are there health effects of NO2? And the second, what would follow from reduction of NO2 outdoors? Perhaps

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the benefits would be greater than anticipated because of PM reduction for example.
So they're distinctive questions.
DR. HENDERSON: Well
DR. SAMET: I think what's the use of the NO2 study, the Australian study, was the fact that it was NOX or NO2 largely that was being investigated.
DR. HENDERSON: I agree with you, Jon, there's two questions being asked here and I think today we just want to ask that first question. Tomorrow we're going to address the other.
That's my opinion. Is that what you want, I mean
DR. COTE: We don't want to address the issue of control strategy --
DR. HENDERSON: That's not the
DR. COTE: here, today.
DR. HENDERSON: purpose of the ISA. If we look at cardiovascular morbidity you say inconclusive. What do people think of that? I don't want to say what I think because it's I want to hear what you think.
DR. CRAWFORD-BROWN: If we're talking about, you know, 10,000 parts per million then the answer is, yes, yes, yes, yes. And if we're talking

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about, you know, 10 parts per billion, I don't understand yet what the level of exposure is. Are we talking about current ambient levels?

DR. ROSS: Current ambient levels. In the Rogers studies they're generally using current ambient levels. Some of them were conducted perhaps in the '80s when the levels might be higher.

But that was the actual purpose of Tables 5.3 and 5.4, that listed, they listed levels from the studies, some examples of distribution data from the EPI studies. And you can see that the levels are in many cases quite low.

DR. CRAWFORD-BROWN: Okay. I keep coming back to the text though.

DR. ROSS: From the EPI studies.

DR. CRAWFORD-BROWN: What we have here is

DR. ROSS: Right.

DR. CRAWFORD-BROWN: is respiratory morbidity likely causal? It doesn't say is respiratory morbidity at current ambient levels?

Is that the question we're asking?

DR. COTE: Yes.

DR. CRAWFORD-BROWN: Okay, because in my

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DR. CRAWFORD-BROWN: are much less strong than

DR. COTE: I think that's actually in the text.

DR. CRAWFORD-BROWN: It is in the text, yeah.

DR. COTE: Yeah. Yeah. Yes, and that's the rub.

DR. HENDERSON: Okay. I'm looking and all cause mortality suggestive evidence, I don't, anybody want to comment on that?

DR. WYZGA: You know, one of the things is that and I think we just need to look carefully, I think that there are a lot of studies out there that's looked at a lot of pollutants and they tended to emphasize the results were positive and sort of NO2 is a little footnote. We looked at it and we didn't find anything.

And I think we need to look carefully and see if there are more of these studies because that might inform our conclusion.

I don't know, I have no opinion until I sort of

DR. HENDERSON: See this whole issue.

DR. WYZGA: Right. Until we see

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everything out there.

DR. HENDERSON: Yeah. Okay, George?

DR. THURSTON: Well I'm sorry, at the risk of being a troublemaker.

DR. HENDERSON: Yeah.

DR. THURSTON: Let me just try one more try, I mean I wasn't really getting into the regulatory aspect. I was sort of asking the question, are we, you know, is the question, is NO2 alone causal? Or is NO2 and everything that goes with it causal?

And I think you might come up with different answers for those two. And some people are saying, well, it's confounding and it's negative. Actually it's not negative, I mean it's actually, it might explain the relationships. You're saying when you change NO2 you're changing other things along with it and, you know, is NO2 and what the baggage it carries with it, causal? Or, do we have to stay with only NO2?

DR. GORDON: That's what I was trying to say.

DR. HENDERSON: Okay.

DR. COTE: Do you want to speak to that, Mary?

DR. HATTIS: Holding everything else

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constant

DR. THURSTON: But

DR. HATTIS: if you reduced NO2, would you then

DR. THURSTON: Well that's not the real world, that's not what's going to happen.

DR. HATTIS: No, but that's being optimistic.

DR. COTE: I think what I would say that we're addressing are oxides of nitrogen which isn't exactly NO2 but

DR. THURSTON: Well

DR. COTE: oxides of nitrogen.

DR. THURSTON: Well I know we're using NO2 as a standard.

DR. COTE: Yeah, an indicator. But yes, I don't think we mean NO2 and PM. Is that your answer?

DR. ROSS: I mean it's fair to discuss the reality as Jon Samet shows in page 37 of the comment, Jon Samet lists things that were discussed before for other pollutants like ozone and particulate matter

DR. THURSTON: Right.

DR. ROSS: is that in a mixture of air pollutants you can have complicated interactions.

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For this document we're really looking at NO2 studies, but recognizing that you can have NO2 as a marker for an air pollution mixture as you're saying.

DR. THURSTON: Yeah, you

DR. ROSS: Where if you lower the NO2

DR. THURSTON: because

DR. ROSS: you're

DR. THURSTON: I guess what I'm saying, I think you might miss all the co-benefits that go with it, you know. And maybe we're not allowed to consider those, but they're, you know, the fact that other things go up and down with NO2 is, some, I don't know, somehow it's being seen as a negative.

But actually it may, you know, mean that we're underestimating the benefits of setting a standard by just looking at that along and ignoring all that goes with it.

And that's what epidemiology does for you. It tells you what everything that goes with it and then I think the toxicology and the human studies, they're great because they can tell you about mechanisms and biological plausibility, but the epidemiology gives you, you know, the plus as I see it of telling you, you know, if it goes down, what will

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the benefits be.

And it's not necessarily a negative that you can put another pollutant in there and pick up some of it and all of that anyway.

So I mean my question was really geared to today, whether we can, we have to just limit ourselves to NO2 alone of NO2 and what goes with it. Tha'ts my question. Maybe there's no answer, but

DR. HENDERSON: We all have to, I mean because they're asking us for advice and so we need to discuss with them, you know, hey we, they're saying we came up with a suggestive evidence for all cause mortality. What do we think about that?

And you've been discussing it at length, I mean you're saying, well, we should take into consideration everything else.

DR. THURSTON: Right, I guess I'm just trying to define the playing field or the, you know, how, what I've got in order to answer that question. You know, what's the latitude I should say of answering that question?

DR. CRAPO: I'd like to try to respond to that because I think that the, this is a, we've faced this problem with every single pollutant we've met. And in every case nothing has operated completely

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independent of every other variable out there.

I think the issue is, do we think that NO2 itself is a significant contributor? If we thought that NO2 is nothing but a surrogate and it had no impact at all at those levels and the whole thing was being driven by particulates, then we shouldn't regulate NO2.

But if you think there is an NO2 independent affect which in this document there's quite a few things to suggest that there is a robust affect that tracks with NO2, if you think that's correct, well I think we should not, then we should recommend and let that become a regulatory issue.

But the issue that there's a confounding with other factors is inherent in the entire air pollution field for everything we do.

DR. HENDERSON: I think you put that very well, James. That's what I'm thinking, I mean, do we think that NO2 has no affect at all? And I think the evidence here says, you know, there are studies that show that it, when it's closely controlled as possible, that there are, that there is a morbidity effect in terms of the respiratory symptoms.

That's what I'm basing my own for the long term exposures it gets, you know, when you look at

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the conclusions it's suggestive, so is there anything in here that you would object to?

I mean we want to see more information as to how that was determined, et cetera or you know, presented in a systematic way. But lung cancer incidence, I have a little bit of a problem with that.

DR. AVOL: This is Ed Avol. I guess in the scheme of things looking at this well first of all let me preface this by saying that I agree actually with what George previously said which I don't necessarily agree with the absolute words that were up there, but I agree with the relative ranking from the previous one.

In the same sense of looking at this, in particular I think there's stronger evidence for respiratory morbidity than there is for lung cancer incidence, so I would not rank those sort of equally.

But I don't necessarily agree with the actual words and that's what my comment previously was about the transparency in the documentation and how you get to this definition.

DR. HENDERSON: I don't, for instance under lung cancer incidence, suggestive evidence that the atmospheric reaction products of NO2 such as nitro pH may be carcinogenic, that's a very true statement.

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By gosh, how much of that is in the air?
It's such a small concentration. I mean in an occupational setting you might get enough, but is that why you said suggestive? I don't know, I don't quite understand the reasoning on that.
DR. COTE: I think that's right, I think it was plausible. But the evidence for, you know, the EPI evidence itself wasn't particularly strong or convincing.
DR. HENDERSON: If the dosimetry were right it would be absolutely true, you know, but it just
DR. COTE: Yeah, no, I don't think we've done that.
DR. HENDERSON: Yeah.
DR. COTE: I mean it's hard.
DR. HENDERSON: Does anybody else have comments on these conclusions that would help them in how they present their data?
DR. CRAPO: I think the lung cancer, I'd call it limited, not suggestive, it's still weak. The correlation is with air pollution.
DR. HENDERSON: Yeah.
DR. CRAPO: And specifically with NO, so it's got limited data to my thinking.

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DR. CRAPO: Well the other thing too is that --
DR. HATTIS: Because you have the nitro aerobatics, it's likely that there is some, but
DR. CRAPO: If the concentration is high enough, we don't know that.
DR. HATTIS: Well
DR. CRAPO: That's why it's
DR. HATTIS: I don't.
DR. HENDERSON: There was a voice on the phone that I could barely hear. Who was that?
DR. POSTLETHWAIT: I think that was me.
DR. HENDERSON: Sorry, you have to
DR. POSTLETHWAIT: Sorry, Rogene, I'll pull the string tighter so you can tell I'm in the room.
In fact considering the five year survival rates for lung cancer, to have incidences suggestive in mortality is inconclusive, seems to be a bit of a disconnect.
Boy, did that get dead silence, whoa.
DR. COTE: I wasn't sure I understood what you said.
DR. AVOL: Well if you look there it says lung cancer, it says suggestive, but mortality

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including lung cancer is inconclusive.
SPEAKER: And most people die when they get lung cancer.
DR. POSTLETHWAIT: Yeah, in a fairly rapid or short period of time.
DR. COTE: Well I guess though that it's the comparison of the incidence, the occurrence of lung cancer in one, and then when you look at all cause mortality, the evidence is not as strong.
So that's just a function of the way, you know, it's kind of just a factual interpretation of what those sets of data look like.
Do you know what I'm saying? Is that clear?
DR. POSTLETHWAIT: Sort of.
DR. COTE: There were very few studies that looked at lung cancer mortality. This is mortality lumped together that includes all cause
DR. WYZGA: Why don't you just take out, including lung cancer.
DR. COTE: Yeah, good idea.
DR. HENDERSON: Yes, that would make it
DR. GORDON: Ila, George and I were trying to look up where you have these definitions. Is limited above suggestive?

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SPEAKER: Yeah, that's not in there.
DR. COTE: You know I was actually
DR. ROSS: Go ahead.
DR. COTE: limited actually just means very few studies available at all.
DR. GORDON: That seems like it would fit the lung cancer incidence as well, limited.
DR. HENDERSON: I would say, yeah, I would rather have limited evidence on lung cancer.
DR. ROSS: Well we don't mean to force anybody into making spontaneous decisions with this. But we would welcome any input, you know, from a science perspective from those of you who have been studying this for sometime.
DR. HENDERSON: And anybody who has not turned in their written comments, please do so because this is a very important task and we truly want to get your ideas and your input.
DR. AVOL: So just to close the loop here for staff, if in fact you're going to assign these descriptors to these conclusions then you're going to work backwards so that the respective chapters lead to this conclusion?
DR. COTE: If we're lucky.

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DR. HENDERSON: That was good. I mean you've heard the suggestions and I mean
DR. ROSS: Yes, thank you, that's very helpful.
DR. HENDERSON: a limited discussion. I would like now to just, while we've got Jon Samet on the phone, to just go through a summary of the issues that we want to provide in the letter to the Administrator.
And I need everybody's help in doing this. I jotted down things as we went along so I'm going to read out what I have.
These are not formal sentences, these are ideas or concepts that I would expect to come from the summaries of the different discussion leaders. Okay, I can do this.
So going through this, I heard it over and over and over again the problem of the multi pollutant confounders and is NO2 a surrogate for just air pollution, that sort of thing. I think that in the letter to the Administrator we have to emphasize that this is a problem and that a multi pollutant approach is where we should be headed in the future.
Second, I heard a, the statement there were a lack of negative studies reported, that there

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needed to be more complete reporting of the, all studies, positive or negative.
I heard many, many, many pieces of advice on better integration. This is not a listing of studies but to integrate the EPI, the clinical and the toxicology studies better.
I heard that discussion of the appropriate monitoring and the bottom line that I heard was that the uncertainties associated with monitoring should be discussed more completely.
I heard that thee needed to be a better discussion of the plausibility of causality as well as to summarize dose response data for those events that were considered causal.
I heard that we needed more quantitative information, though that's going to come a lot in the next document.
I can't read my own handwriting here. We need a clear distinction between short and long term exposure health effects. But I think we've probably just discussed that at length.
And because I can't read my last one oh, we need to condense Chapter 3. A lot of people said Chapter 3 is just too much like a mini CD and they thought that that could be condensed and presented more

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carefully.
Now those are just the notes I have.
Now tell me, what are the other major issues that you'd like to see in that letter.
DR. CRAPO: I think that one thing I'd add is that when you discuss dose response, we need to know if there is any data that would let you consider that the dose response relationship holds at ambient levels and going downward.
I'm really concerned as to whether or not, where the threshold is and whether the calculated dose response relationships that we have are schematically calculated using higher dose data.
And I'm not sure there is any answer but we really, the critical question that needs to be understand is, what is the dose response relationship as you start approaching the ambient and going down from there?
DR. COTE: Well I think what Mary said about the studies in general are all reported below the standard, all is not the right word, but predominantly reported below the current standard.
DR. CRAPO: Yeah, so a real discussion of that issue
DR. COTE: Okay.

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DR. CRAPO: though because I'm not sure we can take that last table we talked about that has the 20 parts per billion relationship scored from a curve and think that that's what's really going to occur from 15 to 10 let's say ppb.
And so I'm not sure we have much information, but I'd like a discussion of that to really because the dose response relationship for us is most important at the really low end.
DR. HENDERSON: Absolutely true, we really need the
DR. POSTLETHWAIT: There's more work on that and it may have been in here somewhere and I missed it.
But are there any data available on what a personal exposure looks like? Because I think what many of us struggle with in this plausibility issue is we see causality being concluded from ppb exposure concentrations which result from, you know, an area monitor averaged over a long averaging time. And it doesn't include the spikes or anything.
It gets directly back to what James was just talking about. There could be exposures that are far more robust than we appreciate. And so having some of that information in there I think would be very

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helpful.
DR. HENDERSON: So you're saying you want more of the personal exposure information?
DR. POSTLETHWAIT: Whatever data is available, because rather than taking the average NO2 concentration over a week long
DR. HENDERSON: Sure.
DR. POSTLETHWAIT: month long, year long, whatever, compared to what people in the study population are really exposed to could be very different.
DR. HENDERSON: Oh, I'm sure they
DR. POSTLETHWAIT: And I'm sure they are very different.
DR. HENDERSON: I understand, okay. Ron.
DR. WYZGA: I think tied very much to that is some indication that the levels we have are those measured at monitors. I think we need some statement as to what the criteria are for siting a monitor, and are they representative of all exposures.
I suspect they may not be representative of exposures for example near roadways which may be much higher for short periods of time.
And so I think that need, you know, need be articulated.

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DR. COTE: I that's what's available, you know, that there are personal monitoring studies, so a description of what those people were exposed to on a shorter term average, the problem's going to be that, you know, the EPI data is generally reported as just the 24 hour averages.
So if you're looking at what peaks are within that 24 hours that are significant, I don't think that that data are available.
But we can go back and look at it harder.
DR. HENDERSON: I also heard that you wanted the criteria for the siting of the monitors. That ought to be pretty easy to do.
DR. WYZGA: Would that show up in this document?
DR. COTE: We could.
DR. HENDERSON: If we wanted it to, I mean that's what we're giving them, the advice, we're saying yes, we want it so
DR. COTE: I wrote that down.
DR. HENDERSON: Don't tell them to do something we don't want them to do because we did that once and we've done that before and they do it and so then we complain.

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Okay, Ed. We actually did that.
DR. AVOL: This is sort of a sidelight question, but I think the criteria for placing a monitor and the locations of the monitor, that is the distribution to where they actually are might be somewhat different.
DR. COTE: Right.
DR. HENDERSON: Right.
DR. AVOL: And I think what we want to know is where the monitors actually are, not what the rules are for where you're supposed to place them.
DR. COTE: Okay. How about, you could do both.
DR. HATTIS: Based upon where the monitors actually are, what translation do you need between the monitor levels on average and the actual levels outdoors where people are exposed?
DR. HENDERSON: Yes. Those are pieces of information we would need.
Are there other issues that we want to be sure in our letter to the
DR. WYZGA: I don't know if it's relevant but someone mentioned, I know there are programs in place that will reduce emissions of NOX. Is it useful to mention that? Do we have some sense as to are

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levels going to go down? And if so, by much. Is that worth putting in this document or does that go elsewhere? I have no idea.
DR. HENDERSON: I don't know. I think it's an important piece of information. I don't know where we I mean they are changing the engines so that they put out less NOX as I understand it.
Is that something that goes, where would that go?
DR. ROSS: It's hard to interpret the health effects evidence based on predicted future levels, given that the health studies are only based on whatever we have now.
But sometimes in the ANPR or in the policy making setting those kinds of considerations are added in terms of what future outcomes will be.
DR. HATTIS: I think projections of future levels are relevant to the next document rather than this document.
DR. HENDERSON: Okay. Well we'll keep that in mind when we, as we're looking at that tomorrow.
Okay, yes George?
DR. THURSTON: Well I thought in terms of the letter, one of the issues that came up time and

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time again was the framework, having at the beginning a framework of evaluation that, you know, laid out what were the criteria that were going to be used and how would they be applied and then applied throughout.

And then come up with conclusions based on those criteria. I mean that's been done but it's, you know, loosely and not in a, you know, comprehensive and consistent way.

DR. SHEPHERD: This is Lianne Shepherd, I wanted to interject a comment that's related to George's comment.

And that is that there should be better cross referencing between the Integrated Scientific Assessment and the annexes. And some of the suggestions we're making might be more appropriately put in great detail in the annex and then summarized in the context of the criteria of how we're integrating this information in the integrated document.

And that might be one of the ways of addressing some of this feedback without lengthening the scientific assessment too much.

DR. COTE: I have to say that I'm committing to doing things like putting in the siting criteria for monitors, I envision that going in the annexes, and not the body of the document.

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DR. HENDERSON: Okay.

DR. COTE: So I think that's a good suggestion.

DR. SHEPHERD: But one of the things I think is missing though right now is good cross referencing between the annex and the

DR. COTE: Yeah, I think

DR. SHEPHERD: scientific assessment so that we can easily find that more detailed information when necessary.

DR. COTE: That's a good comment, thank you.

DR. HENDERSON: Okay, George?

DR. THURSTON: And then the other comment I had was related to an earlier comment by Doctor Crapo I think it was.

That we should look at the epidemiology by concentration level. I mean this tendency to look at this outcome, that outcome, that outcome and then, you know, if we were to try I think it's worth a look anyway to try and see if you look at a certain, if you look at the concentrations in the studies and group them into stratus and then see if there is a tendency for effects to be a function of the and I'm talking epidemiology here, a function of the concentration.

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And look for that, that way rather than trying to look at, you know, that's where we have a lot of studies, a lot of information. And maybe that could be, something could be squeezed out of the epidemiology by looking as a function of concentration

DR. HENDERSON: To see if there's evidence of a dose response.

DR. THURSTON: Yeah.

DR. HENDERSON: Yeah, no, I thought that's what was done routinely but I'm not an epidemiologist so I don't know.

DR. THURSTON: I don't think it's in here, is it?

DR. HENDERSON: I don't know.

DR. THURSTON: I didn't see it in here.

DR. HENDERSON: No, I don't know, I don't know.

SPEAKER: It's there for the animals.

DR. THURSTON: For the animals but not for the EPI, so that might be a way to get at that question anyway.

DR. HENDERSON: Yes, Ron.

DR. WYZGA: Also it was said that the states collect the NO data. I think to the extent that someone could request that those data might be

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available, it might be useful in future studies to consider those data as well.

My understanding is you said the data are collected as part of the method for measuring NO2, but the data are generally not reported.

SPEAKER: Right, not kept, not reported.

DR. HENDERSON: Oh, they don't report the NO2 or they don't report the NO?

DR. WYZGA: They don't report the NO.

DR. HENDERSON: Oh, that's right, that's right, we wanted the NO.

DR. WYZGA: So if I think it would be useful to have those data.

DR. HENDERSON: Okay, I got it. I'd like to remind people that those of you who are underlined are responsible for summarizing your, the group's response to the charge question that you're responsible for, to get it to Angela.

So I am going to use this list to check and be sure that they all come in, but I'm counting on you all to address them. I'm not writing up all these things. In other words, don't, I wouldn't be good at doing it anyway, but

SPEAKER: That's by the end of the day.

DR. HENDERSON: That's by 10 o'clock

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tonight. Now, we're going to eat at 6:00 and then we're all going to rush home and sit down and watch the World Series and while you're watching the World Series I want you to script out your summaries.

But do it as a group, I mean take into account everybody's comments, not just your own. This is the first time we've tried this, but hey, we never had a World Series to hold you in your place for this long.

So I hope that works out.

Okay, are there any other issues that need to go in there?

DR. SHEPHERD: Yeah, this is Lianne Shepherd. There's another comment that I didn't think to mention earlier today, and I think it's relevant both to the exposure discussions and also to the EPI discussions.

And often there are fairly generalized comments made that really are only correct if you have a particular epidemiological study design in mind. And somehow that needs to be attended to better in this document.

For instance, there's comments about there being exposure measurement error when the monitor is, you know, near a local source or something like

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that. And that's particularly important to a timed series study design. That's just one example.

And so we need to be a little careful about when generalizations are made.

DR. HENDERSON: Is there a specific something we should include in the letter? I mean I'm thinking if you know of someone who is going to be writing up the summary paragraph for the appropriate charge question, maybe you could email them, you know, a sentence or two addressing your concerns, Lianne. I'm just

DR. SHEPHERD: Okay.

DR. HENDERSON: Okay.

DR. SHEPHERD: I'll do that.

DR. HENDERSON: Okay, very good.

DR. SAMET: Rogene, I sent Angela a set of bullets, one sentence bullets on the summary of Charge Question 3. And if she wants to distribute those to anyone else who wants to take a look at it this evening, that's great.

DR. HENDERSON: Okay. Do the people who are working on Charge Question 3

DR. SAMET: The chapter

DR. HENDERSON: Oh, Chapter 3.

DR. SAMET: Charge Questions 1 to 3

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really. But really, you know, you told me about this before, I mean I Ted was going to do more on the monitoring and Ellis was going to do a little more on multi pollutants.

DR. HENDERSON: Okay, I think what we'll do, if you'll just, can you make a copy and pass them out?

DR. SAMET: Yeah, I don't know, but anyway I just had a few summary bullets.

DR. HENDERSON: Huh?

DR. SAMET: I just gave you a few summary bullets trying to summarize the major points I had written down.

DR. HENDERSON: Well we want to take those into account, definitely.

DR. SAMET: But if somebody might, some others who might have disagreed or heard it differently, it would give them a chance to take a shot at it.

DR. HENDERSON: How many points did you have?

DR. SAMET: Just four.

DR. HENDERSON: Why don't you just read them off?

DR. SAMET: The emissions of NO2 and

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related species from both indoor and outdoor sources needs to be discussed, both in general and specifically in the context of the correlation of ambient NO2 levels with other co-pollutants, including ultra fine particles.

Two, the relationship between indoor and outdoor levels of NO2 deserve more discussion, particularly the relevance of the perimeter alpha relating ambient levels to personal exposures.

Three, the spatial variability of NO2 within urban areas is very complex and there is inadequate discussion of potential exposure misclassification due to the affect of the siting of monitors away from busy roads, the presence or absence of street canyons, in vehicle exposures and the affect of atmospheric dilution with height above ground.

And four, the inclusion of some of the historical dosimetry information relevant to animal to human extrapolations would be helpful in the subsequent discussion of the animal toxicology.

DR. HENDERSON: Okay, I think most of those we've got within

DR. SAMET: Yeah, I think you've got them all.

DR. HENDERSON: Yeah, yeah. Okay, thanks

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a lot. Any more discussion here of issues?
DR. COTE: I have one thing that I wanted to say. I think there's been a bit of a misperception.
Ron had identified a couple of negative studies that had apparently been missed and certainly as Jon was pointing out, you know, it's easier to miss negative studies than positive studies because when you do the lit search things don't pop up.
But in the annexes we have attempted to report all studies so that I think it's not quite accurate to say that there's a lack or reporting of the negative studies. We may have missed some positive and negative studies.
So maybe the emphasis on publication bias might be a more appropriate or clearer statement.
DR. HENDERSON: I think the main thing is you want to give a balanced report that, you know, that there have been both positive and negative and maybe just refer to the references.
But we can put
DR. COTE: I just wanted to leave the group with the awareness that it's not like we chose to put in the positive studies. We have made a real attempt to put in positive and negative.
DR. HENDERSON: Okay. Okay, are there

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any yes, Ellis.
DR. COWLING: I have a logistical question and this has to do with Angela's habits of work.
My understanding is that you want a one sentence placeholder or do you want a two or three sentence paragraph?
DR. HENDERSON: Two or three sentences, but not two or three pages.
DR. COWLING: No, no, okay.
DR. HENDERSON: Two or three sentences.
DR. COWLING: And you want those delivered electronically to Angela's electronic address.
DR. HENDERSON: That's right.
DR. COWLING: By 10 o'clock tonight.
DR. HENDERSON: Tonight. She goes to bed at 10:00, don't wait until after the game.
DR. COWLING: So how will Angela work? If we send them to her by 10 o'clock, and she goes to bed at 10:00
DR. HENDERSON: Oh, I'm just joking, she's going to put them together and we'll have it all printed out and in your chair in the morning.
DR. NUGENT: That's the plan.

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DR. HENDERSON: That's the plan.
DR. COWLING: Okay. So 10 o'clock is the deadline for whatever a sentence or a two or a three sentence statement.
DR. HENDERSON: That's right.
DR. COWLING: Okay. And this will be a placeholder I presume, rather than a submission but we'll talk about it all in the morning.
DR. HENDERSON: It will be a placeholder and in the morning what we're going to do is discuss, and because of legal requirements we will publicly give our okay to this list or not okay, I mean since it's a list I don't quite see why we would not be okay with the list. But it is legally required that we approve what's going to go in the letter.
But then we will put, the letter will be crafted, put together and sent out for everyone's concurrence. Just like we always have.
But that's why we're putting Angela to so much work.
Okay, we do have a there's a dinner that you can, I mean you've already said if you're going to attend that's at 6:00. That's when we're going to get picked up at 6:00. I'm sure you know that the World Series starts at 8:00 and we will

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DR. CRAWFORD-BROWN: I'm informing you that there is no World Series without my beloved Yankees.
DR. HENDERSON: Oh, I'm so sorry. I'm so sorry. Some people from Boston thought there was a World Series tonight.
Okay, we will see you tonight or in the morning as the case may be.
And I appreciate all your work to get your information to Angela.
DR. NUGENT: Okay, I guess we're adjourned until we meet at 8:30 for the public session.
Thank you.
(WHEREUPON, the PUBLIC MEETING was adjourned at 4:30 p.m.)

CAPTION

The foregoing matter was taken on the date, and at the time and place set out on the Title page hereof.

It was requested that the matter be taken by the reporter and that the same be reduced to typewritten form.

Further, as relates to depositions, it was agreed by and between counsel and the parties that the reading and signing of the transcript, be and the same is hereby waived.

CERTIFICATE OF REPORTER

COMMONWEALTH OF VIRGINIA

AT LARGE:

I do hereby certify that the witness in the foregoing transcript was taken on the date, and at the time and place set out on the Title page hereof by me after first being duly sworn to testify the truth, the whole truth, and nothing but the truth; and that the said matter was recorded stenographically and mechanically by me and then reduced to typewritten form under my direction, and constitutes a true record of the transcript as taken, all to the best of my skill and ability.

I further certify that the inspection, reading and signing of said deposition were waived by counsel for the respective parties and by the witness.

I certify that I am not a relative or employee of either counsel, and that I am in no way interested financially, directly or indirectly, in this action.

MARK REIF, COURT REPORTER / NOTARY

SUBMITTED ON OCTOBER 24, 2007

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