DEPARTMENT OF HEALTH AND HUMAN SERVICES

and

FOOD AND DRUG ADMINISTRATION
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

convene the

RANCH HAND ADVISORY COMMITTEE MEETING

Rockville, Maryland
June 10, 2005

CERTIFIED VERBATIM TRANSCRIPT

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Dr. Ezdihar Hassoun
Dr. David Johnson
Dr. Sanford Leffingwell
Dr. Ronald Trewyn

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Ms. Mary Paxton
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Ms. Julie Robinson
USAF Retired

Mr. Jonathan Silvers
ABC News *Nightline*

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Opening Session

[CONVENE 8:46 A.M.]

M. STOTO: Good morning, everyone. Welcome to the meeting of the Ranch Hand Advisory Committee. I'm Michael Stoto; I'm the Chair of the Committee. I work at the Rand Corporation although I'm not representing them here. And I'd like to begin by going around and asking the Committee members to introduce themselves and then we'll ask the others present in the room to introduce themselves as well. So Dr. Leffingwell?

S. LEFFINGWELL: Sanford Leffingwell.

M. STOTO: And remember you have to put the — turn the mikes on before they will work.

S. LEFFINGWELL: Yeah. Sanford Leffingwell with HLM Consultants, formerly with CDC.

D. JOHNSON: Dave Johnson with the Florida Department of Health.

L. SCHECHTMAN: I'm Leonard Schechtman. I'm the Executive Secretary of the Ranch Hand ...

M. STOTO: You're not on; you're not on.

L. SCHECHTMAN: Okay. Now I'm on. I'm Leonard — I'm sorry; I should know better. I'm Leonard Schechtman, the Executive Secretary of the Ranch Hand Advisory Committee and the Deputy Director for FDA's National Center for Toxicological Research.

P. CAMACHO: Paul Camacho from the University of Massachusetts.

E. HASSOUN: Ezdihar Hassoun from the University of Toledo.

R. TREWYN: Ron Trewyn, Kansas State University.

K. FOX: Colonel Karen Fox with the Air Force Health Study, now Principal Investigator.

J. MICHALEK: Joel Michalek, formal — former Principal Investigator, now with the University of Texas.

M. STOTO: If you want to start over this way? Just introduce yourself please. Okay.

M. MONTGOMERY: Lieutenant Margaret Montgomery, Deputy Program Manager, Air Force Health Study.

J. ROBINSON: I'm Julie Robinson. I'm the prior Air Force Health Study Branch Chief.

M. STOTO: Julie, would you give the mike to the gentleman over there?

J. SILVERS: Sorry. Jonathan Silvers; I'm an independent producer for ABC News *Nightline*.

M. PAVUK: I'm Marian Pavuk with SpecPro. I work on the Air Force Health Study, Brooks-San Antonio, epidemiologist, biostatistician.

M. BLANCAS: Manny Blancas, contractor with the Air Force Health Study Program Management Team.

J. MINER: Jay Miner with Operational Technologies, former Principal Investigator with the study and former Air Force. And I currently work with the Program Office at Brooks Air Force Base.

M. PAXTON: Mary Paxton, IOM Project Officer for the "Veteran's and Agent Orange Update Series."

M. OWENS: Maurice Owens; I'm with Science Applications International Corporation.

M. YEAGER: Meagan Yeager; I'm with Science Applications International Corporation.

W. GRUBBS: Bill Grubbs, Science Applications International Corporation.

J. GONZALES: Captain Jose Gonzales. I'm the new Program Element Monitor with the Air Force staff.

K. CAMPBELL: Kim Campbell; I'm the Management Specialist for the Ranch Hand Advisory Committee.

F. MATSUMURA: Fumio Matsumura from the University of California-Davis.

P. FUJIYOSHI: Phillip Fujiyoshi from the University of California-Davis.

D. BUTLER: David Butler, National Academy of Sciences. I'm the staff officer for the National Academies' AFHS Disposition Study.

A. O'CONNOR: Amy O'Connor, National Academy of Sciences, Institute of Medicine.

M. STOTO: Okay. Thank you very much, everyone, and again, welcome. Len, you have some house — housekeeping items for us?

L. SCHECHTMAN: Okay, just a few brief housekeeping items for today's meeting and for the rest of today. I'd like to remind everyone to sign in on the sign-in sheet at the front desk. One of them, I think, is being passed around, but there are other sheets at the front desk. Everyone at the meeting, including the public, the media and everyone needs to sign in and give their contact information please.

Just for information's sake, to remind everyone, our next Ranch Hands Advisory Committee meeting is scheduled for September 19th and we're hoping to have another meeting thereafter, possibly in November. So I'm asking everyone to please start

thinking about their availability in November and to please also start thinking about agenda items for the September and possible November meeting as well. We'll also address this later as needed.

As far as the agenda is concerned, we have one hour for public comments that begins at 10:45 this morning. And we would also like to recognize those individuals who will be making public comments at today's meeting by name. And if there are any such individuals in the room, if you could identify yourselves for the record right now and if you have any written public comments to submit, we would appreciate you turning those into the Chair at this time.

Not seeing anyone at this time, we'll just move on and note that the agenda also allows for a couple of coffee breaks so that we can have some sidebar conversations where perhaps we'll get a significant amount of science accomplished as a matter of fact. We also have a working lunch scheduled. We will be working through lunch; please do not leave. The table will be well stocked with food, so you won't be disappointed. Okay.

At this point, I'd like to read the conflict of interest of statement into the record to give everyone an opportunity to address this if needed. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such. Based on the agenda

submitted for today's meeting, all special government employees have been screened for their financial interests related to the topics at hand.

FDA has determined that all financial interests and firms regulated by the Food and Drug Administration present no potential for a conflict of interest at this meeting. In the event that the discussions involve any other product or firms not already on the agenda for which a participant has a financial interest, the participants are aware of the need to be excluded from further participation. Such an action will be noted for the record. In the interest of fairness, all other guest participants are asked to address any current or previous financial involvement with any firm whose products upon which they wish to comment. Okay.

M. STOTO: Okay. Thank you, Len. That's an — those conflict of interest things are very important issues, but they often don't apply to — in the same way to the Ranch Hand Committee as they do to other FDA committees because we're not a — we don't deal with regulatory matters. But I think it's important that we take them very seriously.

Approval of Previous Meeting Minutes

M. STOTO: The next item on the agenda is the approval of the minutes from the previous meeting; there's a copy in your folder. I believe it was also sent out in advance for you to look at and I've had a chance to review it. I think that my comments have already been incorporated in this. And we asked Dr. Michalek to review it from a

scientific accuracy point of view and that's been done as well. So I'd just like to ask at this point if there's any further comments or discussion that people would like to have about those minutes?

R. TREWYN: It is possible to make some editing changes at this point?

M. STOTO: Sure. We have to approve them.

R. TREWYN: In which case ...

M. STOTO: Please go ahead.

R. TREWYN: Page 7. Since it's my part, I thought I would actually look it over.

M. STOTO: Okay.

R. TREWYN: First bulleted point, line 3, all the stuff, "particularly substantial increases" adds nothing. The rest of that sentence adds nothing to that statement and I don't think it's necessary. So I would just say let's remove that part.

D. JOHNSON: So that's a full stop after ...

R. TREWYN: After "results."

D. JOHNSON: "Results."

M. STOTO: Okay.

R. TREWYN: Then at the last bullet, second line, "literature that cite cacodylic acid and other" — "toxic" should be in there — "non-dioxin components of herbicides sprayed in Vietnam." I wouldn't expect that all herbicides in the world would be made

part of this report, so and only things that have been reported in the literature as being toxic.

M. STOTO: How about “herbicides used in Vietnam?”

R. TREWYN: That’s fine; that’s fine. And I have one question on the next page which isn’t my — well, this is the general part and ...

M. STOTO: Before we — before we go on, let me just ...

R. TREWYN: Okay. Yes.

M. STOTO: ... see if there are any objections to that or questions, discussion? Okay.

R. TREWYN: The next page, so page 8; let me count down the number of lines here. Line 15, in the sentence that it starts, “Second, clarify that the serum dioxin measurement technique was” and my question is “invented,” if that’s the right word? It doesn’t — was “developed” or, you know, I don’t know that “invented” is the right — is the correct word. So “developed” after the ...

M. STOTO: “Developed” seems like a reasonable word to me.

R. TREWYN: And those are the only changes.

M. STOTO: Any other discussion on that point? Okay, those are helpful changes, Ron. Thank you. Other comments, suggestions for changes in the — in the minutes? Okay. Is there — would someone like to move that we approve the minutes?

R. TREWYN: Move to approve with the modifications.

M. STOTO: Ron Trewyn, okay. A second? Okay. Thank you, Dr. Camacho. All in favor, please say yes.

RHAC: Yes.

M. STOTO: Any not in favor? Okay. Thank you very much; I think that passed unanimously. And thank you to our scribe for again doing an excellent job with preparing these minutes and to Dr. Michalek for reviewing the scientific content. Okay.

Update on the Air Force Health Study Disposition Study

M. STOTO: So now the next item on the agenda — we're right on schedule — is to hear a presentation from Dr. Butler from the Institute of Medicine, National Academy of Sciences.

D. BUTLER: Good morning. Those of you who've been to some of the earlier meetings will notice some similarities between...

M. STOTO: Microphone.

D. BUTLER: There we go; I'm sorry. Good morning. Those of you who've been to some of the other meetings will notice some similarities between these slides and the earlier slides. There are two reasons for that. First of all, I wanted to make sure to catch anybody up who hadn't been at the earlier meetings. And a second reason is that I'm somewhat limited in what I can tell you about the work of the National Academies committee that's been addressing the disposition of the Ranch Hand Study.

The reason for that isn't anything particular to this study, but rather a general rule that the content of discussions and conduct of the committees is not discussed prior to the final release of any National Academies report. So afterwards if you have any questions, I'll do my best to answer them. But I wanted to warn you up front that I have to be a bit circumspect about what I can talk about in terms of what the committee has been discussing to this point. I will, to the extent I'm able, catch you up on what our progress is.

Sorry. This study was one that the Congress mandated that the Department of Veterans Affairs ask us to conduct, so the Department of Veterans Affairs is our sponsor for this study. "Sponsorship" in this particular case means that they give us the money to do the study, but is otherwise uninvolved in any of the conduct or content of it. The Congress specified five primary tasks for a committee of the National Academy of Sciences to address.

The first was the merit of retaining or — and maintaining the medical records; the other study data by which we've come to understand be the demographics, socioeconomic status and other non-medical data collected in the course of the study; and the laboratory specimens that have been collected over the six cycles of medical exams that the Ranch Hand participants have been potentially subject for when the study reaches its currently scheduled termination date of 2006.

The second primary issue was whether or not any obstacles, including and perhaps primarily privacy concerns, exist to retaining and maintaining those records. The third is the advisability of providing any independent oversight of the records, data and specimens and the advisability of further study of this material, and if so, the mechanism that would underlie that independent oversight and that further study of the materials.

The third is the advisability of extending the study itself, which would mean some continuation of medical exams or some other continuation of the study as it presently stands past the presently scheduled termination date, and if so, the mechanism and mechanics behind that extension. And finally, the advisability of making laboratory specimens that have been collected in the course of this study — those would be both serum and urine samples — available for independent research. In the course of all these is you've noted, if you've been reading along, the Congress asked us to try to scope out the costs that might be associated with conducting any of this work.

In order to conduct this study, we formed an expert committee, which is being led by Dr. David Tollerud. Dr. Tollerud is an environmental and occupational physician who was co-chair of the original "Veterans and Agent Orange Study," has since been highly involved in the National Academies studies of Agent Orange-related health effects and is quite knowledgeable in that area. Assisting Dr. Tollerud is a committee of individuals which include epidemiologists, biostatisticians, a bioethicist and specialist in privacy

concerns. And we've also added a consultant to the committee who is an expert in the management of SAS databases since that is the primary means by which the data are stored electronically.

What's the status of this study? Well, so far we've conducted two committee meetings — full committee meetings. At the first of those, we were given our charge by our sponsor and also had Joel give a presentation, a very detailed presentation, on the study itself. At the second committee meeting, we had a workshop for gathering data and I'll give you a little bit more information about that in just a moment.

And just a few weeks ago, a subcommittee of the committee went down to San Antonio to visit the Air Force Health Study research facilities. I have to emphasize how tremendously grateful we are for the cooperation that we received in that study. In that visit, we learned a tremendous amount and along with the complete cooperation that the research personnel had given us throughout the course of this study. We're just tremendously thankful for their cooperation and it's really been key to our work so far.

At our second committee meeting, we had a workshop where we discussed a number of topics related to the questions that we were asked to address. Dr. Stoto was kind enough to come and speak to us. In addition, we asked individuals who were — who've been responsible for gathering data in other epidemiologic studies, and administering the conduct of those studies and the availability of that data to independent researchers.

We were fortunate in having the health attaché for the U.S. Embassy in Hanoi, Dr. Sweeney, who formerly was with NIEHS and who's worked as a dioxin researcher for years to speak with us, and also representatives from the Congressional staff and from veteran's service organizations come and give their points of view. We are holding an additional workshop. I — actually, my first edit of this, I had "mini-workshop" because we're convening it just for a morning on the 20th of June coming up where we're going to gather a little bit of additional data regarding administration of data set — data sets for use by outside researchers.

To that end, we've invited a principal investigator of the VA Normative Aging Study which allows their data to be used by independent researchers to come and speak with us. We'll also have a representative from the Institute of Medicine's own Medical Follow-up Agency which administers a series of databases that have medical and other data on twins from various conflicts and administers those data. National Center for Health Statistics, which of course is the NHANES and other data sets at their command.

And we'll also have some researchers from a National Academies study that was recently completed that addressed access to vaccine health research. So we'll try to learn some stuff from those folks so we don't have to go about reinventing the wheel when there are people around who've had a lot of experience on this topic.

As for our future plans, we're going to be very seriously into report writing for this report over the summer. We'll have a final committee meeting at the end of the summer and we intend on releasing the report in the fall of this year. It's a bit early for me to make an estimate of just when that's going to be, but I will make sure that Dr. Schechtman is — and Dr. Stoto are well informed of our progress, make sure that this Committee is kept aware of when we — when we're ready to release the study.

Just a couple of general slides here. You can monitor, albeit in a rather abbreviated manner, the progress of this study and of any other National Academies study on the "Current Projects" web site for the National Academies. I've listed the web address — general web address there. And if you go to "Current Projects" and put in the keyword "AFHS," you'll pull up our study.

The full text of all of our reports, including a large number of reports on veterans and Agent Orange, is available via the — for free at the National Academies Press web site. And we maintain a site called veterans.iom.edu which is intended to be a one-stop shopping location for all of our reports on the veterans of various conflicts. That finishes my presentation. I'd be happy to take any questions.

M. STOTO: Thank you very much, David. Are there questions? Okay. Paul?

P. CAMACHO: I was going to ask through the Chairman, do — does this Committee — what's the relationship between this Committee and Mr. Butler's committee? Does that committee have any possibility of submitting any position? Is

that a proper role for us? That never — we touched on that the last time, but we never really came to a conclusion.

M. STOTO: Let me — the next item on the agenda is my report about having present information at this. So suppose I'm — I'll do that report. I'll tell you what I said and then we can come back to the question of does this Committee want to say anything else beyond that.

R. TREWYN: And can I ask a ...

M. STOTO: Ron?

R. TREWYN: With your report on that, do we have a handout for that? Do you — did you do a PowerPoint or a written — and so do we have a copy or will we have a copy of that?

M. STOTO: In fact, I did do a PowerPoint and it occurred to me this morning I should've brought copies for everybody. I brought one copy. David, did you post that material on the web site? Often, the IOM does that.

D. BUTLER: I don't believe it is posted at the moment. You're right; it ought to be. The presentations from the first meeting, including Joel's, are up on the web site at the moment.

M. STOTO: Okay.

D. BUTLER: It's a good point and it's something we'll work on.

M. STOTO: Well, let's do two things. One is I'll give — I'll send a copy of my notes electronically to Len and ask that you distribute them to everybody although — because I'll tell you what's in them now. And then secondly, if you would let us know when that material is posted, that way we'll be able to see what the people said, not just me.

D. BUTLER: I'll do that.

M. STOTO: And we'll circulate that to the Committee.

D. BUTLER: I'll be happy to copy both of you in on that.

M. STOTO: Okay. Do you want to try — do you want to try to Xerox these now?

L. SCHECHTMAN: Yeah, we can do that as well.

M. STOTO: Okay. I need them to give my ...

L. SCHECHTMAN: To give your talk first.

M. STOTO: Yeah. Yes?

R. TREWYN: Just one other question, Dr. Butler. Are you going to be with us all day today?

D. BUTLER: Yes, I will be.

R. TREWYN: Okay.

M. STOTO: Okay.

D. BUTLER: Thank you.

M. STOTO: Anything else? David, can you just sit at the table for the time being ...

D. BUTLER: If you'd like me to.

M. STOTO: ... for the next part? Okay. Well, thank you very much.

Report on the Air Force Health Study Disposition Study Workshop

M. STOTO: The — as David said, I attended the meeting on April — the workshop on April 14th. I tried to make clear at the beginning that I was speaking for myself because I can't speak for the Committee unless the Committee decides on what it — what it should say and so on, so we will have an opportunity to see if you want to add anything to that. I also made it clear I wasn't speaking for Rand, which does lots of work for the Air Force on — in different settings altogether. And of course, I wasn't speaking for the Institute of Medicine where I used to work on these issues.

So what I — what I did was I began by talking about my understanding, which I think is our shared understanding about the purpose of the Ranch Hand Study: some of the key issues of the design; what are the endpoints looked at; schedule; noting the fact that the people in this study were relatively highly exposed to dioxin compared to other available human studies; summarizing the amount of information that is available: the number of physical exams, the number of — various kinds of records, showed a picture of this — one of the — one of the Ranch Hand staff in this long stack of paper; and also

emphasized the fact that it was not only the paper, but it was the staff who knew where everything was — that was a valuable resource — and then noting that there had been lots of research results that have already come out of this, both the five-year reports and the reports in the scientific literature, and presentations and meetings, and so on.

And there were two issues that I thought would come up, and in fact, did come up during the meeting that I tried to hone in on. And one of them was the issue of what does it mean to continue the study? And of course, that means different things to different people. I suggested that I personally felt that there probably was not value in doing more physical exams, given the age of the — of the — of the subjects and the amount of information we already have on that.

But there were two other ways of continuing the study that made sense. One would be to complete the research already in progress — the kind of things that we'll be hearing about today — and the other one is to monitor mortality of the study subjects; that can be done relatively inexpensively compared to physical exams and so on. I think that Richard Sussman from NIA, National Institute of Aging, had some other kind of intermediate thoughts as well which I now forget what they were, but they were along those lines.

And — but extending the study, I tried to distinguish that from the idea of retaining the materials, and maintaining and giving access to researchers of those materials. And the point that I tried to make was that although it wasn't the original goal

of the Ranch Hand Study, in fact, it is a — what we have is a longitudinal study of men with very detailed information on a variety of occupational, and other health risks and outcomes. And to me, and I think this reflects the view of the Committee, there was a clear value of retaining and maintaining the study materials.

In order to study, I listed four things — at least the following four: the health effects of herbicides and dioxin in veterans, which of course, was the main original purpose; other aspects of military health, and environmental and occupational exposures; three, chronic disease risks in general; and four, normal aging. We basically have a couple thousand men that we know quite a lot about how they aged over a period of a quarter century or so. And although if normal aging or chronic disease risks were the — were the purpose of these studies, you probably would've designed the study differently; that's not the issue of course. The study is what it — what it is.

The question is, is there value in maintaining access to that material for those purposes and other purposes? I tried to suggest that if researchers in those fields and in other fields knew of the availability of the Ranch Hand Study, in fact, if it were available and they knew about the availability, that they could, in fact, raise funds through the normal channels to do a lot of interesting research and they would be creative in coming up with ideas about what could be done with these — with these data.

So I tried to separate — tried to clarify this idea that there's two different elements of cost. One is the cost of and the logistical aspects of maintaining this material: the data, the specimens and so on, which is not insignificant, but actually may be small compared to the cost of doing additional research. And I don't think that, you know, NIH — let me put it this way. I don't think that — I wouldn't want to ask the Air Force or other agencies to bear the cost of the research, but there might be an argument for some government agency to bear the cost of maintaining the material so that it's available to researchers; that's the distinction I tried to make and I'm — I also raised the issue about the consent to use the records and materials.

The one bit of information we know about this goes back to the last round of examinations where the subjects were asked whether they would consent to their — the use of records and materials for "Agent Orange and military health studies," "Agent Orange only," do not use" or "other." And, in fact, the — almost 96 percent said "Agent Orange and other military health," another 3 percent said "Agent Orange only," and only 1 percent said "do not use." Now of course what that means about being able to use it for studies of normal aging and so on I think is up in the air and that's something that I presume that the IOM committee is looking at. So that's the report that I made. Ron?

R. TREWYN: Yeah. I guess one of the things I think because of the role that this Committee has played, I really think going along with Paul's point, wondering if we really shouldn't see if there are some parameters that the Committee is comfortable with

endorsing related to see as follow-on action so we don't just each have to wind up or, you know, as individuals on expressing opinion, which all of us are certainly willing to do.

M. STOTO: Yeah.

R. TREWYN: But I think that really might be of value because of the time frame. And clearly, I think, there are components of this. I mean, I'll just give you my personal opinion. I really see that there are some aspects that have come out, especially over the last few meetings we've had, that re-analyzing existing data with new information appears to be a very valuable thing to do; that we're finding more significant effects when the numbers are run in a way or analyzed in a different way than they had been as part of the protocol. And I think as I ...

M. STOTO: I would add more deeper understanding.

R. TREWYN: A deeper — yeah. I mean and it's — yeah.

M. STOTO: Yeah.

R. TREWYN: It's nothing wrong. I mean, you have new learnings that come out of the analysis of the data. And even as I reviewed the slides of the things that we're going to hear about today, that it really does appear there is a lot more to be gleaned. And so my view is that there really might be aspects of that where some targeted funding to allow the data to be more fully analyzed from a variety of directions would be appropriate and important.

And then going along with your comments about and then a more broad availability of the materials for analysis by investigators that would go through standard competitive routes, I think would be — would be critical as well because it would be a shame to lose this very valuable information. And then the issue about the specimens, that one is it — I see as a tougher issue having been involved in some tumor banking things over the years of whether this stuff winds up being made available if it is kept and how that would be done.

I think that's going to be a difficult component for the committee to evaluate, but something that certainly — and I don't know whether this group would be able to come to a consensus or not. But I think — I think it would be good if we could at least as a Committee see if there are items of this that we could come to an agreement that we want pushed forward from the group.

P. CAMACHO: That maybe we — maybe we should at least offer as the Committee, a Committee position and then possibly if there's that great a dissension have individual, you know, bullets, if you will, encapsulated. Because my interest is how tied are any of the five features to each other? I mean, we have an independent board. I'm interested in five. I like the idea that the data should be maintained.

M. STOTO: So when you say "five," you're referring to five in Dr. Butler's presentation?

P. CAMACHO: Yes. Yeah, so and I believe that this data is going to be potentially very valuable down the road. You don't know what's happened. You have a huge database; you have a huge data bank; it should be kept. And I agree with the separation of the funding. But you don't know who's going to have funding even five years from now, who might come up with something.

And if the protocols are — if the parameters of this are sort of — I don't know what's the best word for this — "advertised" as it is or it's put out there and people know about it, that it's this database that's available. Then who knows three years from now somebody comes up with a proposal and like you mentioned, our knowledge could be expanded on this. So that's my concern; is do we as a Committee have any input? I mean, can we — and does he have a right to refuse it as taken?

M. STOTO: Well, first of all ...

P. CAMACHO: You know, all of the above.

M. STOTO: ... let me say that the reason I asked David to remain here at the table so he could answer questions like this. And I — but I think the key point is he's here listening to us.

P. CAMACHO: Yeah.

M. STOTO: So one question I'd like to ask you, David, is we'll summarize this discussion in the minutes and hopefully we get at least this part of it ready soon that we

can let you see. I mean, would that be valuable? Would it make a difference if we did something more formal than that?

D. BUTLER: We'll take things in either format. We are interested in learning more. We're trying to vacuum up every piece of information we can get. Those of you — well, like Mike who came to the last workshop, we learned a lot there. It was interesting hearing from the representatives, the veteran's service organizations there. That was a perspective that we hadn't gotten before and that wasn't represented on the committee. It was tremendously useful for us to hear that.

Equally, we would be happy to take information from this Committee. Anything you'd like to produce either in terms of minutes or in terms of a more formal statement, I will make sure gets circulated to the entire committee.

M. STOTO: Okay. David, did you want to say something?

D. JOHNSON: Well, I had a couple of questions that came to mind. One that keeps coming up with is the consent in the process and whether or not the one consent you talked about is — that would be adequate for various researchers to do whatever they — the creative research they come up with.

But as I'm — and my other thought though in thinking about this, it seems like the charge of this Committee, and I don't know exactly — I can't recall exactly how we came up with the National Academy of Sciences to do what they're doing, but it seems maybe we shouldn't be trying to do the same thing here and coming up with different

directions. If we've — I think this Committee — didn't we approve them looking at this issue of ...

P. CAMACHO: Well, this is ...

M. STOTO: First of all — first of all ...

D. JOHNSON: Pardon?

M. STOTO: Let me ...

P. CAMACHO: Go ahead.

M. STOTO: I want to remind everybody that Mr. Silvers' crew from ABC News is here filming this, not that we have anything to hide, but just for people to remember that. Secondly, you're right that the Congress mandated ...

P. CAMACHO: The law — it's 108-183.

M. STOTO: ... this study. I mean, we did — it is true that we made recommendations that such a study be done and in the past, but the Congress mandated this — the study that David is speaking about.

P. CAMACHO: But the question still remains, this Committee has been in existence. Whether we've served on it two years, four years, whatever ...

D. JOHNSON: Right.

P. CAMACHO: ... has been in existence for as long as the study has been in existence.

D. JOHNSON: Right.

P. CAMACHO: So it's like 22 — 20 years — 22 years. So it seems to me that there's a position for this Committee and to state that we ought — we're shirking our duty in a way if we don't in the name of the Committee and this study submit at least a position paper on what we ought to think. And what that — what that board — what the — what Mr. Butler does with it is another — is another question.

D. JOHNSON: Yeah.

P. CAMACHO: My job — I see my position on this Committee, as you know, as one to representing in some ways the veterans' position on this. As a sociologist, I see this very differently from the medical people and epidemiologists. So that's the bottom line and I'm sure Mr. Butler heard it from Rick Weidman. This is — this is a very different issue for veterans.

And we would say or I would say — not speaking for everyone — but I'd venture that for soldiers of the future, there's a piece here that research down the road might break into and that we have an obligation to make sure that that data — this wealth of data, the 20 years of data is available. You don't know what can happen and we said this before the recent conflict started. I remember saying this and we were speaking about this before this recent conflict started. Who knows what somebody might find that might help the soldiers in the future? And that to me is an obligation.

M. STOTO: Sandy, did you want to add something?

S. LEFFINGWELL: I would agree with Dr. Camacho. If we have any thoughts that might be helpful, we should submit them to the Institute of Medicine. The — I've worked on some NRC committees and they feel quite free to ignore anything they get if they don't like it. And I think it's okay for us to put it out there and let them and their expertise decide whether to listen or not.

M. STOTO: Well, I think — I think the issue is whether there's any more that we want to say. You know, we have written, I think it was two letters, about these issues. I think this would probably be the third or the fourth time that David Butler has come out here to talk to us: maybe twice before the study started and twice since then. And I'm sure he's heard quite an earful from us and I've had this chance to present. And so the question is — I mean that I'm happy if people want to add something to that, but I think that's the question.

R. TREWYN: And reminding us of — reminding me of the letters that we had submitted, in fact, we may have already stated our position on the importance of doing this as adequately as we — you know, from the Committee perspective ...

M. STOTO: Right.

R. TREWYN: ... because that really was done on behalf of the Committee. And maybe we've addressed all of those points — now the more that I think about that — in those and don't necessarily need additional action, but I assume any of us individually

can provide our input. And I think before, Dr. Butler, you had your e-mail or something on here and I don't see it this time, but ...

D. BUTLER: I apologize. The best way to get comments into the committee is to use our committee mailbox, which is afhs_study@nas, for National Academy of Sciences, .edu. And the one thing I would do is to remind everyone that anything they submit to the committee also becomes a part of our public record, which means that interested individuals can come by our public records office and review the file.

RECORDER: Dr. Trewyn, the web address is on page 3 of the minutes.

R. TREWYN: Page 3?

M. STOTO: It's in the minutes. Okay. Well, let me — let me float this as an idea. You — I think you all now have a copy of my — of my remarks and so one possibility would be for you to just agree with me and have that be in the record. And I mean that I'm not sure would — it certainly wouldn't add any evidence, any more additional information, but that might strengthen to some degree the way that the — that the Committee thinks about it. Of course, you could — we could also add things as a Committee or as individuals to what I had to say and we could also write a letter saying these things too, but I guess I don't feel that that is likely to make a difference since the ideas are already there. Sandy?

S. LEFFINGWELL: I had one additional thought to related to the point 5, the availability of specimens to researchers. That's a limited resource. It might be best if

that is done to do it in a batch mode with applications considered as a lot every two years, one year, three years — whatever seems appropriate — rather than just considering them piecemeal as they come in. "Yeah, this is good. Well, I don't know if this is good or not." And that way we'd have — the people who are handling it would have a better idea of what could be and couldn't be done.

M. STOTO: There was some discussion at the — at the workshop about a related issue, I think, about who should get access to these data and having a process for deciding that. And some of the — am I right about this, David? I mean, some of the existing studies like the, you know, the — what do you call the study in Massachusetts? — the Framingham Study have a process for deciding who gets access to this data to make sure they're legitimate researchers; that they are not likely to abuse the information and so on.

D. BUTLER: This is a topic that we're going to be dealing with this in this mini-workshop on the 20th. In particular, all I can tell you because I've already sort of — I've already been briefed on what he's going to say, the principle investigator of the VA Normative Health Study will talk about their process: which includes a review of the research proposal, which includes having a member of their staff as one of the investigators on the study as sort of a quality control check, and also a monitor to ensure that the data are being used properly and in a manner that respects the privacy of the participants.

They also, for example, have a system by which you are — one is only given the data that you need to conduct a particular study that's been proposed rather than access to the entire data set; where unique identifiers are generated for each time the data go out so you can't go match it back and by going through several researchers try to reconstruct the data set; and other checks that are intended to make sure both the research coming out is of high quality and that it respects the privacy of the participants. But that's the sort of thing that we're gathering additional data on for the workshop.

M. STOTO: But I guess — but that is the kind of thing, saying if you had some thoughts, it sounds like they would be open to them. And perhaps they could be discussed by the Committee, or endorsed or not or whatever. Ron?

R. TREWYN: Just one more quick question. I note that the — you're anticipating a late fall — just thinking in terms of our meeting schedule, since we're targeting a November, it would sure be great if we had that to review at our November meeting.

D. BUTLER: I would love to have it available then, but I don't have complete control over this schedule. Our review process can be challenging sometimes, and while we try to write a strong report that goes into and sails through review easily, like any other time when you submit a paper for independent outside review, you never know quite what's going to happen with it.

What I can tell you about our review process is, is that we will name a number of individuals whose identities are blinded to the committee, who'll be asked to make comments on this draft. Our own process requires that we deal with each and every one of those comments, even if it's for the committee to say that they don't quite agree with the reviewer's comment and to clarify the text to make sure that his or her point has been properly addressed. And finally, we go through a coordinator who's responsible for looking over our responses and to ensure that they've been properly addressed.

M. STOTO: I think one thing it does suggest is that to the extent that we have some freedom, the later in November the better in terms of the more likelihood that they'll be done. Okay.

L. SCHECHTMAN: Okay. We'll try as late as we can in November. We'll survey the members and the Air Force for availability and we'll try and do it just short of the Thanksgiving holidays.

M. STOTO: Right. Any other comments about — substantive comments?

E. HASSOUN: Yes, about the study design ...

R. TREWYN: Microphone.

M. STOTO: Turn your mike on, please.

E. HASSOUN: ... you have suggested using the medical records, military and civilian, employment history and biological samples. I have some concerns about using biological samples that are kept in the freezer for 20 years — was the — about the

quality of the stored data that will be generated from such samples. I mean, we could use the medical records and the employment history, but biological samples, I don't think it's a good idea to use them.

M. STOTO: Well, you're referring to my slide 6, I think, if I'm right?

E. HASSOUN: Yes.

M. STOTO: And that, of course, is just a description of the existing study.

E. HASSOUN: Okay. So ...

M. STOTO: So ...

E. HASSOUN: ... they're not going to do any more?

M. STOTO: And I — my recommendation was not to collect any more biological samples.

E. HASSOUN: Okay.

M. STOTO: But I think the issue is for the samples that do exist ...

E. HASSOUN: Yes.

M. STOTO: ... should they be made available? What would it take to make them available? What would it cost and so on? And that really is the — that that already is within the charge of the Committee.

D. BUTLER: That's right.

M. STOTO: Yes.

D. BUTLER: Two of the members of our committee, Drs. Kalman and Santella, are specialists in management and analysis of biologic samples. And they are addressing those sort of issues in detail and that will be addressed in the report.

P. CAMACHO: The other piece is it brings up, if we had a batch mode with the samples, do we — do we necessarily have the — have to have the same restrictions on all the data or on parts of the data? It seems to me the SAS files, you know, the access to the — to electronic files and access to records is a lot different than having access and utilization of samples. I wonder if there's different pieces and then what kind of restrictions?

If you're going to follow the VA, I have to — I have to be a little worried. I mean, they have "mine guards" over there and I wouldn't — when I say — when you want independent research and they're going to assign somebody to make sure the research goes okay, that can be interpreted a lot of different ways, especially by those people who have familiarity with the agency. So I'm going to spring — I wouldn't have put it that way, you know, but that's just to clue you in on that.

D. BUTLER: Well, as I said, we're gathering information from a bunch a sources. The Maverick Study is one example of how this has been administered; we have others. And as you noted, one of our other charges is to look at the advisability of independent oversight over any future use of the materials. And that was a topic that

the veteran's service organizations addressed. One of them, Rick Weidman from VVA ...

P. CAMACHO: Right.

D. BUTLER: ... addressed in his talk to the committee at the last workshop.

P. CAMACHO: I think credibility is very — I think — I believe it — personally, I think that the credibility would be greatly enhanced with a fair and independent oversight board that reviewed — that reviewed projects and that allowed different modes or different, let's say, levels of access, or sizes or, I guess, of access depending on the data and the — and the kind of study you're looking at. Some of these studies, you're not going to need any kind of personal information pieces, and you're not going to need access to samples and so forth. It's just I just feel strongly that the future potential of this data should be preserved and utilized. Thank you.

M. STOTO: Sandy?

S. LEFFINGWELL: I don't know whether it's commonly done in government agencies, but at NIOSH we used to try to protect data by offering to run statistical analyses from the database rather than release any part of it.

M. STOTO: Okay. So I think that the main new information that came out in our discussion, it really had to do with methods for giving access to the data and the materials to people; the idea that there might be some group to make decisions about this in some organized way; that the government agencies who maintain the data —

whatever agency maintains the data might actually offer to do analyses rather than give the raw data; that there might be different kinds of ...

P. CAMACHO: Levels of access.

M. STOTO: ... levels of access for different aspects of the data and so on.

P. CAMACHO: And the Census Bureau would be another place, look at some of the census protocol.

M. STOTO: Yeah. Turn your — turn your mike on.

P. CAMACHO: Looking at some of the census protocols that they use on all the sub-studies like the, for instance, the economic study survey.

M. STOTO: I mean, the National Center for Health Statistics has dealt with these issues a lot and I saw that they're in the workshop too.

D. BUTLER: Yes. We'll have someone from that office. They're still talking about just who ...

M. STOTO: Okay.

D. BUTLER: ... come by to talk to us about how they do it.

M. STOTO: Ron?

R. TREWYN: And I believe, again, thinking back on the letters that we wrote, I believe our stance of this whole Committee was that maintaining these records and having the stuff available for future study I believe was the position of this Committee.

And so I think — I think we're on record already from our advice as a Committee being to do that. So I ...

M. STOTO: Yeah.

R. TREWYN: The more I consider it, I think we already have covered that ground and ...

M. STOTO: So I guess I suggest that, you know, I mean, I think this discussion, which will be reflected in the minutes, suggests that there — I pretty much got what the Committee had in mind, and that we had some additional ideas about access that David has recorded and that will be in the minutes which we'll try to get. Maybe we can — we can get this part of minutes transcribed quickly so that we can give it to the committee in time for its next — the meeting at the end of the month. David?

D. JOHNSON: As this data is kept and used in subsequent studies, who has a responsibility of maintaining it and, you know, giving it out to folks who are requesting it? Who has that responsibility?

M. STOTO: Well, that ...

D. JOHNSON: Or is that something that they're ...

M. STOTO: That's for ...

D. JOHNSON: ... they're working on now?

D. BUTLER: That's something that our ...

D. JOHNSON: Okay.

D. BUTLER: ... committee will address.

D. JOHNSON: Okay.

D. BUTLER: And again, we ...

M. STOTO: Or should ...

D. BUTLER: I want to emphasize — I'd like to emphasize that we will be offering, you know, alternatives and recommendations to the Department of Veteran's Affairs and to the Congress in this report, but we don't have any decision-making capability on this. This is information we provide so they can make the decisions.

M. STOTO: And I guess the data and the samples belong to the Department of Defense?

D. BUTLER: That's my ...

M. STOTO: Yeah.

D. BUTLER: That's my understanding, yes. Well, not to get all technical about it, they also belong to the subjects.

M. STOTO: Okay. Okay. Anything else on this subject? Thanks everyone and especially thanks, David, for your presentation and discussion.

Air Force Health Study Comprehensive Report

M. STOTO: Now just — I want to turn now to this question of — the issue about the comprehensive study report, but it just occurred to me that there's no person named

on that one. Is there someone from the Air Force or SAIC is prepared to talk about the plans there?

M. BLANCAS: The agenda that we have indicated you were going to speak.

M. STOTO: Me? Okay. I will do that then. I mean, I hope that someone can respond to this, so is that — would that be directed to Karen?

K. FOX: Yes, we will give you somebody to respond.

M. STOTO: Yeah. Okay. I was — I was in — there's a shopping mall across Rockville Pike here and I was there just after our last meeting. And there is a place across the — a restaurant called "The Mosaic Café." And the first time I looked at it, there was a truck blocking the first two letters and I thought it was "The SAIC Café." These guys are everyone now, you know.

So there is a two-page description of this — of this study in your handout and we sent it out in advance. It's entitled "longitudinal study," which I think is a little bit of a misnomer. But my understanding about this is that this is a contract that is either in place or soon to be in place between the Air Force and SAIC to write a report that summarizes the results from the five-year — the regular five-year blue-cover reports that this Committee has been reviewing.

They — those reports, of course, dealt with one examination at the time — at a time and they used a consistent set of statistical analyses and so on. And the idea, if I

get it right, is that they want to pull together in one approximately 50-page — if I have that right — report that summarizes all of that.

K. FOX: Plus any other research that we've done, so all our published reports will be ...

M. STOTO: You turned your mike off.

K. FOX: Oh, not just the every five years reports, but the — also our additional research that we ...

M. STOTO: The stuff published in the scientific literature and so on?

K. FOX: Yes. That is going to be rolled into this study.

M. STOTO: Okay, and there is an outline at the — in the first part of that handout about what they would do. The results are to be organized by subject area rather than by examination period or anything like that. And I think this all makes a lot of sense and would be a very useful document. I guess I have two concerns. The first one is that just the name "longitudinal study" is inappropriate; that suggests the results you get from following people at multiple observations over time and this is a kind of a summary report.

K. FOX: This will not have that title on that.

M. STOTO: Okay. That's a — that's a pedantic point. The second one, which I think is more important is — has to do with the paragraph that ends — it's at the bottom of the first page and carries over into the second page about the report being written in

simple language without p values and only statistically significant results be discussed. But the word “statistical significance” — the words “statistical significance” should not be — not be used.

And I guess I feel that it is very important to make this material accessible to a — to a broad audience. And it’s going to be a challenge to do that and to summarize everything that’s been done, but sort of — and I — and I also think that it probably does make sense to focus on the results where you actually found, you know, the outcomes for which you actually found results in the conventional way. So using statistical significance to guide your — how you — what you emphasize, I think, makes sense.

For instance, you know, some of these areas where there’s never been a statistical significant result in the course of a — of a quarter of a century, we probably should just say “and we didn’t find anything with respect to so-and-so” and then go on. I think the challenge is to do that without saying what you’re doing, I mean, essentially. If you don’t use “statistical significance,” how do you describe what you — what you did? And there will also be a situation where you may want to, you know, in a certain analysis, you find an elevated risk for group A, but not for group B, you know, the — and, you know, the officers, but not the enlisted men, for instance, or the other way around.

And to be complete, I think you need to give the whole analysis there, but to say — but — and you can’t just leave out the part that was not significant because the fact

that it was not significant is part of the story; that it was significant here and not there. So I guess I — my main point is that I think that the goal of this paragraph is correct, is to make it accessible, but the — but the specific way that you — that this paper proposes to go about it by just not using the words is not likely to be effective.

K. FOX: All right, we'll take that into — the contract has been awarded, but there's always — we can always change ...

M. STOTO: Right.

K. FOX: ... if we — so we'll take this back and discuss it. Do you want to say anything?

W. GRUBBS: Bill Grubbs, SAIC. Dr. Stoto, in response to your comment, I think under the "Introduction" section, the last bullet, "description of the writing strategy," on the — on the outline — do I have that right?

M. STOTO: Yeah.

W. GRUBBS: That basically what your comment was in the last paragraph that goes to the next page, that could be outlined in the description of the writing strategy to give the reader an idea of what to expect to see.

M. STOTO: Yeah. So that one — so that paragraph would basically lay out the strategy for what gets featured and what is ...

W. GRUBBS: That's correct.

M. STOTO: ... gets less attention in this report?

W. GRUBBS: That's correct.

M. STOTO: I think that that's probably right, yeah.

W. GRUBBS: Okay.

M. STOTO: Other comments? Ron?

R. TREWYN: I've always got a comment; you know that, so I'll go back to my favorite topic since I haven't raised it yet today. Back from the observation in 1999 about the number of the — of controls that were actually stationed in Vietnam versus the controls that were not stationed in Vietnam and so my hope is that under group when — and that's just one example because I think there are going to be examples. As I looked at the slides for today of when they were in country versus, you know, other groups in country, that there are ways of slicing these — the groupings in ways that are meaningful.

And I think very often we have got either insignificant findings or marginally significant findings when, in fact, you wind up grouping these studies — these individuals in different ways, all of a sudden, the significance goes way up, which clearly some of the published reports and some of the things in train are showing that; that when you — when you assess the groups or assign the groups somewhat differently and re-analyze the existing data, that all of a sudden the significance goes way up. And I think that's, again, it's a — it's a key element that I think needs to come out of this.

So even in some areas where to date there have been not huge observations of importance to the health, that in fact there are indicators that by slicing this in different ways that in fact in some areas — and cancer being one, but it could be in other areas now — that if one went back, and sliced some of these others and analyzed for these other health effects in that same way that the — it could be significant.

It gets to the — my standard argument of why this data needs to stay there, and be worked and analyzed because I think it's only been really in the last couple or three years where some of these things have come out by doing this that it really gives us some highly, highly important observations that we had missed in the past. So just want to harp on that a bit.

M. STOTO: Karen, do you want to respond to that?

K. FOX: We understand what he's saying. We're going to try to keep on — don't touch it ...

M. STOTO: Keep your hand off it.

K. FOX: Don't touch it. We will look to make sure — that probably would go into a summary paragraph just, again, what's the strengths, weaknesses type of thing that we — what we didn't cover.

M. STOTO: I guess I think that the point you made at the outset when you said that this was all — you're going to incorporate the results from the scientific literature as well is the opportunity to bring some of that in.

K. FOX: Correct.

M. STOTO: Because I think that Ron is right; that stuff is beginning to come out, and it's very interesting and we'll see it some more today.

R. TREWYN: And just following up — I mean, as also a Vietnam combat veteran — these issues in looking at it from the veteran's perspective, I think it's been one of the arguments that veterans have been pushing for years; that when they would argue that there's a cover-up involved, which we used to hear at various Congressional hearings and whatnot, well, in fact, what we're finding is that by reassessing the data using, you know, with new findings that have come out as through the course of this that while all of a sudden some things that showed no significance by re-analyzing they are significant. So I think this really does help us to really be very clear about those points so the veteran's community really believes they're being served as part of this.

M. STOTO: Now the challenge here, I think, is the timing. The skin cancer results have been published, haven't they — the ones that show in country and out country?

J. MICHALEK: I'm sorry; repeat that question.

M. STOTO: The results about length of service, and in country and out of country, and skin cancer and so on have been published?

J. MICHALEK: Yes. There's a paper published, but what's published is different from what you'll see today.

M. STOTO: Okay, but the issue is that there's a number of things today that are new.

J. MICHALEK: Yes.

M. STOTO: And I presume they cannot go into this report because ...

K. FOX: Why not? We know there's a — we're — they are in the process of being ...

M. STOTO: Okay.

K. FOX: ... done and I don't — the results that can be put in.

M. STOTO: Well, it's not that simple. I mean, one thing might be that if you — if you publish them in this summary report, then they — some journals may not want to have them.

R. TREWYN: Chop up the data.

J. MICHALEK: Yes. I don't think that, you know, that's been a concern from the beginning; that the blue covered reports would interfere with our ability to publish in peer-reviewed journals. I don't think that's ever happened and we've got a 25-year history now of that. Your words are correct, but I don't think we've ever experienced that.

M. STOTO: Okay.

K. FOX: What — how it's been written is that it's only what's been published, and what's been published and in press that we're waiting to be published, *i.e.*, that the journals have accepted ...

M. STOTO: Have been accepted, yeah.

K. FOX: ... but has not published yet. Those are being added.

M. STOTO: Okay, and what's the schedule you said? The contract for this has been awarded?

K. FOX: Yes, it has.

M. STOTO: And how long do they have to ...

W. GRUBBS: I had a feeling you'd ask that question. Our first draft report is due to the Air Force September 23rd. I'll be talking with members of the Air Force; it's in development now over the summer, but that's a first-draft schedule.

M. STOTO: Yeah.

W. GRUBBS: And then it will go — undergo, I believe, two reviews. So ...

P. CAMACHO: I turned them off, go ahead.

W. GRUBBS: ... probably by the end of the year you would have a final report.

M. STOTO: Okay, but so the stuff that's being presented today ...

R. TREWYN: Yours is now off.

M. STOTO: Oh. The material that's being presented today probably will not get into the — at least into the first draft?

W. GRUBBS: I have not reviewed it for inclusion in that; that's correct.

M. STOTO: Okay. Paul, did you want to speak about that or ...

P. CAMACHO: Well, do you — who's on that? Can I ask, do you have any political scientists or sociologists on the team? You're going to save your — so well here's my point — you're going to save yourself a lot of grief with — if you get a nice chunk of "how did we come to this point?" Before you even did all the research, what was all the palaver about this: the spraying and the whole thing? If you lay that out properly to begin with, you won't have people throwing grenades at you; that's the bottom line I'm trying to get you to ...

W. GRUBBS: Right.

P. CAMACHO: Otherwise, that's what's going to happen and I — there's no doubt. These guys may be old now, but they still ...

W. GRUBBS: Can throw grenades.

P. CAMACHO: ... can still can throw, so you should do that. I mean, really, if you have a nice picture about the controversy and everything around it, just be up front with that saying, "Here's how we came to the study" and then "this is what we did." For good, bad or the otherwise, this is what got done so that nobody can throw a rock at you saying, "You were hiding things" because that's the past history about that.

We're looking at this now today, but if we went back 25 years and talked about the committee hearings of 25 years ago, you wouldn't — they'd have the — they'd have

the police up there, the Capitol Police up there because they were loud, boisterous and very angry hearings.

W. GRUBBS: My current plans were to take what you've seen in introductions to the report — to articles, the existing material — and put them in a unified manner in the first chapter of the introduction.

M. STOTO: Yeah.

W. GRUBBS: So I wasn't planning to reinvent anything, but use the existing reviewed materials.

M. STOTO: So you've got the first two bullets here are "Background" and "History." And we did discuss this with reference to the last five-year report that we reviewed the last time and including the fact that the kind of the purpose of the study has somewhat — the focus of the study has somewhat changed over time, right?

W. GRUBBS: Yeah.

M. STOTO: Yeah. David?

D. JOHNSON: A couple of questions, so is the plan for this to be sort of the final review of this study?

K. FOX: With the time left for this study to be in existence, this probably will be the last to do the final of what the — we can accomplish within this — the time period that we have.

D. JOHNSON: And the review process for finalizing this is what or how does the review process work?

K. FOX: SAIC will present the first draft to us. Then the technical team, Air Force Health Study technical team, will review it and we will send back our changes. And then SAIC will give us a second draft and we will review that. And then they will give us a third draft and we will review that.

D. JOHNSON: Is there any ...

M. STOTO: Well, we should discuss that. Yeah.

D. JOHNSON: Is there any review within this Committee?

M. STOTO: Right.

D. JOHNSON: Or is there ever — I don't mean to bring up — is there the possibility of a public comment before it's finalized or something?

M. STOTO: Well, first of all, I think that we should expect that this Committee see it; that is our — it is our responsibility to do this. If we're going to meet in September — what day are we meeting in September?

L. SCHECHTMAN: 19.

M. STOTO: 19th and the first draft ...

K. FOX: Is the 23rd.

R. TREWYN: We'll have a rough draft.

W. GRUBBS: Dr. Stoto, what I'd recommend ...

M. STOTO: Yeah.

W. GRUBBS: ... if you're having a November meeting, that would give the opportunity for a first draft, their review, for us to ...

M. STOTO: Okay.

W. GRUBBS: ... address those comments. And then before we make a final report, very similar to the report that you just reviewed ...

M. STOTO: Okay.

W. GRUBBS: ... that would be an opportunity to review the materials and that.

M. STOTO: Does that make sense to the Committee, that timing?

D. JOHNSON: Could you review time — timing again?

K. FOX: What would happen would be that on the 23rd, we would — the — for just as we did the big study just recently, the Cycle 6, what happened was ...

D. JOHNSON: 23rd of?

K. FOX: Cycle 6 ...

M. STOTO: September.

K. FOX: The 23rd of September is when we, the Air Force, received it from — receives it from SAIC. Just like the previous one, we reviewed that, sent it back. What you got, the Committee got for the cycle 6 was our second — our second stab. That's what we would be giving to you then in the November time frame is that you could then look at the one that — what we've cleaned up so that it's all — it's almost ready to go.

M. STOTO: Okay, and there would be — and it's still an opportunity in that time to make changes? Is that right?

K. FOX: Yes.

M. STOTO: Okay.

D. JOHNSON: Approximately how long would we have to review it?

M. STOTO: Good question.

K. FOX: We can get back with you with actual, the time-lines to see when we could fit that in and all.

M. STOTO: But something like maybe two weeks in advance of the meeting, the November meeting?

K. FOX: I think that would be possible, yes.

M. STOTO: Does that — does that seem reasonable? Yeah.

D. JOHNSON: I mean, would you make assignments again so we'd have certain areas?

M. STOTO: Yeah, and I think that we should make assignments on that.

K. FOX: Dr. Camacho made the comment about the history. We are also trying to, SAIC's been tasked to develop a paper outlining the history of this study, the — some of the whole broad picture, the whole 20 years trying to explain what happened, how we developed what we developed and that. So there is — that is also another

tasking that we are trying to do to give — to give historical for somebody else; that if they ever did ...

P. CAMACHO: There's a good literature ...

K. FOX: ... something like this kind again.

M. STOTO: Turn your mike on.

P. CAMACHO: There's a good literature review. You're saving yourself a lot of trouble doing this — by doing this. There's a good literature review. I mean, seriously, this goes back to 30 — well, how — 35 years. It's been 36 years for me that we remember hearings from 35, 34, 30 years ago and then when all this erupted. I think if you frame that, you're going to — it's going to be appreciated by people and they won't feel like you're trying to bypass something because that's really the whole issue behind how this came about in the first place.

And if you lay all that out, you save yourself a lot of grief — a hell of a lot of grief. And so there's a good literature review there and if your person e-mails me, I'll give him what I think he ought to look at in terms of published in books, articles and stuff that's been published all around the political social frame of this. And I think if you do that, you're going to save yourself a lot of grief. Am I — am I — would you ...

R. TREWYN: I agree.

W. GRUBBS: We'll get your e-mail address and we can be in contact with you.

M. STOTO: So this will be a separate report from this so-called "longitudinal study?"

K. FOX: That is correct.

M. STOTO: And what's the timing on that?

J. MINER: We're developing that right now.

K. FOX: The SOW has not been completely developed.

M. STOTO: Okay.

K. FOX: So again, that's another time-line, always with the goal to be completed before the 30th of September '06.

M. STOTO: Okay. So let me — let me sort of suggest that it would be helpful for us to look at both the plan and the draft of that one as well. I think we ...

K. FOX: Understood.

M. STOTO: Yeah. Sandy?

S. LEFFINGWELL: Looking at this section on how the statistical significance will be addressed raises another question. How will clinical significance be addressed? A lot of potential problems with that will go away when you consider inconsistencies among or between subgroups like officers, and enlisted and stuff like that, but maybe not all of it will. And if you simply say "increase" or "decrease," you know, if there's a three-point difference in mean SGOT between groups, then the people who say who

are at an increased risk may think, “Gee, we’re all going to turn yellow and die,” and that isn’t necessarily so.

M. STOTO: Yeah.

S. LEFFINGWELL: I don’t know how you deal with it, but you kind of keep the need — need to keep that in the back of your mind.

M. STOTO: Yeah. That, of course, is an issue has come up in the regular reports as well. Do you want to have any response to that?

K. FOX: I guess I’m the medical oversight, so I will be looking at all this to try to make it medically relevant.

S. LEFFINGWELL: Good luck.

M. STOTO: Okay.

K. FOX: Thank you.

M. STOTO: Ron?

R. TREWYN: Know the contract’s already been let; heard that. Want to back up though on the data component of this because, and again, sort of restating my standard position. A lot of the really significant information is coming out now from this by the re-cuts and re-analyzing. And if it’s only published material, if I heard you correct that it’s only things that have actually been published, I can even go back to the original big cancer paper that was something like 98 pages or something that I got sent that was out for review.

Well gee, the journal did not accept the 98-page manuscript and it was — it was paired down. And I suspect there was a lot of significant data that was paired out of that in the process. So you can wind up in some of these by having that limitation; that there really could be things that are going to be talked about today and things that have been very recent, but have not yet been published in a peer-reviewed journal or whatever.

If those are going to be left out of this report, my concern is we're going to have most of the 50 pages being "no significant findings," and yet, there are some big things coming out these days. So I guess just curious. So we are published only, not significant data that's unpublished at this point?

K. FOX: At this time, it is published only. That also includes technical reports and any — it doesn't have to be journals also, so it's published. Whatever we've released, we will be looking at.

M. STOTO: I think this is an important issue and I guess I suggest we come back to it in November when we look at it.

R. TREWYN: That's fine.

M. STOTO: And you know at that point, we'll know pretty much what are the results that are — that are available.

R. TREWYN: Right.

M. STOTO: And if we — if we think that there's some important result that just hasn't been published yet, if there's one or two or those, we may be able to find a way

to work that in. I think that there probably aren't a lot of areas where there are important results that haven't yet been published, but there may be one or two and it may be worth making an exception for something like that. Well, we can look at that in November and make a recommendation.

K. FOX: We always look forward to your recommendations.

R. TREWYN: We know better.

M. STOTO: Okay. Any other comments? David?

D. JOHNSON: Well, is there a — is there a mandated time when this has to be completed?

K. FOX: 30 September '06.

M. STOTO: That's when their budget runs out.

K. FOX: The door is closed.

D. JOHNSON: Right. So I mean that one thought is, you know, you want to try to wait. You want this report to include as much — as much of the analysis as possible, but then at some point you have to say, you know, that's the end of it. And then you can include in the report that, you know, the possibility exists for further — explain what it is.

K. FOX: Or we can say that there's certain things that — what we've done in the past is what proposal for future things. We can also say that that's — we could always put a paragraph outlining what is future being looked at.

D. JOHNSON: Right.

M. STOTO: I recall in the past having seen the schedule for when new research stops, which is either coming up soon or already passed. Is that — isn't that right?

K. FOX: Yes. We're about — what we've got in the works right now is about all we can handle until the end.

M. STOTO: So they're not going to be doing new studies, you know, be initiating new studies. So there — okay. Does that ...

D. JOHNSON: Yes. Thanks.

M. STOTO: Anything else? Okay. Next on our agenda is a break; after that we have public comments. Let me ask again whether there's anybody here who would like to make a comment?

J. SILVER: Would questions count as comments?

M. STOTO: I'm sorry?

J. SILVER: Do questions count as comments?

M. STOTO: Questions count as comments, but answers are not required. Would you like to ask a question?

J. SILVER: At that point.

M. STOTO: At that point?

RECORDER: Please ask it on the mike.

M. STOTO: Okay. So let's do this; let's take a 15-minute break now, come back at 10:25 and then we'll go into the public comment period. And then immediately after that, if Dr. Matsumura's ready to do his presentation, we'll do that. Okay. Well let's — Ron?

R. TREWYN: I would just add that if this — if the agenda's been published, I think you don't want to go into the public comment period until 10:45; just that's when it was published.

M. STOTO: Yeah.

R. TREWYN: If it — if this has been published, so just to ...

M. STOTO: You're right, okay. So let's do this. Let's — can we do this? Maybe Dr. Matsumura can go after the break and then we'll — after your presentation, we'll see if there are additional comments and that'll be within the window of the published agenda. Okay. Thank you.

[BREAK 10:12 A.M. - 10:28 A.M.]

M. STOTO: I'd like to get started, everyone; return to the table. Okay, everyone, welcome back from the break.

RECORDER: Turn your mike on, Dr. Stoto.

M. STOTO: Well, I wish I had a gavel. Welcome back, everyone. Our next presentation, Dr. Matsumura, will make on behalf of it looks like himself and two colleagues.

Molecular Epidemiology Study

F. MATSUMURA: Thank you very much. I would like to thank the Committee for having asked us here to give us the opportunity to present our data. Second, I'd like to introduce Dr. Fujiyoshi once more and he's a graduate of MIT. And he has a lot of good background, and now molecular biology and the statistics. It's a powerful combination and that I would like to present.

Of course, some of you very familiar, but the — this particular field of molecular epidemiology is very exciting new field and it is a combination of the classic epidemiology and the molecular biology. And for us toxicologists, this will increase the sensitivity of detection; that is very important because before anybody shows overt symptoms, there are lots of things going and that's what we would like to learn. Second, we would like to offer some evidence of connectivity, meaning that in a case of epidemiology, it is correlations. But there are lots of correlations; they cannot say it is really related and we would like to offer some possibilities. And, of course, that's a goal we are trying to reach.

Brief background, okay. Okay. All right. Thank you. Yes. This particular study was helped, of course, by the AFHS and that our protocols follow exactly the way that the Ranch Hand Study has been conducted. And namely, we got the 313 adipose samples and the — from carefully matched the comparison group from those veterans served in the Southeast Asia tour, so meaning that they are well matched. And again,

we follow the exactly same protocol, so therefore, we got the data from CDC regarding the residues of dioxins in the serum lipids. So the data that we are using is identical.

Again, the diabetes has been determined by two-hour post-prandial data which has been provided by Dr. Michalek. So therefore, we now can compare the data side-by-side with, yeah, whatever that he have found. Well, in terms of the selection of the molecular marker, well, the key point is that we had to be very careful what we select just simply because running the 300-some samples and duplicates and then the running all those PCR, it takes time and effort. So we had to run the animal tests, namely chronic studies involving some mice. And after careful consideration, we have decided to pick four so because of funds, time, we could not select too, too many.

So we decided to pick those four. And the ones that we decided — well, the first one is the glucose transporter 4 because it is very important in diabetes and it's the — it is the one that is affected by dioxin very well. Then we have decided to look at the NFκB, which sound like old Greeks, but the key point being that this one is a master indicator of inflammation. And inflammation, I'll come back to that, is a very important disease too in our mind.

So we are very lucky to have this particular molecular marker. Then we have picked the C/EBPα, which is showing adiposity. So whenever those lipocytes decide to convert into four adipocytes, C/EBPα is called "master switch," so that means we are — we all have pre-adipocytes. And when we start eating too much, starts converting then

into adipose, full adipocytes. And once they get to that, they will never go back. So 40 million adipocytes are reacting too in that direction.

Then we have decided to have the Src — S-r-c — which is mediating the action of dioxin, so therefore, we wanted to have that. Then finally, we have to use the standardization using what we call "GAPDH" and which has been used as a housekeeping gene to normalize. In addition to various standard, we have to use. One sample was used as an internal standard throughout all the studies and this person happened to be — had lots of materials. So therefore, we could use that sample for comparison to all runs we have studied.

Well, initial study, we were worried about not finding statistical significance. So we discussed with Joel and we have decided to pick this particular approach of dividing the — those each service group into four quartiles, meaning that top 25 percent highest dioxin ratios, then next 25 percent. So each service group has been divided into quartiles. Then, of course, first things first. This is an epidemiological study, so therefore, we have to find some correlations.

So there, Joel and Phillip worked pretty hard analyzing all sets of data. After while, we started realizing that our — even our golden standard, GAPDH, had some effect of dioxin. So we had to come up with some way, so we started dividing two parameters, meaning that if there's the same standard that was used, one divided by —

divided by the other one would eliminate the effect of the GAPDH. So therefore, we did all the combinations of the studies.

The result shown in Figure 1 in the upper left, if you could see, this is the one that we studied: the glucose transporter and standardized, normalized by GAPDH. And when you look at it on the left side, represents the comparison group and the right side represents the RH — Ranch Hand group. And when you look at it, you start seeing that in the RH group, you see that steady rise in the expression of the glucose transporter 4. In the case of the C group, there is a steady decline for the first three groups, then there is a little kink. And we thought that is strange.

Well, we looked at the inflammatory parameter and as we expected in the case of the C group, there's a steady rise and that was expected. But again, there's a little kink. Then the RH group responded exactly to the opposite. So it is strange that we have this V shape that two groups showed different reactions to the concentration of dioxin. Now since we wanted to look at the ratio, we divide the — use the ratio glucose transporter divided by NFκB we call "G:N ratio."

When we did that, this correlation became pretty good: straight line, steady rise responding to dioxin. And that same time, C group showed a very similar, clear-cut difference between top to bottom. Again, this kink was there. So our hypothesis was that well maybe this highest exposure group among the C group maybe responded just

like the RH group. So we decided to eliminate those risk subgroups: namely, obese and the adults with the family history of diabetes.

When we eliminated that particular subgroup, that kink disappeared. So that give us some idea that there are subgroups among those veterans who have some degree of pre-disposition or risk factors. So again, interim conclusion was that the ratio, G:N ratio, gave us the best and I'll explain to you why. Of course, one is going up; the other one is coming down. When you divide it, you make it much more responsive. So again, we could see and the statistical significance was there. Then there are some groups among them who are more susceptible to dioxin. So, of course, any question ...

M. STOTO: Can we ...

F. MATSUMURA: ... will start raising ...

M. STOTO: Excuse me.

F. MATSUMURA: Yeah?

M. STOTO: I wonder if we can ask some questions as we go along?

F. MATSUMURA: Yes. Oh, please do so. Yeah.

M. STOTO: Turn your mike on, please.

F. MATSUMURA: One more?

M. STOTO: This is new material to a lot of us ...

F. MATSUMURA: Yeah. Yeah.

M. STOTO: ... that we probably need to ...

D. JOHNSON: Being not that familiar with the GLUT4 and the NFκB, are these — have these been shown to correlate with clinical findings?

F. MATSUMURA: Yes, the glucose transporter 4 has been described for the diabetes, the patient type 2 diabetes. NFκB has been also described and I can explain that to you before — later.

D. JOHNSON: Okay.

F. MATSUMURA: Yeah. All right. Any other questions? Yes?

M. STOTO: Can I ask you to go back one more slide?

F. MATSUMURA: Yeah.

M. STOTO: I mean, it's the graphs — Figure 1.

F. MATSUMURA: Graph, yeah.

M. STOTO: What's the difference between the left- and the right-hand side?

F. MATSUMURA: Okay. This one is all RH group and this left side is the C group.

M. STOTO: And how does that compare to the graph Figure B?

F. MATSUMURA: This one is exactly same; this one is the C, comparison group, and this one is — the triangle is the RH group.

M. STOTO: Now but at the bottom ...

F. MATSUMURA: Yeah.

M. STOTO: ... there's the same ...

F. MATSUMURA: This?

M. STOTO: ... label on the axis, right, for C?

F. MATSUMURA: Yeah. This one?

M. STOTO: GLUT4 to NFκB.

F. MATSUMURA: Yeah. Yeah, all the same. All exactly same. This side is dioxin residue and the y-axis is always a difference in that the — oh no, y is identical.

M. STOTO: Maybe it's mislabeled, but the y-axis for part C and part D are the same.

F. MATSUMURA: Yeah. Yeah. It's exactly same.

M. STOTO: Well, then why are the figures different?

F. MATSUMURA: No. No. It's the response to dioxin; they vary.

S. LEFFINGWELL: They eliminated the obese from the controls.

M. STOTO: Oh okay, so Figure D ...

F. MATSUMURA: Yeah. Yeah.

M. STOTO: ... they eliminated the obese from the controls?

F. MATSUMURA: Yes. Yes. Yes.

M. STOTO: Okay.

F. MATSUMURA: I'm sorry; I should've explained much more. Yes. This should be, yes, identical to this except the adipose eliminated. So when you eliminate the obese and the family history, then that's what happened.

M. STOTO: Okay.

F. MATSUMURA: Okay. So the next question is that, yes, we wanted to know this particular use of the quartiles would be appropriate or not. I mean, after all, that the — there was strange way of doing the statistics, so we wanted to know whether that's have any problem or not. Then the question of the slope difference: one is responding to a negative way; the other one is positive way. So how come they are responding in different ways? Then the question is that what kind of subgroups we can study to see responses within that subgroup would be different from others?

So to do that, we decided to answer all those questions, in addition, analyzing the relationships to G:N ratio, then try to find the affected subgroups — most affected subgroups. Well, first question, why one has a negative slope; the other one has the positive slope? Well, we — when we look at the whole population, then we get same answer actually. You see that the — there's a negative slope and among RH. And this one shows C group, RH group, then the whole population. Well, whole, yeah, group population was, yeah, analyzed.

You know that the, yeah, the C group has the cluster at the lower level of dioxin and the, of course, RH group, have the higher level of dioxin. So there is more spread here and the cutoff is here. So, but within each group, it start showing the same direction. So we start feeling better at least that the, of course, scattering here and the p value here was not that good at this particular moment — stay. But the — at least the

RH group was — the p value was always not really, really good, but still there was a significance. Then the most important thing is that there is a difference between those two groups which was statistically significant.

Well, at least this one is justifiable that use the quartiles which give the initial statistical difference between the top and the bottom, so it looks like there is a correlation. Of course, when you use all those scatter plots, you may not get the really clear-cut result so that the — our approach can be justifiable. Now regarding the second questions on the subgroups, we looked at the many subgroups and those are the ones which give the best result in terms of the slopes that we were concerned.

Among C groups — group, yeah, subgroups, the one which give the steepest negative relationship to the dioxin residues was obese and the non-diabetic group and the — if the — those give 0.09 p value. Now among the RH group, the ones which give the steepest positive slope, both lean and diabetic. Of course, you can say that why, you know, comparing two different groups? But we will get to know which of the component of the RH group or C group are giving the steepest lines to contribute to the overall slope differences.

Then we asked the question, since there is two — there are two differences, obese, lean, and non-diabetic and diabetic, we decided to look at the non-diabetic group with family history of diabetes. And we have to combine C plus RH, C plus RH so that difference between this and that is obese or lean. And when you do that, we could see

again same kind of trend and the difference was statistically significant, meaning that probably the difference between the C and RH group is that one behaves as though they are becoming obese. The other one behaves as though they are lean.

And, of course, the — you say that, well, that might mean that those people really are obese. No. When we compared those carefully matched groups, we couldn't see any difference. That means appearance-wise, both groups have the similar weight distribution, and yet, C group is behaving as though they are obese and RH group is behaving biochemically as though they are lean.

So again, conclusion: the subgroups differ in terms of the G:N ratio responses to dioxin. Obese subgroups tend to behave negative way and the lean subgroup would behave in a positive way. Well, how do you explain that? Well, there are three possibilities. One is that if you keep increasing the dioxin exposure in humans — not in animals; I am not saying that — well, it could be that the gene ratio may start changing because after all, they have been exposed to 30 years — over 30 years for a long, long time so that we have to start thinking the different possibilities and the scenarios.

The second one maybe that yeah, well, dioxin causes also wasting syndrome and that there's a pressure biochemically to cause the loss of body weight. Okay. So that's another possibility. The third possibility is that long-term exposure to dioxin may start inviting some counteraction by the body, meaning that something like a glucocorticoid receptor might be going up, and that we could show it in the animal test.

If you keep dioxin pressure for a long time, they start activating glucocorticoid receptor which has been reported to happen in some cases of human diabetes.

Okay. So that well, we wanted to test whether obesity and dioxin exposure has any similarities or not. Then in that particular case, how do we detect? So we decided to look at the weight gain so that means that Phillip could dig out several sets of data to show that there are differences between the time tour of duty, then the '92, '90, '97 and the — then the — he took also that we have changes. Then we started finding that increase in the body weight between '92 to '97 that coincides with their "tender age" or middle age when you start gaining some weight, so that's the time frame we used to assess.

Well, when we did that, now this side is not dioxin residue. It's a change in the body fat, and again, this one is G:N ratio. And when you use that, here is the slope we have been looking for. This one we have to use both C plus RH, but we have to use non-diabetic patients. Then when you look at that, here is the statistics: p is less than 0.001, highly correlated.

So G:N ratio is very sensitive in detecting at least one of the risk factors obesity, very, very straightforward. Difference is also statistically significant, but once they develop diabetes, difference disappears. Okay. So that means it's too late to measure by this particular parameter. So you can see that obesity and the diabetes, it has — it has been really well documented.

M. STOTO: Excuse me.

F. MATSUMURA: Yes?

M. STOTO: I think Dr. Leffingwell has a question.

F. MATSUMURA: Yeah. Yes. Yes, please.

S. LEFFINGWELL: On the ...

M. STOTO: Mike, please Sandy.

S. LEFFINGWELL: On the left-hand picture here and a similar picture on Figure 2 ...

F. MATSUMURA: Yeah.

S. LEFFINGWELL: ... the core of that looks an awful lot like a shotgun blast.

F. MATSUMURA: Yeah. Yeah, it is.

S. LEFFINGWELL: Here, it looks like the slope is strongly influenced by outliers. The central cluster looks like it would have a much steeper slope.

F. MATSUMURA: Yeah. We have our values too, so that the correlations have been studied.

S. LEFFINGWELL: Okay.

F. MATSUMURA: Yes.

S. LEFFINGWELL: Do you know anything about the outliers — who they were and why they might be outliers?

F. MATSUMURA: Yeah. Well, we debated same kind of, yeah, questions, but we finally decided not to look at the individual data anymore. Some were taking some diabetes drugs; some were not taking and there are complications. And we did not even know the — who they are; we didn't want to know. So in this case, we did not eliminate any outliers or we did not even consider. So it could well be that some of those outliers might be contributing and you are more familiar with that type of situation. But we did not wish to address those outliers at this particular moment. Any other — yes?

RECORDER: You're going to have to go to a mike, ma'am. Could you state your name, please?

M. PAXTON: Mary Paxton, IOM. The diabetic status is defined as of the last exam — '97 exam?

P. FUJIYOSHI: Yes.

F. MATSUMURA: Okay. Phillip answered that it is. Any other question? Okay. All right. So the next question we raised is that by using the same analysis, G:N ratio versus change in the body fat, and we asked the question that what kind of factor would let them become more susceptible to change in the G:N ratio? And surprisingly, when you take a known diabetic, no family history — two risk factors — and look at the C group, you don't see any change. Well, that is natural in a way that those are healthy guys, and so therefore, they have homeostasis to balance it.

But the same analysis, same group — known diabetic, no family history — when you look at RH group, here it is, 0.003, and difference is also significant, meaning that somehow, RH group behaved as a whole as though they have the risk factor already. My mother died of diabetes so I must have a genetic risk factor. Okay. So when obesity is added, it starts expressing this type of symptom.

Now to show that, you can see that in the case of C group, which overall did not show — healthy ones did not. But if you select family history of diabetes, here it is. Same as this except that those other guys who did not have the risk factor, it's almost identical. And in the case of the same group, yeah, it shows again negative correlation than some of those statistics significant.

M. STOTO: Wouldn't you expect in the lower right-hand corner that the slope would be even more ...

F. MATSUMURA: Yeah. That's we thought, but the, you know, but again, this and this, statistically no difference. So the — yes, that's what we expected, but we did not see no additive. Yeah. Yeah. Good point; we thought about that too.

M. STOTO: There's also that one big outlier is in that — in that group there too.

F. MATSUMURA: Yeah. This group had a slight less number and we thought maybe that contributed. Okay. So gene ratio is again proved to be useful and start detecting those with genetic risk factor, family history on this. Then next, known diabetic, the RH subjects behaving, responding to weight gain as though they already

had the risk group — risk factor. Well, we decided really that at this stage, we have to relate G:N ratio to diabetes. So what kind of parameter can we compare? And we gravitated back to the golden standard of fasting glucose.

So when you use fast — fasting glucose or post-prandial, yeah, glucose levels, you can see that known diabetic people show no effect of the G:N ratio, which is understandable. Those are the guys who are — who can manage, but among diabetic people, again, for the sake of getting good statistics, we have to combine C plus RH. Then there is a negative correlation, clear cut again ...

M. STOTO: Can I ...

F. MATSUMURA: ... 0.009. Yes?

M. STOTO: Can I ask why is the G:N ratio negative in some of these cases?

F. MATSUMURA: Well, that means, yeah, those people who are showing high response is one that having a good ...

M. STOTO: No. No. I ...

F. MATSUMURA: ... glucose.

M. STOTO: No. No. No. I mean — I mean, G and N are both positive.

J. MICHALEK: These are log units.

M. STOTO: The log units?

F. MATSUMURA: Those are log units.

M. STOTO: Okay.

F. MATSUMURA: Yes. Yes. Yes. Okay. All right. I misunderstood, but these can be explained because those are the ones showing the, you know, the high glucose and those are the ones showing the low glucose. Okay. That means G:N ratio is a reliable marker of diabetes since it is highly correlated and we could see it. So the next question we wanted to ask is, okay, fasting glucose really good enough to detect obesity? So when we did that, we could see that when you look at the known diabetic patient, again, the C plus RH, you could see steady rise which was again statistically, highly significant.

So that means, yes, we show that G:N ratio can be related to the fasting glucose. Fasting glucose can be related to obesity. So last question is can you detect the same relationship between dioxin and the fasting glucose? Of course, well, at least among C group, we could show that dioxin is related to fast glucose. Actually, this is identical to what Joel has found. So we just confirm that by using this type of approach, you can also detect those differences which have been already found. But among RH group, we could not show.

So this one looks like more like you can see that, yeah, we have to use some little bit of fancy statistics to include both of them in the same graph. Okay, so, but we could not show the correlation there, but we could show correlations there, okay, directly affected by dioxin. And we could detect by using this method difference between C and RH again.

Just quickly the explanation of NFκB and glucose transporter. Well, when you look at the literature today regarding diabetes, there are tons of references indicating that the obesity-induced diabetes is mediated by inflammatory cytokines, meaning that those people who get obese, they start producing copious amount of inflammatory signals and particularly the one called "TNFα." And this is one which is produced both by adipocytes as well as by the — by macrophages. And they interact; they produce inflammation. And this inflammation is translated by a lipocyte to start losing weight.

And, of course, and when they start losing weight, they start releasing, again, huge amount of lipids into the blood stream. And these are also aided by the liver; liver shows also the ability to absorb some lipids. At the same time, they start releasing glucose just simply because this type of inflammation is connected to what we call "stress response." And in that, they start breaking down the glycogen, and therefore, increase the blood level of glucose. So therefore, it starts making sense that those types of changes are predictable in terms of obesity-induced diabetes.

At the same time, most recent studies indicate that high lipid, particularly neutral triglycerides, will start affecting the beta cells or pancreas. So therefore, they stop producing insulin as well. So the initial action of TNFα inflammation would cause the increase in the response, which will increase the rate of insulin resistance. Then later, it's only to the problem of secreting enough amount of insulin to the blood stream, so that's why we are seeing this particular result.

The main conclusion is that we could obtain the definite molecular epidemiological evidence, indicating that dioxin is acting as a diabetogenic risk factor among the Vietnam veterans. And those are the most surprising finding is that we could even see the same effect in the C group. Therefore, the major health implication of our finding today is that, yes, we could find those effect of dioxin even among C group, and again, C group is not much different from the general public of the United States.

So that when you really start comparing, you start seeing the effect that if I get the, say, obesity and I already have the genetic factor, yes, dioxin could add at least the third risk factor to promote this type of disease. So therefore, we think this type of research should be continued. I liked your comment that the funding may not come from here. I should try to continue that this, yeah, is the quite the lesson that we are learning.

And finally, acknowledgment; I really would like to thank here that all the people who helped us in doing this. Those, of course, volunteers and they came and donated painful samples from their, yes, liposuction. And also, of course, Joel participated, and the health studies people from the Air Force and SAIC. And really, we could not have done this work without their help. Thank you very much.

M. STOTO: Okay. Thank you very much. I'm going to ask for questions in a moment, but I just want to remind anyone who's come here for public comment period

that we'll postpone that until after this — we finish this discussion. Okay. Thanks. Any comments or questions for Dr. Matsumura?

F. MATSUMURA: Yes. Please.

M. STOTO: Don't forget your mike.

E. HASSOUN: Yeah. I'm wondering why did you choose to do epidemiological studies on markers of diabetes, but not of markers ...

F. MATSUMURA: Yeah. Yeah. Yeah.

E. HASSOUN: ... of any other diseases?

F. MATSUMURA: Yes. Well, we started when Dr. Michalek started finding the correlation — first correlation to diabetes. Later on, other problems start dropping up, and today, we are going to hear about cancer. But at that particular time, only correlation that we knew was diabetes. And after that, of course, racial study start coming out. But we wanted to have some endpoint which, you know, has been well certified. And so therefore, that's how we picked that one.

M. STOTO: If I could just follow up on that?

F. MATSUMURA: Yeah.

M. STOTO: I mean, now that there are some other things that look like they're ...

F. MATSUMURA: Yeah. Yeah.

M. STOTO: ... beginning to appear in this, I mean, are there similar studies that could be done, molecular studies?

F. MATSUMURA: Yes. Yes. Inflammation is becoming a big topic. And even in the case of prostate as well as breast cancer, this connection is becoming very player so that, yes, heart is also. So it's been well known that people that have inflammation, such as gingivitis, and they cause inflammation because the blood cells start getting excited. Whenever there is an invasion, they start increasing inflammation and that — and the heart attack has been well, well documented.

And hypertension is another area, so that it seems to be that now people are realizing more and more that inflammation could be real problem. And when inflammation comes, usually it is accompanied with the immunosuppression. So that even those cases, such as asthma and, yes, immunosuppression autoimmune, now there are some copious amount of papers published at least alleging that there are connections among those. So that means we are realizing that dioxin is tremendously inflammation causing agent, so that's where we are focusing our research right now.

M. STOTO: Ron?

R. TREWYN: Just curious if you know with your controls if the control group were exclusively individuals outside of Vietnam, or inside Vietnam or a mixture of both?

F. MATSUMURA: Well, probably Joel can answer. At least they served in the Southeast of Asia, yeah, tour.

J. MICHALEK: No. That factor hasn't been sorted out yet and the data set he's using doesn't have that information in it.

M. STOTO: David? Your mike, please.

D. JOHNSON: The handouts that you gave us ...

F. MATSUMURA: Yeah.

D. JOHNSON: Several of the figures don't have the axis.

F. MATSUMURA: Yeah, I'm sorry. I did not realize until I came and looked at the printing. I — my associate pulled the figures out of our manuscript and when they — when printed, somehow it appears in the — on the slides. And sorry about that, and yes, that probably I should somehow add it. And if the Committee so wishes, we can send you revised ones so that y and x are well marked.

M. STOTO: I think — I think it comes out okay if you print it in color because I did print mine, but maybe ...

D. JOHNSON: Well, the ...

F. MATSUMURA: Yeah.

D. JOHNSON: But, you know, I wanted to make a point. The one that we received prior to the meeting, I think, is a little different than the one that he — that he gave us that's in our packet.

F. MATSUMURA: Yeah.

D. JOHNSON: There were a couple of slides that — couple of conclusions that aren't in this — the one that you gave us today ...

F. MATSUMURA: Oh yeah. Yeah. Yeah. Yeah.

D. JOHNSON: ... that were in the previous one we had.

F. MATSUMURA: Yeah, previous one. I ...

D. JOHNSON: Because I know I had a question I was going to ask you about, but then it didn't show up in this — in this one.

F. MATSUMURA: Okay. What happened was that I did not know the time frame, so I was assuming that's probably 40 minutes. Well, then I got the final agenda, it was 30. So I had to cut it and I wanted to make it simpler, so that's what happened. And, yeah, I apologize for that. Yes.

M. STOTO: Well, let's do two things.

F. MATSUMURA: Yes.

M. STOTO: One is ask the question now anyway.

F. MATSUMURA: Yeah.

M. STOTO: The other one is maybe you can give us an updated version of this.

F. MATSUMURA: Yes.

M. STOTO: And maybe even a copy of the manuscript if you're ...

F. MATSUMURA: Yeah. Yeah. It has been provided to SAIC and so we can get it printed that way. Yeah.

D. JOHNSON: I had it on my laptop. It'd be difficult for me to ask the question. Is that it? Is that ...

M. STOTO: While he's looking for that, let me ...

F. MATSUMURA: Yeah.

M. STOTO: Maybe I'll ask a different question. I mean, these ...

F. MATSUMURA: Yeah.

M. STOTO: Have other people been finding these results in other studies, similar results?

F. MATSUMURA: In — there's Joel's studies or other ...

M. STOTO: No. Other molecular epidemiology studies.

F. MATSUMURA: Well amazing, we looked at the — really searched, but there are no such studies and there's no indication among the general public what the levels of NFκB. There's no data to show human beings are not being really studied.

M. STOTO: And is that because there are not many data sets where they have measured serum dioxin? Is that the reason?

F. MATSUMURA: Not just on the subject of dioxin, I was quite surprised that any other medical scientist must have studied. Lots of people studied the urine and blood, but nobody studies the adipose and so we really could not find anything to compare to. So these are very valuable data, so that — and the samples too. So it is really — I did not realize that the, you know, adipose tissues can be so responsive to biochemical input.

So, of course, now there are many papers saying that, yes, adipocytes are highly, highly active and highly responding tissue. But of course, most people assume

that adipose tissues are just storage sites and they're not responding. That is not true at all; they're highly regulated. That's why people have a problem reducing their weight because they're so regulated. Once the point is set, so many biochemical changes to keep it in that particular level. So we started realizing all that by doing this particular study. But to answer your question, there aren't really any data studying the adipocytes of human beings.

M. STOTO: I'm trying to get at the, basically the ...

F. MATSUMURA: Yeah.

M. STOTO: ... discussion we had this morning ...

F. MATSUMURA: Yeah.

M. STOTO: ... about the value of these data.

F. MATSUMURA: Yeah.

M. STOTO: And — right. Joel, did you want ...

J. MICHALEK: I can say it a little differently. I believe this is the only study in the world where the control group as well as the index group has been measured on the contaminant, namely dioxin. In all other studies, all other federal studies, including the NIOSH studies, CDC studies, the controls are never measured. And this study is unique in that 98 to 99 percent of both the controls and the exposed have been measured for dioxin by the same laboratory. That is absolutely unique and the study that Dr. Matsumura just described is unique.

This is the only study that I believe exists on these markers in humans and relating to dioxin. This is it; this is unique. We asked him to do this in retrospect because we were seeing associations between dioxin and diabetes and we wanted to know whether there was a biological basis for what we were seeing in the epidemiology studies. And that's why Dr. Matsumura's here today.

M. STOTO: So one of the unique factors is the measurement of dioxin in the control group. The other one is the adipose ...

J. MICHALEK: The adipose ...

M. STOTO: ... tissue markers.

J. MICHALEK: The adipose markers, the diabetic markers that he's measured are uniquely measured in humans and the dioxin is uniquely measured in both cohorts in this study. It is unique.

M. STOTO: And just remind me about the adipose measures. Were they — were they done as part of the '92 tissues?

J. MICHALEK: The adipose was a simple BMI calculation made on the basis of height and weight.

M. STOTO: Okay. So ...

J. MICHALEK: Those are BMIs.

M. STOTO: Okay. So that can be done on the whole data set?

J. MICHALEK: Yes.

M. STOTO: Not just the ...

J. MICHALEK: Every person in the study has a BMI measure periodically and so changes in BMI were easy to compute.

M. STOTO: Let me — let me go — David, are you ready?

D. JOHNSON: I couldn't find it.

M. STOTO: Okay. Ron?

R. TREWYN: I'm just curious. I remember going back into the 90s, we always used to argue over whether there was any significance to when we were monitoring sed rate in these populations. And I was curious whether your inflammation marker, if you've done any examination of that, if there's a correlation to sed rate in any way?

F. MATSUMURA: Yeah. Well, in the follow-up study, we are looking at the TNFα directly so that we are hoping that we will have, yeah, more data on that. But the NFκB is the real master switch for inflammation, so we are catching it at different types of inflammation as well. So that means NFκB is a nuclear transcription factor which coordinate the old inflammation coming from outside, then integrate to express that we'd better do something about this inflammatory state.

So therefore, we were lucky to hit that particular one. But yeah, inflammation now, in the case of breast cancer, yes, they started realizing that up to 20 percent of breast cancer is related to the inflammation. And that when you reduce this NFκB activities, then the whole thing start regressing and NFκB is related to metastatic state.

So that means we used to think that is totally different reason, but those up to 20 percent of breast cancer, when you reduce the NFκB, they start going back. So it means the cancer can be reversed by affecting NFκB.

So same way somebody activated the liver, NFκB separate from any other tissues then that show the diabetic insulin resistance developing immediately. So that means this type of information is now coming to focus, so we are at the front of the inflammation-related etiology of several different types of diseases. And similar studies have been reported on the subject of hypertension, particularly among women. And I noticed that the special studies indicate that, yeah, hypertension among women is one of the most visible effects of dioxin exposure, so that could also be related to inflammation.

M. STOTO: Sandy?

S. LEFFINGWELL: In epidemiology, we tell the story of snow in the Broad Street pump and they sometimes forget that the final step of that story was taking the handle off the pump.

F. MATSUMURA: Yeah.

S. LEFFINGWELL: Does this suggest that we need to recommend any intervention to any portion of these veterans?

F. MATSUMURA: Yeah. Inflammation, yeah, well of course, you know, it's the — those — some of the studies on the bomb and the studies on the, what we call

"reactions," yeah, those can be a — can be a parameter, you know. Those physiological, yeah, assessments can detect pretty subtle effects as well. So that once we know what the major culprit, I think some of those physiological measurements could come into play. Because not just the molecular parameter, some, yes, physiological responses could be pretty sensitive or behavioral if we know that, yeah, what we are doing.

M. STOTO: I guess I thought that Dr. Leffingwell was asking about whether maybe we should screen particular groups of Ranch Hand veterans who might be at high risk because of their exposure or something like that? Is that ...

S. LEFFINGWELL: Or recommend taking Celebrax or who knows? Is there something that we can tell these people, if you're at risk, do this to minimize your risk?

M. STOTO: Okay. So you don't have an answer to that? Karen, do you ...

K. FOX: All I've got to say that this is basic science and I don't think we've gotten very far enough to say that you start recommending people taking drugs or anything for that. I — that's a far leap. I think there's a lot more research that needs to be done before you start recommending people taking medications.

M. STOTO: And I guess we already know that people who are gaining weight should be careful about diabetes and so on, so okay.

F. MATSUMURA: Okay.

M. STOTO: Any more questions or comments? I have one more question.

F. MATSUMURA: Yes?

M. STOTO: What are the plans for publishing this?

F. MATSUMURA: I have sent the manuscript last week.

M. STOTO: Okay.

F. MATSUMURA: So we'll see what happens.

M. STOTO: Well, good luck. Thank you very much. David?

D. JOHNSON: I have a question. By us — we are not necessarily as a Committee endorsing the findings in the study? We've just had it presented to us? Is that correct? We're not reviewing this and getting the Committee's approval on the study or that sort of thing? We're — it's just being presented to us? Is that correct?

M. STOTO: Yeah, but I don't think — they don't need our approval ...

D. JOHNSON: Right.

M. STOTO: ... for this. I mean, it would — it would be helpful if we can get a draft of the manuscript, and we might be able to comment in a way that would be helpful and when you do revisions and so on. So if you can — if you can do that, give it to Len and they can distribute it to us. Would that ...

D. JOHNSON: Right. I mean, whatever you would decide as Chair, but I think my question is more basic. I mean, is the role of this Committee to approve or put our stamp of approval on these ...

M. STOTO: No.

D. JOHNSON: ... the — these things that are presented to us? I didn't think so. I just wanted to clarify.

M. STOTO: Our role is to advise.

D. JOHNSON: Advise in what way?

M. STOTO: About the scientific conduct of the study and any kind of ...

P. CAMACHO: This is for our information.

D. JOHNSON: This is for our information?

P. CAMACHO: Yeah. We're advising ...

RECORDER: Could you use your microphone, please?

P. CAMACHO: We're — my understanding is we're advising the Ranch Hand Study, *per se*. This was just for our interest and that's it.

M. STOTO: Right.

P. CAMACHO: We're not providing — if somebody wants to provide the gentleman with comments, that's up to them. But we're, as a Committee, not advising. Is that correct? Is that how you see it?

M. STOTO: I think, you know, our — what our mandate is with respect to this kind of study is somewhat vague. And I think that — I think that if we can be helpful, we should do that and — yeah.

D. JOHNSON: We're not responsible for the conclusions of this study or the — or the — what the authors are saying?

M. STOTO: We're not the authors.

D. JOHNSON: We're not authors of this study.

M. STOTO: Yeah, and I — and I think that — I think that we stand ready to help any of the Ranch Hand Studies, the spin-off studies and so on if asked. But I don't think we can be responsible for the — Ron, did you want to ...

R. TREWYN: And I just wanted to add that we have a long history on this Committee of being ignored with our advice anyhow, so it's — it doesn't, you know, this is ...

M. STOTO: And some history of being heard too. Okay. Thank you again. Thank you very much.

Public Comment Period

M. STOTO: So now we're at the point where we'll see whether there's any questions from — I mean, any comments from the public? Okay. Well, it — okay, did you — no? Okay.

P. CAMACHO: No comments.

M. STOTO: Well, thank you. So let's move now, if we could, to Joel's presentation. And Joel has, what, four parts? Maybe what we'll do is the first part, maybe second, and then have a break to get lunch, and come back and continue over lunch. But let's at least do the first part before we do that if that's okay. Okay. Thanks.

Update on Air Force Health Study Research Activities

Summary

J. MICHALEK: Mr. Chairman, thank you very much. These slides were made while I was still employed with the Air Force; my affiliation has changed. I'm now Professor — Assistant Professor at the University of Texas Health Science Center-San Antonio. This is a combined slide set that has several parts. And the first part, what I'm going to do right now, is simply an overview of the Cycle 6 report. Subsequent to that, we'll hear about a new analysis of diabetes of cancer; a summary of a paper on sleep abnormalities which is now in submission to a journal; and finally, a short, very brief presentation of our interactions with the IOM.

This is a — simply a series of slides summarizing the executive summary of the Cycle 6 report. Obviously, this is well covered territory for the Committee since you all proofread line-by-line the 2,000-page manuscript several times through an iterative process with us and as we're all painfully aware. And so I'm going to talk through this and it's going to be plain vanilla to you as I know it will be because of your careful attention to this document.

So what do we have: 1,951 individuals attended the Cycle 6 physical exam; 777 Ranch Handers, 1,190 — 1,174 comparisons. We used standard epidemiologic methods to assess the issues. The issues were addressed with four statistical models

as we all know. Number one, is there simply an — or a difference between the Ranch Hand and control groups on any measure of health? That was model 1.

Model 2, was there a connection between health and the initial dose estimated in the Ranch Hand group that they had when they were in Vietnam; that's model 2. Model 3 was a kind of a combination of those asking whether Ranch Hands with high dioxin levels were at increased risk relative to comparisons. And finally, the last model was asking simply whether health is related to dioxin as it was measured in 1987 which we used to call "current dioxin," which is certainly not current anymore.

There were four sources of data for the report: laboratory which was done at Scripps Clinics. This is all automated, quality control, standard clinical lab data which was collected through Scripps and sent to SAIC and subsequently analyzed statistically by SAIC. I should say all the statistical analyses done in the report were analyzed by SAIC and the report itself was the responsibility of SAIC through a contract with the Air Force.

Questionnaire information was collected at Scripps through a two- to three-hour interview conducted by personnel from the National Opinion Research Center-University of Chicago. Physical examination was conducted by physicians at Scripps Clinic, California, operated as a subcontractor to SAIC. Medical records were brought to the clinic by the individuals. And as they approached their physical exam, they brought in copies of the records that were reflected — their visits to their doctor, is their

family doctor in the previous five-year period. This was a repeated feature of the study that all medical or disease outcomes in the study are verified by record review and that those records are an essential piece of that confirmation.

So we're now going to march through these findings of which you're no doubt familiar. We have — I'm going to refrain from any commentary; I'm just going to tell you what it is. Body mass index increased with dioxin. In the cancer section, we found a mix of associations that were difficult to interpret. We found no evidence of consistency, either internal or external. And so the interpretation — final bottom line interpretation of the cancer section is negative; that we didn't see anything remarkable relating dioxin or herbicide exposure and cancer in this report.

In neurology, we expected to see some association with bilateral peripheral neuropathy to reflect what we had previously published, but we didn't see that. And we found only a hint of that with the pinprick and it was not bilateral. So neurologists would probably not find that remarkable or indicative of peripheral neuropathy and that was associated with dioxin. So in other words, there were — there was a mixed pattern of associations in the neurology section which did not point to a — to an overall association between adverse neurological health and herbicide exposure or dioxin.

M. STOTO: I think David has a question here.

J. MICHALEK: Question, yes?

D. JOHNSON: Just for clarification, on the first one — general health, body mass index and the dioxin increase — we don't — they were just associated? In other words, we — we're not saying that ...

J. MICHALEK: That one causes the other? No. These were ...

D. JOHNSON: Causes the other?

J. MICHALEK: Yeah. These were associations.

M. STOTO: Some of us have thought that perhaps people who are heavier retain their dioxin longer.

J. MICHALEK: Yeah, and now we're — now we're talking about two different concepts of the elimination rate of dioxin and body fat versus the association between body fat and dioxin. Those are two different pieces of information. We already know that the half-life is longer among heavier people than lean people and that's been published many times. In other words, the way in which you eliminate dioxin is influenced by your body fat, which is probably not too surprising because dioxin is lipophilic and relies — resides in the adipose tissue and circulating lipids.

Body fat is worth a remark here; that the fact that body mass index is associated with dioxin is an important fact because body mass index is also associated with many adverse health effects, including diabetes, and so it has to be carefully controlled. You should probably also note for the record that the time this report was written, we did the

best anyone can do to adjust these analyses for known risk factors for the diseases being studied.

So, for example, when studying diabetes, we adjusted for age, and body fat and family history. When studying cancer, we adjusted for age and occupational exposures outside of the Air Force, reported exposures to metals and chemicals. And the reaction, skin to sunlight, was an adjusted factor and so with — so was eye color and hair color. So this study is unique in its ability to adjust for risk factors of that kind.

D. JOHNSON: If you were to say, "1987 dioxin increased with body mass index," you'd be saying the same thing, right?

J. MICHALEK: Yes — or no. This body mass index was measured in 2002. And so the body mass index measured at Cycle 6 in 2002 and 2003 was associated or increased positively with dioxins measured in 1987 — 15 years prior.

M. STOTO: But I think the point is that there's an association, not a causal ...

J. MICHALEK: No, it's purely an association. For others in the audience who don't know this, we're unable to establish causation in any epidemiology study that I know of. In the area of psychology, we studied the Weschler Memory Scale, the — and the SCL-90R — SCL-90R and found no association between any measure of memory or any indication on the SCL-90 with dioxin or herbicide exposure.

In the gastrointestinal section, we found an association indicating higher risk, higher triglycerides within the enlisted ground crew in the high dioxin category. That's of

interest because the enlisted ground crew have the highest dioxin levels of occupational — of the three occupational subgroups within the Ranch Hand cohort. We have seen associations of this kind between triglycerides and dioxins in previous reports and articles that we've written.

In dermatology, we saw a pattern of increased frequency of reported acne after service in SEA in the enlisted ground crew and in the high dioxin category. However, we didn't see any association between, at the physical exam, between skin lesions indicated by the dermatologists and dioxin, which rendered this finding difficult to interpret. And that is so stated in the executive summary.

And otherwise, the dermatology results were not remarkable. In other words, there was no other finding in that section that was worth mentioning at this point or which was consistent with any known adverse relation between dermatological health and dioxin or herbicide exposure.

In cardiovascular, we continued to see an inconsistent pattern of associations between many different measures of cardiovascular health and dioxin and herbicide exposure, which rendered that bottom line, the — which rendered the overall interpretation is negative. I should probably mention here that we continued to see, outside of this report, an association between military occupation, namely being enlisted ground crew and risk of death from cardiovascular disease. In other words, the risk of death from cardiovascular disease is significantly increased among the Ranch Hand

enlisted ground crew and that's recently published in May of this year in *Military Medicine*.

The complication is we're unable to find a corresponding association in the data that we received from Scripps Clinic to support what we see in the mortality. And that's an issue that's still under study by our group at Brooks City Base. We still have not found a way to understand or explain that pattern of data. We had many different measures in hematological health and found no association that was suggestive of an adverse relation between hematological health and dioxin or herbicide exposure and no association between any measure of renal function in herbicide or dioxin exposure.

We continued to see an association between measures of diabetes, adult onset diabetes, and dioxin and herbicide exposure in the cohort, which was consistent with previous reports and published articles by us as indicated on the slide. The simplest way to put it is that the risk of being adult onset diabetic and taking insulin was increased among Ranch Hands with high dioxin levels. And we saw an adverse association between high hemoglobin A1c, which I have no way to interpret increased dioxin. Perhaps after I'm through here, someone would remark about that.

Another slide summarizing the associations between diabetes and dioxin which continued to emerge in this study relative to the current report and which will look familiar to anyone who's read previous reports. There was no consistent or interpretable association between any measure of immune function and herbicide

exposure and dioxin in the cohort and a corresponding interpretation for pulmonary function. That ends the summary of the executive summary of the Cycle 6 report. I'm ready for questions.

M. STOTO: Okay. Thank you. Does anybody want to address that hemoglobin A1c issue? I mean, any clinicians, what does that mean? And that's a marker of ...

S. LEFFINGWELL: Yeah. That the hemoglobin A1c is an indication of the average blood sugar level over the previous 90 days. So that statement seems to be sort of equivalent to the positive association between diabetes and dioxin.

M. STOTO: It's certainly consistent with that at least?

S. LEFFINGWELL: Yeah.

M. STOTO: Yeah.

S. LEFFINGWELL: Yeah.

J. MICHALEK: Thank you.

M. STOTO: Okay. Any other questions? Ron, did you want to ...

R. TREWYN: Oh, I would just — I'd just say, I mean, obviously, we're back to the point that except for diabetes, as following the protocol and whatnot of the — of the study, that very little of significance was found.

M. STOTO: Clinical significance.

R. TREWYN: Clinical significance.

J. MICHALEK: I would say that's a reasonable interpretation based on Cycle 6 report.

R. TREWYN: Okay. And so then — and I assume we'll get into this in more detail — so then the discussions that went on the last time about therefore the need to, again, if one is going to be sensitive to the issues and concerns of the — of the Vietnam veteran's community, if one does not preface this in some way with other observations that have been made that are not necessarily via the protocol, but other published findings and whatnot, there's not going to be much of value coming out of the Cycle 6 report for the veteran's community.

J. MICHALEK: I'm ready to take a step back at any time now because I no longer work for the Air Force. But the Cycle 6 report has a preface attached to it which is new — we never did this in previous reports — warning the reader that other findings exist and are in the published literature which may not agree with what's in the Cycle 6 report. That document is there and it's on the first page of the manuscript.

M. STOTO: I would be careful about saying, Ron, "not of much use," but maybe "nothing new."

R. TREWYN: It's not informative.

M. STOTO: But, and I think that comment — the preface is important. We did discuss this at a previous meeting. Can I ask Joel or someone else what the schedule is for the release of this Cycle 6 report? Karen?

K. FOX: We're not — we don't have a particular date, but we are expecting it to be shortly ...

M. STOTO: Okay. So it — would it mean ...

K. FOX: ... with a month, two months at the latest.

M. STOTO: It's with higher-ups in the Air Force now or ...

K. FOX: Yes, it is.

M. STOTO: Okay. Yeah. Is it likely to be ready to be discussed at the September meeting?

K. FOX: We're hoping, but I — we don't ...

M. STOTO: Yeah.

K. FOX: We're — our control is no longer there. It's no longer at our level.

M. STOTO: Right. Okay. I guess I — guess we could say that the — probably the Committee feels that the sooner the better that this comes out.

R. TREWYN: Well, and I guess I would be curious, we certainly at the last few sessions, we went through and there were a lot of suggestions with regard to additions to the — to the report, again, for clarity purposes. And I would be curious as to the status of those, whether any of those suggestions, you know, whether modifications had been made? Is it the same report as we saw? Where does all that stand because I don't know. Since our last go-round, I don't know that we've gotten any update on that.

M. STOTO: Karen?

K. FOX: We did take into consideration your recommendations, and some of them were included and some were not. Some were not capable of being included at this time, but we — it is not the same report. I mean, I think a vast majority of it is, but we did take some of your suggestions into the fact and it did get changed.

M. STOTO: Okay. Thank you. Other questions or comments? Okay. Well, let's — since it's still before noon, let's do the — at least do the diabetes and check mark pattern discussion if that's okay.

Diabetes

J. MICHALEK: Thank you. Up until recently, the thrust of the analyses that you see in this study, both published in open literature and in the — in the cycle reports are based on what we call "main effects adjusted statistical analyses" that generally don't involve what are called "statistical interactions," meaning that the statistical analysis depends on a main effects, usually linear model, which means a model not involving product terms, and which does not involve any kind of stratification except in model 1 where we had stratified by military occupation to officer, enlisted flyer, enlisted ground.

The other attribute of all published work out of this study, including the big reports and the published papers, is that they had relied on risk factors that were derived from the medical literature associated with the diseases being studied, as I mentioned, regarding diabetes and cancer. Within the last two or three years, we began to question

our models and all of our assumptions knowing that the study was coming to an end. Is there any extra information that we had not used that might be important?

Two such concepts were considered. First, that the concentration of the dioxins and the herbicides may not be uniform across the years of the war. I posed this question to Dr. Butler and to Dr. Jeanne Stellman. Is this true or isn't it true that dioxins in Agent Orange — putting aside Agent Blue or the others that were used very early in the war which we knew had higher contamination — is it true that Agent Orange itself changed? And Dr. Stellman speculated — or it wasn't ...

R. TREWYN: Not blue.

J. MICHALEK: Which one? I forgot which one it was.

J. MINER: Purple.

J. MICHALEK: Purple, okay. I forgot which one it was. Is it true or is it not true that this is the case? And Dr. — both Dr. Stellman and Butler suggested that yes, it is true; that earlier in the war that the Agent Orange was more heavily contaminated with dioxin than later in the war. And secondly, I realized from studying our own baseline report that the Ranch Hand unit was not spraying herbicide every single day of the war. They were — you can see that from the — one of the tables in our baseline report which shows the number of gallons sprayed by month across the whole war and you can see that there were months where there was no spraying at all.

I speculate that was because either battle conditions, or weather or whatever. Operational conditions that occurred in the chaos of that conflict dictated whether or not there was any spraying that month, so there were months when there was no spraying at all. Using that data from the baseline, the 1982 Cycle 1 report for this study, we enumerated the number of days of spraying for each Ranch Hand individual across this tour of duty.

Secondly, using the tour data, which we had been using for many years of the actual tour dates, we resolved the actual last year of service in the Ranch Hand unit of every single Ranch Hand veteran. So we knew that for a particular person, for example, in 1968 was his last year of service as a Ranch Hand individual. And subsequent to that, he was no longer in the Ranch Hand unit. He either went back to the States or he did something else. He wasn't in the Ranch Hand unit after 1968.

This is information that we had never used before. Two years ago or less, a year and a half ago, we began to assemble a database which would involve not only our usual risk factors of body mass index, and family history of diabetes and age, but we also merged the information on the last year of service and the number of days of spraying. It was with that new data set that I revisited the diabetes data, which had always puzzled me as to why we saw a so-called "check mark pattern," which I'm going to describe to you in these slides, again, trying to understand whether or not the check

mark pattern itself was an artifact of lack of adjustment. So that's what these slides are about.

So these slides are based on the same data sets we've used many times over in this study. In particular, these data are based on Cycle 5 and they've also been re-accomplished with Cycle 6 data, but the slides I'm showing you today are based on Cycle 5 data. The background is that in 1997, we published a paper in *Epidemiology*, first author Henriksen, which showed an association between dioxin and diabetes in the Ranch Hand cohort of an increased risk of adult onset type 2 diabetes with dioxin among Ranch Handers.

And yet, the overall difference between the Ranch Hand and control group was nil. In other words, there was no difference between Ranch Hand and controls on the overall prevalence of dioxin. This apparently contradictory result was published in *Epidemiology* in 1997. As you'll see in a minute, we represented that with the term "check mark pattern," the reason being that if you were to consider the Ranch Hand group, you would see a trend of increased risk with increased dioxin such that those with high dioxins had a risk greater than the controls and those with low dioxins had a risk less than the controls.

And that was a pattern that was difficult to describe, and to interpret and to present. And I presented that for the first time in 1991 at a dioxin conference. In subsequent years, we attempted to model that statistically to try to provide a purely

mathematical explanation for that pattern and we failed. That paper was written and rewritten many times, and rejected by journals and we were unable to publish that. So we have an ongoing interest in this apparently paradoxical finding.

Subsequent to 1997, the National Academy of Sciences reviewed the Henriksen paper in context with all other work in epidemiology and diabetes and concluded that there was a plausible association between dioxin and type 2 diabetes and that led to a VA decision to compensate Vietnam veterans for type 2 diabetes. But to this day, up until recently, the check mark pattern itself was a puzzle to me at least.

So we have another look at the diabetes data now adjusting for two new additional factors that were not considered in any previous report or article by us: days of spraying in Vietnam and a calendar year of spraying represented in a way I just described with the last year of service and counting up the number of days of spraying in Vietnam. We did this twice using Cycle 5 and 6 data. And the slides I'm showing you today are based on Cycle 5 data which was collected up to 1997. And we're measuring time to onset from service in Vietnam up until the date of diagnosis.

Here's a picture of the cumulative days of spraying by last year of service in the Ranch Hand unit. You can see on the vertical, days of spraying; on the horizontal, last year of service ranging from 1962 to 1970. And we already know from other data that the peak years of spraying were '68, '69, and the maximum spraying occurred in this latter two years of the war. You can see quite a spread; you can see a decrease here in

1970; highest occurring in ‘68, ‘69; and then prior to ‘65, quite a drop because at the very beginning, of course, there was a much smaller operation than there was later in the war. And you also see quite a spread from down near 0 all the way up to over 800 days for some people.

It makes sense in any epidemiological study to consider the possibility that some of the individuals in the exposed group may not have been exposed at all or actually were exposed to a degree much less than others. And this is a standard approach to occupational data to consider that possibility. It makes sense to me to exclude individuals who were there less than 30 days of spraying when the median number of days of spraying was around 300.

It also makes sense or is of interest to consider last year of service as a risk factor, considering the possibility that the herbicides may have been more contaminated earlier in the war than later in the war. So, of course, what I’m leading to now are some of the mechanisms of this analysis. Before getting to those details, here are some numbers showing the full sample size available for this approach: 3,049 individuals in the data set as of Cycle 5 who were available for analysis, excluding individuals with diabetes that occurred before they went to Vietnam or Southeast Asia; there were only five such.

Individuals who were not fully compliant to at least one physical exam were excluded. Individuals with missing dioxins were excluded, leaving 2,469 individuals for

analysis. The analyses I'm going to show you are based on a stratification at 1969 on last year of service. We computed the last year of service in the Ranch Hand unit for each Ranch Hander. We computed the last year of service in Southeast Asia for each comparison. So this strata right here is comprised of individuals, comparisons and Ranch Hands stratified by that factor.

So the 648 comparisons are those whose last year of service in Southeast Asia was 1969 or prior and the same for — is true here only now we're restricting Ranch Handers to those whose last of service was in the Ranch Hand unit was 1969 or earlier. And what you find here is, in terms of demographics, is an expected — to me anyway — case that the individuals who were there earlier are older than those who were there later. You can see that by the birth years, but otherwise, they're fairly unremarkable regarding the other demographic pieces of information. And the same is true with regard to these risk factors.

So is it true or is it — is it plausible that the dioxin, the Agent Orange was more heavily contaminated earlier in the war than later in the war? In order to get to understand that with our data, I stratified the cohort as to whether or not their last year of service — this is Ranch Hands only — was prior to '69 or not prior to 1969. The results are that individuals who were there prior to '69 have higher dioxin levels than those that were there — whose last year of service was not prior to 1969.

The point here being that this is consistent with the idea that the herbicides were more contaminated earlier in the war than later in the war. It's also opposite to the pharmacokinetics because one would expect based on simple first-order whole-body elimination that individuals who were there a long time ago would have less dioxin in their body measured in 1987 than those that were not there a long time ago.

M. STOTO: Can I — can I just verify ...

J. MICHALEK: Yes.

M. STOTO: You say less than or equal to '69. You mean ...

J. MICHALEK: That means during or prior.

M. STOTO: And, but there's only really one year after that, right?

J. MICHALEK: Well, there was 1970 and '71. Yes, that's true.

M. STOTO: Why did you cut there rather than 1968?

J. MICHALEK: You couldn't use '68, but — and the results are not very sensitive to that cut. You can use '68; you can use '67, '66. As you move back in time and change your concept of the cut, you get smaller and smaller numbers because there were very fewer and fewer Ranch Handers who were available in any unit prior to '68, '67. So when I write this up in a manuscript, you will see all of those other options described. I'm only showing you this one because it's the one that best describes the pattern of interest, which is the elimination of the check mark pattern.

My impression of this is that this is fairly remarkable that we were able to do — reverse the pharmacokinetics of dioxin by simply asking when were they there. I think that's an important concept. We were able to reverse the first-order whole-body elimination by asking a simple question as to when were you there; that's the point of this slide. And the point of the slide is consistent with the speculation that I heard from Dr. Butler and from Dr. Jeanne Stellman that earlier in the war, Agent Orange was more heavily contaminated.

The other important point of this slide is it's the only data in the world from with which one could make this assessment in humans because this is the only cohort that's been measured to the extent the Ranch Handers have been measured with regard to dioxin and all the other attributes of their service in Vietnam. The other question I asked was does the number of days of spraying relate to the dioxin in their bodies? And the answer is yes, it does.

I stratified days of spraying; you can see it in the footnote. No, actually not 30 days, but 90 days. Individuals who had more than 90 days, I called "high." Individuals with less than 90 days of spraying, I called "low." And I asked among the Ranch Hand veterans, is there a difference in their dioxin levels as regarding this attribute? And the answer is yes, there is except among enlisted flyers, which isn't quite as strong as it is among the other strata.

So we have two factors now that are based on operational information. They were taken from outside of the statistical realm. They are not based on p values. In other words, they are based on information, number one, that made logical sense to me based on occupational cohort studies, namely to consider the possibility that some men may not have been exposed as much as others; that was the days of spraying, and from the external information that I — that I received from sidebar conversations with other people. It had nothing to do with p value.

Probably the most important and remarkable thing is that remember that among the many reports and articles in the study, I don't think we ever found a significant group difference on any disease outcome in the study — even that even includes diabetes. There was never a case where we found a significantly increased risk of any disease between the Ranch Handers and the controls. And this slide is a representation of that.

This is the Cycle 5 data on a Ranch Hand versus control adjusted for all the risk factors in the footnote. That includes family history, and body fat and age. We see no significant increase in the risk of type 2 adult onset diabetes without adjusting for these two factors — these two new factors that I just mentioned. And with further without accommodating these two new factors that I just mentioned, we see a kind of check mark pattern that was present in the Henriksen paper; namely, we see a trend within the Ranch Hand group of increased risk where the relative risk is less than 1 with

individuals with low levels and it's greater than 1 in individuals with high levels and actually reaches significance.

But that is another reflection of what we call the "check mark pattern," which was clearly evident in the Henriksen paper in 1997, which is also evident here in the Cycle 5 data. Now after — I'm going to approach these two factors one by one: the number of days of spraying, and separately, last year of service and then we'll combine them. Assessing the strata on number of days of spraying, restricting to those individuals who sprayed — these are Ranch Handers — who sprayed at least 90 days. The group difference on adult onset type 2 diabetes is now significantly increased.

Considering last year of service during or prior to 1969, again adjusting for the same risk factors that we've always adjusted for — namely, body fat, age and family history — we now see a significant group difference on adult onset diabetes, relative risk 1.65. Revisiting the so-called model 3 analysis that is in all of our cycle — in all of our reports and in all of our papers, restricting to individuals who were in service whose last year or service was during or prior to 1969, we no longer see the check mark pattern. That's the numbers in red.

We see the pattern that was expected prior to this analysis ever being in any report or article and that was that if we were to see a dioxin effect on health, we should expect to see a — not only a trend in the Ranch Hand group, we should expect to see a

group difference. And both of those attributes are not present after consideration of the last year of service being during or prior to 1969.

In other words, in our attempt here and now in the year 2005 to accommodate the concept that Agent Orange may have been more heavily contaminated earlier in the war, we are now able to eliminate the check mark pattern that was present in our previous articles and published — and reports. Restricting marginally on the number of days of spraying, the same pattern obtains; that means the check mark pattern is eliminated. We have a relative risk of 0.97, close to 1.0, which means the check mark pattern is almost eliminated, but not quite.

And putting them both together, of course as you would expect, the check mark pattern is further eliminated; that the relative risk increases significantly with dioxin among Ranch Hand veterans and there is a significant group difference between Ranch Hand veterans and controls on type 2 onset diabetes. All of what you've seen today is new.

It accommodates information which has not been used in any of our articles or reports, but which has been available to us all these years sitting on our desks. Namely, the number of days of spraying, it was printed in the chapter of our Cycle 1 report, but never used. And the years of service, which were always available to us through our tour file because we know not only years of service, many other details about their tours.

By the way, we are still, as I understand, trying to resolve the actual location of the tours of duty of the controls. Actually, where were they during their time in Southeast Asia? That is a very — Dr. Trewyn, I know that's from — and I'm speaking out of context because I don't work for the Air Force right now, but I know this is a very laborious task to enumerate all of those tours of duty for all of the controls. And the Air Force people are trying very hard to do that. And soon enough, I think we'll have that, but I don't know exactly when.

So what we've got here is that the days of spraying and calendar year of service are, in fact, effect modifiers. They change the way dioxin relates to diabetes in this study clear enough from the slides I've showed you. And these data support the hypothesis that, yes, the Agent Orange was more contaminated with dioxin earlier in the war than later in the war.

And that simple operational pieces of information, such as the number of days of spraying, do relate to dioxin measured 15 years later by CDC in these same men, suggesting that simple epidemiologic methods — measures made from data collected, so to speak, "on the job, on the ground, in Vietnam" are related in the expected way to the dioxin measurement we've been using which gets to the point that I wanted to make and which is not on this slide; that the actual detailed information from which our Cycle 1 table was made are now in the hands of Dr. Jeanne Stellman at the University — I'm sorry; Columbia University in New York.

She has the daily spray records that were made by the Ranch Hand unit on the ground, during the war which tell for each day of the Ranch Hand unit how much was sprayed, how many planes were loaded, how many gallons were loaded in those airplanes, and what kinds of herbicides were loaded. That was a detail we never had and she has it.

So what I'm getting to is that the analyses I've shown you today can be refined based on information that already exists and which has been — was collected in 1965, '64, 1968 during the war, which is in her hands and which she's used to construct an exposure index for Army ground troops for the IOM. And, of course, the caveat is as an epidemiological study, other factors may be important that we don't know about. And that's all I had for diabetes.

M. STOTO: Okay. Thank you very much.

P. CAMACHO: Can we say, "I told you so," all at once? This is — this is why we said in the background, when you do the background piece because back in 19 — just for the heck, "ha-ha's," in 1982 when I ran this commission for Senator Dorris in Massachusetts, the first thing that everybody knew was that, yeah, but they have these spray records. Where'd they drop the stuff? They dropped it here in the DMZ. We know who was in the DMZ at that time. Guys laid all this stuff out. This is — this is what you don't, you know, you don't know because you're younger.

The screaming that went on about that, you know, you knew exactly who was in Leather Neck Square 33-23-13, part of the 26th and — but, and the guys had all this stuff down. That's what they were screaming at the committee about and that's what you were saying when you said separate these guys by who was getting — who was getting, actually using the spray as opposed to somebody in the office. He's part of the ground crew, but he's looking out a window watching them, you know. That's part of the whole bit, but that's the "I told you so."

R. TREWYN: Yeah, and I just want to again, not to quite do that, but close. I think, again, my whole issue on the comparison group and I recognize it's going to be difficult because they flew in; they flew out; they, you know — and it's probably going to have to be, you know, less than X number of days, you know, TDY in Vietnam or something to really separate. So you're going to have to do something like you did of 90 days here, maybe it's 30 whatever.

But this goes back, I don't know, four or five years ago, three or four years ago when NIAID was looking at some stuff in Vietnam and had — they had a committee formed to study what should be done. A group out of Canada, the Hatfield Group, went in and did environmental sampling in Vietnam in a variety of sites and looked at — now, I mean, in recent times, so as early 2000-something or other — looked at soil levels that they could detect of any possible breakdown products of the herbicides that were sprayed.

In the most heavily sprayed areas, they found nothing. Where they found huge off-the-scale levels of problematic compounds was in where base camps were located because those things were sprayed probably almost every day to make sure there wasn't a blade of grass coming up in or around the base. And so the issue of if these crews were stationed in Vietnam, they were exposed to nasty stuff, whether it was always Agent Orange. Maybe they were spraying different stuff in the base camps than they were out of the airplanes and that opens up a whole new area of concern and issue.

But I think this certainly clarifies that the issue of utilizing the data in different ways, of how you package it, and learning from where you are at any particular point and adjusting the studies appropriately, hugely important. And I assume these same sort of analyses are then going to be run on birth defects, heart disease, cancer, all those important things where there could be — where maybe no correlation before, but with this sort of slicing and dicing, maybe the significance appears.

J. MICHALEK: During our attempt to model the check mark pattern in 1993 and '94, '5, we enumerated over 50 endpoints in the study that represented a check mark pattern. That included many of the lipids and hypertension, for example, that was mentioned earlier. Hypertension exhibited in the check mark pattern. So yes, it's possible that the consideration of these factors could clarify that data.

M. STOTO: And we're going to hear about, I guess, the same kind of thing with respect to cancer next. But I guess I'm — the concern is that this group is coming to the end of its period when it can do work, which makes it relevant. I hope that David Butler is listening to this, but for the ...

R. TREWYN: No, he's not.

M. STOTO: ... for the — for the — for the next study. I mean, this is — I mean, it's just getting to the point we're beginning — we're beginning to — we're still learning new things from these data, I think, is the — is the point to be made.

P. CAMACHO: You know, there's a side to this too; it's a — it's a lessons learned in the military since we're all computerized now. Keeping data on where people are and running against it because you're going to have whatever chemicals ran into in the first Gulf War and who knows what anybody's running into now? And so that should be recorded. Some unit is running through Iraq and then ran, "What is this stuff?"

You find out and know what, you know, you find out and you recorded this. You're going to get into this with the depleted uranium stuff sooner or later. You're going to end up facing this; somebody, the Army's going to end up facing this sooner or later and they'll — 20 years from now.

R. TREWYN: And I would just throw out again, just since people who know my history, I always have to argue that I know everyone here falls in love with dioxin as the — as the culprit. But again, there were certainly a lot of other nasty things in some of

the other compounds: in blue with cacodylic acid and there are other things, components. And so it may not always be dioxin-related, but it doesn't mean that some of the parameters that you already have can't, again, with time that they were there, number of days spraying, may not show the correlation to dioxin, but it could to other aspects.

J. MICHALEK: Well, the detail that Jeanne Stellman has on those documents can be helpful. The other point to make about the documents that she has and the data we've used, it's totally free of any pharmacokinetic assumptions. The number of days of spraying, the last year of service in Vietnam are totally free of the — of the complications we have with regard to the pharmacokinetics of dioxin itself. So they are clean in that sense and that's why they're of interest to me.

R. TREWYN: And I would just like to — oh, excuse me, David — just like to throw out then linking to some of the molecular markers that are out there, being able to really do some fine tuning of this. Maybe it takes away a lot of the shotgun pattern that you're seeing if you — if you have that level of specificity that you can get down to, and really could turn into very definitive studies and not having to try to explain away the shotgun effect of what you're seeing.

M. STOTO: Thanks. David?

D. JOHNSON: I guess if I could just kind of recapitulate it. You're saying that when you studied dioxin association with diabetes between controls and Ranch Hands,

you found a certain level of association? When you then refined that by taking the number of days, that association became stronger?

J. MICHALEK: That's right. When we excluded the relatively few Ranch Handers who were there less than 90 days, those who were on TDY or those that were days — there when there was no spraying at all, when there — those are excluded, the association becomes stronger between herbicide exposure or dioxin exposure and diabetes.

D. JOHNSON: So you found some new associations you hadn't found before?

J. MICHALEK: They're stronger ...

D. JOHNSON: Stronger.

J. MICHALEK: ... than what we saw before, yes.

D. JOHNSON: But in each case that you looked at Ranch Hand versus control, you also looked at dioxin level, biomonitoring so to speak?

J. MICHALEK: Yes.

D. JOHNSON: And you found associations there as well, similar?

J. MICHALEK: They were stronger after we did this method of analysis, yes.

D. JOHNSON: That's my question. I mean, if you also — and in some cases you looked at Ranch Hand versus control. Another situation — in the other analysis that we did, you looked at the 1987 dioxin, which is actually — it really bypasses the —

if you — if you do biomonitoring and look at it actually in the blood, it kind of bypasses the exposure pathway and how many times you're exposed. It's telling what's there.

J. MICHALEK: That's right.

D. JOHNSON: So you made — we made some associations there with the biomonitoring so to speak between diabetes and dioxin. So by refining this exposure scenario, did the associations become better than what you had just using direct blood monitoring? Do you — do you understand what I'm saying?

J. MICHALEK: All right. The analyses I showed you were based on the so-called "model 3 approach" where we had Ranch Hand categorized to low, medium, high or background, low, high. That approach led to a stronger association than we had seen previously after we accommodated last year of service and days of spraying.

That model depends on dioxin, but it's not the simple model 4 analysis that you're contemplating. It is not a simple association between 1987 dioxin and diabetes. That hasn't been done yet. All I did in these slides was the so-called model 3 analysis after adjustment for last year of service and days of spraying. All of that remains to be done; it hasn't been done yet.

D. JOHNSON: Can I ask a — let me — can I ...

P. CAMACHO: I thought you — what you were saying was could you reverse it? In other words, you took the biomarkers. Now could you match back those markers against ...

J. MICHALEK: Are you asking whether day — actual days of spraying relates to diabetes?

D. JOHNSON: My — I think my question is this. If you showed that by breaking it down into the number of days, that's a — that's a strong ...

J. MICHALEK: By excluding individuals who were there less than 90 days that had less than 90 days of spraying, that's what we did, yes.

D. JOHNSON: That refined it to make a stronger association than just using control versus Ranch Hand? That would — but is that better than just — than looking at the actual dioxin level in the blood?

J. MICHALEK: We did that.

M. STOTO: Why don't — why don't you go back ...

D. JOHNSON: Do you understand the question?

M. STOTO: ... two slides, I think, is the — is the relevant one, this slide.

J. MICHALEK: At the top in the red is the model 3 analysis that you see in all of our reports and articles. "Comp" means comparison: background, low, high. We see a relative risk of 2.12 in the high category.

M. STOTO: Excuse me, Joel. That's not the same one that I ...

J. MICHALEK: This is dioxin, diabetes. Which slide are you looking at?

M. STOTO: Okay. I see where that one is. Okay. Yeah.

J. MICHALEK: With more than 90 days of spraying; the association is strengthened after you eliminate individuals who were there with — who had less than 90 days of spraying. The categories on the right-hand side depend on dioxin on the biomarker: background, low, high. So the biomarker's built into this analysis already. You might be — you might be interested to know how dioxin itself is a continuous variable. It relates to the risk of diabetes after adjustment for days of spraying. That has not been done yet, but I expect to see consistent results because that's the same biomarker that's used in this slide to make those categories: background, low, high. Is there another way that I could say this?

D. JOHNSON: Well, I guess my question, if you take somebody's blood level for dioxin and you know what the level is, you know what they — that's a — that's a better — that's a stronger indicator of what their exposure's been than modeling how many days they were exposed, you see, because it's a — it's a concrete — it's a number.

J. MICHALEK: There are complications associated with the dioxin measurement that we have described many times. An individual can have a low level of dioxin because he was never exposed at all or because he was exposed and then had a whole-body elimination back to background levels. We had no way to resolve that — those two possibilities.

One way to address the possibility is to eliminate people we know from the records were there only a few days and that's what this analysis does. So it at least

partially addresses the possibility that some people weren't exposed at all. We know some of the individuals who were there less than 90 days had zero days of spraying because the unit didn't spray at all while they were there. They didn't spray for who knows what reasons having to do with the war.

D. JOHNSON: Right. They would show up with zero — they wouldn't ...

J. MICHALEK: No. They would not show up necessarily with a zero dioxin. They would have background levels like you and I do.

D. JOHNSON: Right.

J. MICHALEK: Maybe around 4 ppt.

D. JOHNSON: Right, but they'd be very low.

J. MICHALEK: And those ...

D. JOHNSON: They would be very low.

J. MICHALEK: They would be low, yes, but I'm getting to is that all of these sources of misclassification degrade our ability to assess associations. They've biased the study toward the null and any attempt we make to address those can only help. And that's what happened here I think.

D. JOHNSON: Well, I could see how if you take it one place in time, you take the dioxin level, that doesn't tell you how high it's been throughout a period of time. I can — that was a good point you made there. I can see how that would — that it

doesn't answer that, but yet, at the same time, it actually finding it in the blood is a pretty strong indicator.

J. MICHALEK: It's a strong — but I'm telling you again, there are many complications and caveats associated with the dioxin level. It's a great measurement, but there are caveats: the one — the one I just described plus the variation in the half-life with obesity.

D. JOHNSON: So let me ask this. So are you suggesting then that with the limitations — they both have limitations looking at the number of days that ...

J. MICHALEK: I'm saying that with this combination of data, the dioxin measurement in combination with the operational information that I've just described, days of spraying and years of service, the association is strengthened between dioxin and diabetes.

D. JOHNSON: I see. Thank you; that clarifies — that clarifies it.

J. MICHALEK: Okay, and there are many historical examples, by the way, of occupational studies that simply used the number of days on the job as a metric. And that's what the NIOSH studies did and they found an association because of their dioxin measurements.

D. JOHNSON: So your model — your model considered both the biomonitoring and the days?

J. MICHALEK: Yes, it did.

D. JOHNSON: That's excellent.

M. STOTO: Sandy?

E. HASSOUN: Also one comment.

M. STOTO: Oh.

E. HASSOUN: Sometimes ...

M. STOTO: Please go ahead.

E. HASSOUN: Sometimes in toxicology, I mean, the effect of one single high dose is different from ...

J. MICHALEK: Right, I understand.

E. HASSOUN: Yeah. So it could be, I mean, you cannot correlate with the level ...

J. MICHALEK: Right, I understand.

E. HASSOUN: ... I mean, much farther than the days.

D. JOHNSON: He clarified that very well.

E. HASSOUN: Yeah.

S. LEFFINGWELL: Okay. I can begin to sort of grasp why the greater than 90 days strength might be better. But now what's happening with the less than 90 days?

J. MICHALEK: That number and you can — you can play devil's advocate because you can see that p value of 0.02 down there and yes indeed; that is a detraction and that certainly spoils the story that the relative risk is less than 1 in the

background category among those who were there less than 90 days. And perhaps a delineation of those cases may help explain that and that has not been done: to list them out, and to consider their service in the Air Force, and what they did and when was their diagnosis.

And all of those can be studied; it hasn't been studied yet. But I think my interpretation is that there is a — that there's an overriding consistency between all these data which is consistent with surprisingly speculations made outside of the analysis by my colleagues. And I thought that was remarkable.

M. STOTO: I guess I'd be a little bit concerned about overdoing that. I mean, it is a significant p value, but it is based on 15 cases of diabetes. Is that what that ...

J. MICHALEK: Yes, as opposed to, you know, higher numbers in the upper strata there.

M. STOTO: Ron?

R. TREWYN: I would just like to add the point. You said these can be studied and that's only if the material is available after September of '06 can they be studied; just ...

M. STOTO: Thank you for reminding us of that.

R. TREWYN: Just wanted to make sure he was listening.

M. STOTO: Yeah. Okay. Other questions or comments on this? Please come find a mike, please, or you can come up here if you'd like.

M. PAVUK: Maybe just one more comment on the — Marian Pavuk, SpecPro, Air Force Health Study. Maybe just one more comment to the measurements of dioxin, one problem with it is also that the measurement was — the first measurements were done only in 1987, which for some veterans was more than 20 years after the service in Vietnam. And that kind of weakens the usefulness of the measure, but nevertheless, the actual measurements in blood, I agree with you, is the best measure of the exposure that we have at this — at this point. It's a much better measure than saying how many days that they were there or they were not there.

D. JOHNSON: I think I understand that, but I believe also he went on to say by taking the blood level plus adding in ...

M. PAVUK: Right.

D. JOHNSON: ... the information of the greater ...

M. PAVUK: That's the advantage.

D. JOHNSON: ... that becomes an even better ...

M. PAVUK: That strengthens the overall ...

D. JOHNSON: Strengthens the ...

M. PAVUK: ... exposure assessment of the cohort.

D. JOHNSON: Right.

M. PAVUK: But I also should note that what would really strengthen the overall exposure assessment would be measuring of all dioxin, and dibenzofuran and dioxin-

like chemicals and congeners which is currently underway at CDC. And I think they have about 700 samples that they finished analyzing, but as you can imagine, it may put the — shed the results of the study in quite different light if the results they find do not necessarily correspond to what we are seeing here.

We see the categories of comparison — background, low and high — based on TCDD levels only. Those other chemicals assess similar or the same toxicological property, but maybe the veterans may have been exposed in Vietnam and after coming back from Vietnam to different levels.

So what I'm — what I'm going to is that there is a slight possibility of exposure misclassification that people that we see they are being comparisons or background or being low and high maybe based on TCDD. They don't belong to that exposure category based on total toxicology TEQ, toxicological equivalence, than just TCDD only.

J. MICHALEK: To amplify what Dr. Pavuk just said, we were greatly interested in pesticides in the control group. And unfortunately, CDC's not measuring — is that true? — they're not measuring the pesticides.

M. PAVAK: Only DDT and DDE.

J. MICHALEK: Yeah. Yeah. And you should also know that the — I — and once you entertain the idea of excluding from the cohort, those that had little or no exposure, we already have identified, but never taken advantage of the fact that some Ranch Hand veterans were administrators and were not flyers or enlisted ground crew

— not very many, but a few. And some Ranch Hand veterans denied any exposure at all and we found that among the enlisted ground crew when we questioned them in 1989 about what they did on the job in Vietnam.

Some would say, "Well, I never touched it. Leave me alone." And they would leave the questionnaire blanket — blank. There were a few like that. And so what I'm — what I'm getting to is the logical approach in any study like this is to do your best to eliminate or minimize exposure misclassification. And all of those little pieces put together may help clarify some of the patterns we see in the data.

M. STOTO: I guess I either wasn't aware or I was aware and forgot about these — this other testing that CDC is doing. And is that something that the Air Force is sponsoring and what'll happen with those results?

J. MICHALEK: Actually ...

K. FOX: The Air Force is — we did 106 of the comparison Ranch Hands that were new to the study for Cycle 6. They've got that additional testing; we've gotten that back. If we have money, we are hoping to be able to expand that and pay for additional Ranch Hand comparison groups to be analyzed and to get the full battery of tests on them.

M. STOTO: But ...

K. FOX: All the blood has been — is at CDC awaiting for us to be able to finance it.

M. STOTO: Okay, but given that the schedule of the study, I mean, will that still be ...

K. FOX: That is correct.

M. STOTO: Is that ...

K. FOX: We are trying to do the best we can. And we're hoping we'll find out whatever we have left over for this year, we're hoping to put toward to run it.

M. STOTO: Well, no, that's not the issue. The issue is who's going to ...

K. FOX: But yes, you're correct.

M. BLANCAS: They may not have enough time.

K. FOX: There will — may not be enough time to analyze everything.

M. STOTO: Okay, but it — but it is information that will be available if the study is archived in some way?

K. FOX: That is correct. It will be in our database.

M. STOTO: Okay. One more question, plans for publishing these results?

J. MICHALEK: Just before leaving my Air Force job, I had the information you saw on these slides in a draft manuscript. I have since proposed to the Air Force that I be funded to finish the paper and I'm awaiting some decision on that. The idea would be that I finish writing the paper as well; I'm a faculty at the University of Texas. But that has not been resolved at this point.

M. STOTO: Well, I think that the Committee would agree with me; that the importance of getting these — this information out into the public domain. Is that — yes?

R. TREWYN: Here, here.

M. STOTO: Okay. Well, I think that it's probably a good — would be a good time to take a break for lunch now. We, in order to keep going, we'd like to have a working lunch. Let's take 15 minutes to gather up a sandwich, and cookies or whatever else and then we'll start again at about a quarter to — a quarter to 1:00. Thank you.

[LUNCH 12:30 P.M. - 12:55 P.M.]

J. MICHALEK: All right. Well, the Chairman has asked that I continue while we're eating lunch. That'll save us some time because I have a 6:00 flight and I know others in here have flights that have to get out of here to go to the airport. But before I go move on, I would like to emphasize that in my opinion, and I think shared by many of us, this is probably the best epidemiologic study ever done. It is based on the — some of the best data ever collected in humans. It is — it is a noble effort on the part of the government.

This effort was launched in 1979 at a time when no one knew what we would find. And our government committed these resources to an effective 30 years of follow-up giving us almost all available resources that were — there was unprecedented scope, unprecedented quality and unprecedented consistency to answer a question of

unprecedented sensitivity. That is noble and that has — that's exactly what we're viewing today is the end result of that kind of effort.

It's complicated because of all the things we've talked about today. It's convoluted in that some of the variables we consider as covariates may in fact be endpoints; we're not sure: BMI, for example. It's convoluted; it's complicated and it's fundamentally based on a — on a circumstance for which data was lacking; namely, there was no dosimetry in Vietnam. We didn't have a patch on the uniform that changed color when someone was exposed to a chemical. We didn't have any of that.

The government launched this study; their mandate was apply the standard epidemiologic template to a — to a problem of unprecedented complication. Our government did that and that's why we're here today. And so I wanted to clarify that to — so that people who don't know that know it now. And the fact that we're able to hear today, to sit and look at this data and speculate is attributed to the — to the years and years of hard work and dedication of literally hundreds of people from the very beginning until now have made this possible and I'm proud of it.

Cancer

J. MICHALEK: So now we're talking about cancer. Again, in the last year before ending my employment with the Air Force, I approached these two areas because they were areas of extreme interest: diabetes and cancer. They were also

areas of fertile ground for an analysis because the prevalence is so high in both cohorts. It gives us large enough numbers so we can — we can entertain analyses that we couldn't do in other areas. And this analysis follows up other attempts to understand the cancer data that we've already published.

Once again, we're going to depart from the analysis in the big report and all of our published papers to entertain two additional factors: namely last year of service in Vietnam and number of days of spraying as — and look again at the cancer information in the study. And once again, we have never seen in any of our reports or articles an association between cancer and dioxin in any what we would call "main effects adjusted model," which I call "simple main effects models."

And by the way, the concept of stratification is mentioned several times in the protocol of the study, which was written in 1977 as an approach to be used as necessary to elicit information about health and exposures to dioxins and herbicides. And so using a parallel approach to what I just showed you with diabetes, we are now going to look at all-site SEER cancer further adjusting for years of service in Southeast Asia. Well sorry, I'm reading the slide incorrectly.

We had previously published a paper adjusting for years of service in Southeast Asia and the proportion of time spent in Vietnam. That was the Akhtar paper that was published in *Journal of Occupational and Environmental Medicine* last year. And now

we're going to consider separately last year of service in Vietnam in Ranch Hand veterans and the number of days of spraying.

This data set is up to September 30, 2004. It's all available cancer data as it existed a few months ago. It is based on the all-site SEER definition. SEER, S-E-E-R, stands for "Surveillance, Epidemiology and End Results" section of the National Cancer Institute. They publish a series of reports and have made standard definitions of cancer categories. And we're using their all-site SEER definition, which is simply all cancer — all cancers, both skin and systemic minus the — some related cancers of basil cell and squamous cell carcinoma.

In this analysis, I'm measuring time to onset from the date of the first physical in 1982. I'm sorry; I lost my place. We're measuring from 1982, namely from baseline. And the reason we do that is that there's an issue of latency with cancer which is addressed in many papers; that we shouldn't expect to see cancers within 15 years or within ten years of exposure, which has not been mentioned in any analysis of diabetes, but which it is mentioned in analyses of cancer. And so we began this follow-up in 1982.

And that's not a critical assumption; it can be changed. And the same attributes are true of this data as in all other data. It's all verified by medical record review and all analyses are accomplished with proportional hazards models adjusted for known risk factors, including military occupation, year of birth and sun reaction — skin reaction to

sunlight and smoking history. And we're going to restrict to individuals who were compliant to at least one physical exam as we did in the previous.

Here is — here are the sample sizes again excluding individuals with cancer prior to baseline, prior to the first physical exam with 93 people and individuals not compliant to at least one physical and those with missing dioxin levels. In this analysis, 84 Ranch Hand veterans were excluded on that basis leaving 2,583 subjects for consideration. This is the repetition of a slide you saw earlier showing days of spraying by last year of service in Vietnam. In the Ranch Hand unit, that's the last year of service in the Ranch Hand unit. In controls, that's the last year of service in Southeast Asia. Across the horizontal and on the vertical is the last year — is the number of days of spraying, and of course, this slide is specific only to the Ranch Hand veterans.

So I'm going to stratify and I have to tell you what you already know and that is that stratified analyses are subject to criticism simply because you're not looking at the entire cohort when you stratify. And they're especially subject to criticism when the strata are based on the p value, which is a path — a forbidden path in epidemiology to make such strata. This strata — these strata are based on operational information that I received outside the box so to speak that are not based on p values.

I believe that 30, 60 or 90 days may be a reasonable cut point for lack of exposure. In diabetes, we use 90 days. And here, I'm using 30 days. So individuals with less than 30 days of spraying were excluded instead of less than 90 days. And we

have a sample size issue here that's not — is — which is more critical than it is in diabetes because we're going to stratify further. And so the cell counts are going to get small and so my decisions based on who to — who to kick out or who to exclude are influenced by that.

And in the analysis of cancer, I'm going to stratify based on last year of service in the Ranch Hand unit of being in 1968 or prior. And then you might ask, "Well, why 1968?" And I'm telling you, well, that's where the data has led me and there is an Achilles heel of stratified analyses that the strata are leading me to the result. Well, in fact, I will tell you as I write this up into a manuscript that as you show the different cut points on '65, '66, '67, '68, '69 that as you move back in time, the relative risk I'm going to show you gets stronger and stronger and consistent with the possibility of a — of an exposure effect on dioxin in cancer.

However, the counts get smaller and smaller because you have fewer and fewer people who were there in the early years of the war. And so it's a matter of displaying in such a way so the reader sees that and that's what I'm going to do when I write this up. So in these slides, I'm using 1968. Another complication of the — a complication of the cancer data that's not there with diabetes is that years of service in the Southeast Asia region is a risk factor for cancer for all-site SEER cancer in the control group. And that was just recently published in the *Journal of Occupational and Environmental Medicine* just April of this year, just last month or two months ago.

That greatly complicates the picture on cancer and dioxin because now it requires that we somehow adjust for how long a control was in the region, whereas with diabetes, we didn't have to worry about that. And by the way, I checked that years in SEA is not a risk factor for diabetes in the control group, whereas it is a risk factor for cancer in the control group for reasons that we don't understand completely or don't understand at all. And we can speculate and the speculation is in the article.

So we have the same approach that we used for diabetes, but now which is further complicated by the need to adjust for years of service in Southeast Asia because of the risk factor of that effect — the effect on cancer in the control group. And so you see the different strata here that are the same ones we talked about with diabetes, only now I have further stratified by less than two years in SEA or not. And then you ask, "Well, why would I use two years in SEA?" The simple reason being that that's the median — number of years in SEA in the control group.

It is the fact — a fact that individuals in the control group who were there less than two years have less cancer or less cancer prevalence than were those that were there more than two years. And the story's even more complicated than that, but it's described in our published paper. The same kind of demographic table you just saw only now I've got the early service and increased spraying strata, which means these people were in the region during or prior to 1968 and the Ranch Handers had at least 30 days of spraying. And here you see the model 3 strata: the comparison

background, low high. And it's showing the demographic information that we've — we're used to looking at in all of these analyses: year of birth, pack years of smoking.

And as always, the individuals in the background category are older than the — in the high dioxin category because those in the high dioxin category are mostly enlisted, and those in the background category are mostly officers and officers are older than enlisted. And here's the complement strata of those that were not in the previous one I just showed and the pattern is somewhat different in that the — there's no clear — well, it's still true; that the individuals in the background category are older than those in the high category.

Early years of service and increased spraying, again, this is the strata of during or prior to '68, and more than 30 days of spraying and the complement. And there's no — are no remarkable patterns here that are causing me to stop or interrupt my presentation here. So after you get — study those slides, you'll see what I mean. So again, I asked the question, "Do these data support the idea that the herbicides were more contaminated earlier in the war than later in the war?"

And so here with this data set, I've repeated the same analyses I did earlier with diabetes, only now we're looking earlier, during or prior to '68 — yes or no — on dioxin in the Ranch Hand group. And yes indeed, it's — the data is consistent with the idea that the — and in opposite to the pharmacokinetics that individuals who were there earlier have higher dioxin levels than those who weren't there early in the war, which is

consistent with the idea that the herbicides were more heavily contaminated earlier in the war than later in the war.

Now here I've — and then I'm asking about days of spraying. The days of spraying relate to their body burden of dioxin as measured by CDC and the answer is yes. And here I've given you more detail than I did in the diabetes slide. I broke out days of spraying by tertiles and there you see a significant trend in the enlisted flyer, and enlisted ground categories and even in the officers of increased dioxin levels with increased days of spraying in the Ranch Hand group telling once again that that simple calculation based on data — old by the way, a very old version of a herbs tape which was represented in our baseline report — that data correlates with what CDC measured in 1987 up to 15 years after exposure.

Here is a slide summarizing the cancer data without any adjustment for days of spraying or last year of service, SEER cancer — all-site SEER cancer — and we see nothing at all. The associations are all in the neighborhood of 1.0, which suggests no adverse association between exposure category and cancer. Let me get my pointer. Yes?

D. JOHNSON: Go back on slide for a second. Is that correlation there for the dioxin and number — and the number of days of spraying? Is that the baseline dioxin we were talking about earlier?

J. MICHALEK: These are dioxins measured in 1987 basically. I'm using what's called a "current dioxin," which was for 90 percent of the Ranch Handers, it was measured in '87. And for those others, it was measured in 1992 and 1997.

D. JOHNSON: So this shows — this data indicates there is a correlation between the number of days of spraying and that baseline number?

J. MICHALEK: And there's no correlation between the 1987 dioxin and the number of days of spraying as represented on the herbs tapes in the Ranch Hand group. So here you have these people — these 184 enlisted ground with between 382 and 1,000 days of spraying had higher dioxins than those enlisted ground that had less than 289 days of spraying.

D. JOHNSON: So ...

J. MICHALEK: Those are in log units, so you can do an anti-log of 3. You're going to take "e" to the third power. If you have your Excel spreadsheet, you can do that. I think it turns out to be about 20. These are like averages of about 20 ppt in 1987.

D. JOHNSON: So there is a correlation, but going back to the discussion we had earlier, you'd think that dioxin, that a serum dioxin would be a good determinant of the number of days of spraying. But yet, you found that when you added that in, it ...

J. MICHALEK: There's more ...

D. JOHNSON: ... it increased the level of ...

J. MICHALEK: Yeah.

D. JOHNSON: ... specificity.

J. MICHALEK: Between dioxin and the health endpoint. There's — dioxin isn't the whole story in other words. Using this on-the-job measurement enhanced the association between dioxin and diabetes.

D. JOHNSON: Right.

J. MICHALEK: The dioxin by itself was associated, but when I further adjust for what actually went on in Vietnam on the ground ...

D. JOHNSON: Right.

J. MICHALEK: ... the association became stronger.

D. JOHNSON: Became stronger, okay.

J. MICHALEK: Yeah.

R. TREWYN: Joel, can I ask a question on that?

J. MICHALEK: This is based on old data from the herbs tapes, yes.

R. TREWYN: Does — do the days spraying, does that equate to time in Southeast Asia? So I'm wondering here ...

J. MICHALEK: Oh.

R. TREWYN: ... if you're actually looking at ...

J. MICHALEK: Yeah. Okay. I haven't — well, first of all, let's be careful here. We're talking about Ranch Handers only, okay, and these are days of spraying or days while they were in the Ranch Hand unit in Vietnam where spraying ...

R. TREWYN: Right.

J. MICHALEK: ... was actually going on. And so I haven't run that correlation, but I expect it's going to be highly correlated with how long they were in the Ranch Hand unit.. I mean, that's another metric that could be considered.

R. TREWYN: Well, and just thinking back to the fact that time in Southeast Asia is a factor for ...

J. MICHALEK: The control group.

R. TREWYN: ... for the control group, I mean, maybe what this is saying ...

J. MICHALEK: These are Ranch Handers only.

R. TREWYN: Yeah. So there would be, I mean, the — looking at the complicating factors here since time in Southeast Asia alone causes an increase when we get to the cancer part, that this — some of your complicating factors may be that it's beyond just spraying. It's also the time in Southeast Asia.

J. MICHALEK: Well, most Ranch Handers didn't go anywhere else but the Ranch Hand unit; that most of them were Ranch Hand unit veterans and that's about it. They didn't spend much extra time in SEA. I don't have a good description of that in these slides. The other thing to remember is that two years is about the 75th percentile

of the Ranch Hand experience, whereas the median of the control experience. So we're capturing quite a proportion of the Ranch Hand unit with the two-year cut point on the years in SEA.

So we see a significant and a consistent pattern of association between the herbs tape calculation of days of spraying and dioxin in the Ranch Hand group. I already showed — talked about this slide. So here we have the — let me see; what is this now? I lost my train of thought. Just a minute. Okay. This is the corresponding slide to what we saw with diabetes where I simply accommodate days of spraying and during or prior to '68. I'm restricting to white people to adjust for race, not accounting for the less than two-year risk factor on years in SEA. I'm not accounting for the additional complication of the association between years in Southeast Asia and cancer in the control group.

And we see a suggestion of an effect here. We have a significant trend. If you look on the red information, "n" equals 788. That's a statistic suggesting that the entire cohort, the risk of dioxin — of cancer increases. But yet when I break it with dioxin, p value of 0.01, but when I break it out using our model 3 analysis, I don't reach significance in the high category.

And the complement category, those that did not have early years of service and increased spraying, I see nothing at all. But once again, you can look at that high category and see a p value of 0.05. But in that case, there's only four cases in the high

category and so probably not a lot of weight should be placed on that — on that reduced risk. Now I'm restricting to individuals who were there less than two years in Southeast Asia and here we're now taking into account that additional risk factor that we saw in the control group.

And now you see the risks are — relative risks are increased in the Ranch Hand group because now we've restricted and we are eliminating comparisons who were there a long time. And so that drives down the cancer rate in the comparison group and so the relative risks are higher in the Ranch Hand group, but not — do not reach significance. Now I'm going to take the combination of the additional pieces of information on the days of spraying, and service during or prior to '68 and less than two years in SEA. And now I see a significant increased trend of increased risk of cancer with increased exposure category. I see a significant trend.

And so this is the corresponding story in cancer that we saw in diabetes and it's more complicated than diabetes because we have to further stratify. And then you'll ask, "Well, why should I stratify? Why can't I just use the main effects model?" Those models have been tried and they failed. And the reason they failed is that the interaction terms regulating years in SEA in the main effects are not significant. There are textbooks that warn against using such interaction terms to detect stratum-specific effects in epidemiology studies and so I guess this is an example.

We do see a significant trend; however, we do not see a significant difference on all Ranch Hand versus all controls. And I don't have that slide in here. So in other words, this — we've really reached the end of the road on cancer and we've gone as far as we can go. We've adjusted for days of spraying, years in the region and last year of service. And we're down to this strata and we're down to relatively small numbers — 15 cases in the high category. And we see a significant increase in risk; however, the analysis is limited because of the three levels of stratification.

M. STOTO: Joel, could you just remind us what that relative risk of 1.4 over on the left is?

J. MICHALEK: That is the — that says that for every unit change in dioxin in the combined cohort, this is the — what do you call it? — either the beta from the Cox model. That's the change in risk for unit change on the x-axis, which in this case would be dioxin. And that's significant, so this is the ...

M. STOTO: It's dioxin in a continuous measure or ...

J. MICHALEK: Dioxin as a continuous measure. So this is the coefficient of dioxin in a main effects Cox model with dioxin as a continuous measurement and this is a continuous variable. And this is the number we interpret as a test for trend. And so we're seeing a significant increase in the risk of cancer with dioxin as a continuous variable adjusted for all of these risk factors you see in the footnote. Another way to say

it is over and above all of these existing risk factors, we see an association between dioxin and all-site SEER cancer in this strata — in this stratum.

M. STOTO: And why does it make sense to adjust for years in SEA?

J. MICHALEK: Because years in SEA is significantly related to cancer in the control group.

M. STOTO: Okay.

J. MICHALEK: Just recently published. Then of course the next question might be whether spray category itself, did days of spraying by themselves relate to cancer in the control group just eliminating dioxin from the picture altogether? So I stratified by tertile of days of spraying to low, medium, high. Those are the same tertiles you saw earlier in an earlier slide relating days of spraying to dioxin in the Ranch Hand group. And the answer is no; the relative risks are all around 1.0.

So in other words, days of spraying is not sufficient information with which to elicit an exposure effect on cancer in the Ranch Hand group. You must still entertain or use the serum dioxin levels to answer that question. So first, the conclusions are that days of spraying and last year of service in SEA are effect modifiers. The picture is more complicated with cancer than it was with diabetes because we had to further adjust for years in the region.

We do not attain a group significant difference on cancer after these adjustments, but we do find a significant increase in the risk of cancer in the Ranch Hand group and

we see a significant trend. These analyses, like I said, are different from those in our published papers and our reports because they accommodate information that was never used in any other reports. But the analyses are more complicated, but they are consistent with the idea that the herbicides were more contaminated earlier in the war and that the days of spraying relates to dioxin.

And after adjustment for these factors, we see a significant association between cancer and dioxin. They are complicated by the association between years of service and cancer in the control group, which was a surprise to us. We didn't expect to see that and that further frustrates our attempt to find a clear association between dioxin and herbicide and cancer in the Ranch Hand group. I know that's a mouthful, but that's the way it is. Thank you very much.

M. STOTO: Ron?

R. TREWYN: Well, as you wouldn't be surprised at the fact that it isn't as good a correlation with dioxin doesn't bother me a bit because I've never been in love with that being the only factor and complicator in this. And I think truly one of the things, and many of us have argued for for a lot of years, that the question that Congress asked was not the question that was really bugging veterans, which was did their service in Vietnam cause adverse health effects? And if that was the case, then there should be some compensation, something done about it.

So the fact that your recent publication really does show that with regard to cancer, that years in Southeast Asia correlates, I think it points out that there is really some valuable, valuable information, again, to be gathered here. And I think it's important stuff. I will just have to add that in ten years of sitting in on these off and on, I've never seen you lose your place. And three months as a professor and it happens, so just let you know that there's a trend that's going to happen here, so ...

M. STOTO: Will you come to — can you come to the mike?

J. MICHALEK: Dr. Pavuk was pointing out he had brought a copy of the Akhtar paper, which was — it's not the — it's the — it's the trend in the control group paper. First author was Pavuk, correct? First author Pavuk, published in *JOEM* in April of this year which shows — that paper showed a significant increase in the risk of cancer in the control group with years in SEA. Furthermore, the risk is further increased by their dioxin levels in the control group, which is a surprise.

And we speculate in the paper that the risk — increased risk of cancer with increased years in SEA may have something to do — this is a speculation; we don't have any data to support this — may have something to do with efforts made by the World Health Organization to eradicate malaria during that same time period. There was many — they were spraying for mosquitoes using DDT and other pesticides throughout the region during the same time period. So we think perhaps that might have something to do with it, but we have no data to support that.

D. JOHNSON: Joel, can I ask a couple of questions?

J. MICHALEK: Yes.

D. JOHNSON: Earlier — is there time for it?

M. STOTO: Yes.

D. JOHNSON: Earlier this morning, we've kind of gone through, summarized all the findings. And it seems like I recall that the only significant findings were between diabetes and dioxin. Is that correct?

J. MICHALEK: That's true in the Cycle 6 report, yes.

D. JOHNSON: Cycle 6. And on this slide, the conclusions here it says that dioxin is an — or the years of — period of service, spray days, *et cetera*, are effect modifiers between dioxin and SEER. Now is that saying that there's — there is an effect without those? There's an — there's an effect between dioxin and SEER, which is then modified? So is there any kind of association between dioxin and the SEER, overall SEER cancer data?

J. MICHALEK: No.

D. JOHNSON: No. So ...

J. MICHALEK: That's ...

D. JOHNSON: But that's ...

J. MICHALEK: In other words, these ...

D. JOHNSON: Okay.

J. MICHALEK: ... these factors change or affect the association; they alter the association. After adjustment for them, the association is changed. That's what I mean by an "effect modifier."

D. JOHNSON: So we're starting with no association between dioxin and SEER?

J. MICHALEK: Starting with none whatsoever.

D. JOHNSON: And when we add these, do any of them become significant then?

J. MICHALEK: Only in combination; one by one, they're not, only in combination.

D. JOHNSON: Oh, if you — if you put all of them together?

J. MICHALEK: All of them together, yes.

D. JOHNSON: Spray days, years in ...

J. MICHALEK: Spray days, years in SEA, yes.

D. JOHNSON: Then we end up ...

J. MICHALEK: Last year of service, yes.

D. JOHNSON: Then we end up with a significant association?

J. MICHALEK: Yes.

D. JOHNSON: And what was that? Do you remember what the odds were, the relative risk was?

J. MICHALEK: Well, in the — in the model 3 analysis, the — in the high category was 2.2.

D. JOHNSON: 1.4 you ...

J. MICHALEK: In the high category ...

D. JOHNSON: Oh, high.

J. MICHALEK: ... it's 2.2, but the overall group difference was not significant as opposed to diabetes. So the effects in cancer are weaker than they were of diabetes using this approach, but reached — still reached significance in the high category and in the trends statistic.

M. STOTO: So this is similar to the diabetes one in the sense that there — there's noise in the data essentially that ...

J. MICHALEK: Yes, and what you're not seeing in these slides is that if I — if I change the cut point on last year of service in Vietnam back to 1966 and 1965, these relative risks increase, but these counts get smaller and smaller. And so we lose significance, but the relative risks increase. And I'll show that in the manuscript.

M. STOTO: But I think the point is that there are some people, some individuals included in the — in the entire, in the large data set where there's some relationships that are unrelated to the thing that you studied here.

J. MICHALEK: Yes.

M. STOTO: And when you take those out, in this case, the people who served ...

J. MICHALEK: Later in the war ...

M. STOTO: ... less than two years ...

J. MICHALEK: ... and had very few days of spraying.

M. STOTO: Right. When you take those out, you have a ...

J. MICHALEK: A weaker effect.

M. STOTO: No, a stronger effect.

J. MICHALEK: Stronger, sorry, when I take those out, yeah.

M. STOTO: Right.

J. MICHALEK: That's right, stronger, but again, limited because I am unable to show a significant group difference.

M. STOTO: Right, so when you take ...

J. MICHALEK: And counts get small, yes.

M. STOTO: You're reducing your sample sizes.

J. MICHALEK: Right. Those sample sizes get small because we are stratifying. I am frustrated because I can't find a simple main effects model to capture everything and reflect this kind of result. It's just not there. And I think that's another reflection of the fact that in spite of our — all of the quality of the data that's been collected in the study, it is a complicated study. There are many intervening factors and things that happened that we can't measure. We're only now attempting to do that and we're seeing, even with these simple things like counting up days of spraying, that we can

alter the results. That tells me personally that there are factors involved here that we have not properly accounted for.

R. TREWYN: As I recall, this data does include deaths from cancer too, right? So ...

J. MICHALEK: Yes.

R. TREWYN: Okay.

J. MICHALEK: It's all cases verified by record review.

D. JOHNSON: There's a lot of — lot of things to consider in this analysis here that you're presenting and I guess it's hard to get a sense of well, is there a significant association with overall cancer in dioxin or ...

J. MICHALEK: There is with regard to SEER site cancer, all-site SEER cancer and you're seeing it on this slide. Again, in this stratum, the numbers are there on the slide in red showing a significant increase. The weakness of this approach is that it's stratified just as it was with diabetes. It's weaker than the diabetes analysis because I had to further stratify.

I didn't have to do this with diabetes, but I did here. I had to stratify by years of service in SEA because I already know that that's a risk factor for cancer in the control group. I know many controls, half of them in fact, were there a long time and they have an increased risk of cancer. They were there much longer than the Ranch Hand veterans.

M. STOTO: Sandy?

S. LEFFINGWELL: A second weakness of course is that you're forced to lump different types of cancers.

J. MICHALEK: Yes, and soon as I try to consider individual cancers, of course, the numbers become too small to analyze. That's right; that's another frustration or a limitation of the cancer data.

M. STOTO: So ultimately people want to know, does — questions like exposure to this stuff cause cancer? And we can't answer that directly in these data sets.

J. MICHALEK: Cause is a very strong — the simpler question is herbicide associated with cancer in the study? The answer is complicated.

M. STOTO: Yeah. I mean, the answer is that if you look at everybody ...

J. MICHALEK: If you look at everyone, you see nothing.

M. STOTO: You see nothing.

J. MICHALEK: The answer is no.

M. STOTO: But if you eliminate people who essentially where there's a reason to think they — there would be noise or counteracting factors and a variety of things like that and focuses on a — on a group where you think the comparison is more likely to be kind of pure ...

J. MICHALEK: Fair.

M. STOTO: ... then you find ...

J. MICHALEK: Then you can see ...

M. STOTO: What — it's like when you do a randomized clinical trial, you try to identify patients who may not be representative of the whole population, but would be a good test for that hypothesis and ...

J. MICHALEK: Another good analogy, I like — I like to think about clinical trials, would be as if in a randomized parallel group, double-blind placebo controlled trial, you found out some of the people in the treated group didn't take their medicine and so you kick them out. And now you see a treatment effect; whereas, if you leave them in, you don't. That's the — that's a good analogy.

M. STOTO: Okay. Any other questions or comments on that? It's very interesting. Okay. So let's go on to — oh, I'm sorry. Please come up.

M. PAVUK: Maybe just one comment on this comparison between dioxin and diabetes and cancer. There is a difference that you may have noticed. The sample sizes with SEER cancer by stratification, you go down to one-quarter of the — of the total cohort from the very beginning. So basically, we're saying that we see something in about 25 percent of the whole cohort after all the stratifications, while in diabetes, you still keep about half or 50 percent of the whole cohort. So just maybe a little bit pushing it, you know, from overall — answering your overall question.

This is a subgroup of the whole cohort where these effects are seen or are visible. And also when you look at this from the point of cancer epidemiology and

cancer epidemiology studies and you look at sample sizes that are in low two-digit figures like 10, 12 and 20, that doesn't usually, you know, doesn't bring much confidence in that kind of analysis *per se*. And this is the, I think, the biggest limitation of this study to examine — in examining cancer endpoints is the small sample size.

We would need 20,000 veterans to examine cancer endpoints, you know. You look at the leading cancer journals, you do not get a paper published if you do not have 400 cancers — prostate cancer, lung cancer or some other cancers — unless you're using, you know, some novel approaches and different, new polymorphism, things like that.

D. JOHNSON: And you're saying we have 10 or 20 here?

M. PAVUK: Well, I mean, we are down to very small numbers. Our total number of SEER cancers is about 400. We have about 150 prostate cancers, so prostate cancer is the only individual site that we've been doing analyses and submitted a paper that is being reviewed right now. But we have small numbers and we are limited in our — in the conclusions ...

D. JOHNSON: So the main ...

M. PAVUK: ... we can — we can make.

D. JOHNSON: I'm sorry. The main weakness is the small number with the stratification?

M. PAVUK: Certainly.

D. JOHNSON: The stratification itself is not a problem?

M. PAVUK: No.

D. JOHNSON: It's the small number?

M. PAVUK: It is the small number. I mean, I think ...

D. JOHNSON: Could you — could you — could the biostatisticians just expand on that a little bit more? You know, even though — even though it's a small number, you're still reaching significance by your statistical calculations. So it's kind of hard — it's hard to grasp them, so why — so the small numbers ...

J. MICHALEK: And that's where ...

D. JOHNSON: ... is usually when you ...

J. MICHALEK: That's where the fishing expedition analogy comes in that you're — you lay yourself open to this kind of criticism when you do stratified analyses. The strength of this analysis is that it's based on operational information that was given to us outside of the p value consideration, like days of spraying and years — last year of service. And we were forced into the adjustment on years in SEA because of what we found in the control group.

So I think the stratification can be — is strengthened by those considerations. We're — the sample sizes are what they are. We can't control those and the more we tried to adjust, the smaller the numbers are. And I think we, from this point of view, this analysis has been pushed about as far as it's going to go.

M. STOTO: Let me just, I think, clarify the point you made. I think it's an important one. I mean, if you just took the data that you had and just kept on trying to subset it in lots of different ways until you got something significant, you could — you could find a way to do that.

J. MICHALEK: Right.

M. STOTO: You know, maybe, you know, whether or not they were born on a Tuesday or something like that would ...

J. MICHALEK: Right. Yeah.

M. PAVUK: Maybe answering your question, the fact that we see significant results with small numbers strengthens our findings. We wouldn't see significant results if there was nothing going on there, so ...

J. MICHALEK: That's right.

M. PAVUK: ... the fact that we are seeing the results with the numbers that are there is ...

M. STOTO: Well, I ...

M. PAVUK: ... is positive.

R. TREWYN: Encouraging.

M. PAVUK: It's encouraging.

J. MICHALEK: Well, yeah.

M. STOTO: Well, I guess I'm not sure that that's true. I mean, the p values are the p values and the issue is whether you went fishing for them by sub-setting. And the point that Joel was making was that there was external information that led to this stratification as opposed to all the other possible stratifications.

J. MICHALEK: And further pursuit of that external information leads to consistent results which I haven't shown you. If I change the cut point to '66 or 1965, the numbers get small, small, small, but the relative risks get big, big, enlarged. So that's consistent and that's going to be shown.

D. JOHNSON: My question was sort of a clarification for more basic biostatistics and that is you're — we're saying that they're small numbers and so it's — it makes it weak, but yet it's still reaching statistical significance. Can you explain — can you further on that, you know, why is it weak if you're — if you're meeting statistical significance? I know there's an answer. I just wanted to — if the statistician would answer that.

M. STOTO: That — I'm a statistician and ...

D. JOHNSON: Okay.

M. STOTO: ...the answer there is the multiplicity. It's that, I mean, the p value of, you know, 0.03 there, for instance, is meaningful in the sense that you came into this analysis knowing this was exactly what you're going to do. If they got to this by trying

500 different ways of sub-setting and this was the best one they got, this would not be meaningful.

D. JOHNSON: Okay.

M. STOTO: And so it's the fact that they had this external information that led them to this particular way of sub-setting that saves them.

J. MICHALEK: So ...

P. CAMACHO: From the calculation of chasing a p value.

J. MICHALEK: Yeah. That's right. So ultimately, it comes down to, "Here it is, reader. Take it or leave it." You've got the full main effects model and the entire cohort where we see nothing. Secondly, we have this stratified analysis taking into account extra information in which we see something.

M. STOTO: And you have — and you have to believe then that they really were led by this extra information rather than fished around and then came up with a post-time ...

J. MICHALEK: Right.

M. STOTO: ... story.

J. MICHALEK: Yes, and the extra information is tied to the operational characteristics of the war, not to a p value.

R. TREWYN: Can I just — because I actually wrote that down when you say "not allowed to stratify based on p value." I wrote that down when you first said it and

this is obviously where the discussion is. And I guess not being a biostatistician, it would seem to me that in some cases attempting some stratification may in fact help the investigators involved in the process identify some variables, some attributes that they should've taken into consideration.

I mean, so I mean I can almost see the argument from my side of it as a biochemist why you should at least try some of that because maybe in your design you didn't set up the experiment appropriately. And so I think that would be a valuable tool. Again, you can't just use it just for the hell of it. But if it — if it winds up leading you to something that you had not considered in how you designed your overall experimental protocol or how you, in this case, sort of carved the cohorts, I would think that would be a valuable tool to apply.

M. STOTO: Yes, that's true. That's true and the key thing is how do you choose those subsets and so on.

J. MICHALEK: Now and from the — from the laboratory experimenter's point of view, you're correct that the laboratory experimenter has the liberty of running a new experiment now to check. See, we don't.

R. TREWYN: That's why — that's why I did that.

J. MICHALEK: Yeah. That's correct. That's a hypothesis-generating approach.

D. JOHNSON: Let me go back to that point one more time for the statistician. Let's say you've got 10. You've got a p value of 0.05, so it's significant. And you've got

10, “n” is 10, and you’ve got another p value looking at it again, a p value of 0.05, but the “n” is 500. Does the 500 mean more than the 10?

M. STOTO: No.

D. JOHNSON: They’re both equally — they both tell us that equally the significance is much ...

M. PAVUK: In the eyes of biostatisticians.

M. STOTO: Well, that’s right in the sense of a p value ...

J. MICHALEK: Well, if you’d gotten a 500 by a fishing expedition, in other words, either a random number during a — keep reshuffling the file and doing it over, and over and over again until you found something neat like that, well, that’s just baloney. That’s nonsense.

D. JOHNSON: But in other words ...

M. STOTO: But that could be ...

D. JOHNSON: So my question ...

M. STOTO: But that could be true.

D. JOHNSON: My question is if you’ve got a p value of 0.05 with a — with a study population of 10 and a p value of 0.05 with a study population of 500, does one of them tell you more? Is one of them stronger than the other?

J. MICHALEK: Yes, because they — well, you’d have a narrow confidence interval with a — with a larger sample.

M. STOTO: No.

J. MICHALEK: No?

M. STOTO: The p value is — corresponds to the confidence interval and they're just the same. I mean, the issue is, but the p value only has meaning in a — in a technical sense is if you have a prior hypothesis that you — that you arrived at before you analyzed the data. And it basically says, you know, if you only had one hypothesis, you analyzed the data, what's the chance of getting something this extreme if there was really no effect going on? And a p value of 0.05 means 0.05 no matter what the sample size is.

D. JOHNSON: Right.

M. STOTO: So they're really comparable that way and the — and the difference that we've been talking about here is how close are you to that kind of pure sense of only having one prior hypothesis.

D. JOHNSON: So let's go back to his comment on the small number.

M. PAVUK: Maybe Dr. Johnson is alluding to power. If you have more people, you have more power to detect the association.

M. STOTO: Well, no that's ...

M. PAVUK: And also if you find a result with higher number of cases, I agree with you that the p value is the same; it doesn't change. But from the point of how interpretation of the epidemiological data from the study, the results that you find from

500 cancer cases versus one from 15 cases is much bigger. I think the importance of the study and conclusions are different there.

M. STOTO: Well, when you have ...

M. PAVUK: I hope you agree that ...

M. STOTO: No, it just ...

M. PAVUK: ... it makes the difference.

M. STOTO: No, I don't agree. When you have a — once you've — power is important when you're designing the study or if you have a negative result, but we have a positive result here and the study's been done. And so what really matters is the p value. And the p value of 0.05 is a 0.05 if, in fact, you had the same two or prior, you know, *a priori* hypothesis.

So the real issue here is to what degree are we close to having an *a priori* hypothesis? And Joel's argument, which I think is a valid one, is that they would've come to — they came to this way of disaggregating based on information external to the study, not based on the data in the study itself.

J. MICHALEK: That's correct.

M. STOTO: Sandy?

S. LEFFINGWELL: Not sure I would agree that it's all in the p value. If your smallest cell is 10 and you have a p of 0.05, you'd probably have a considerably higher risk ratio than you would if your smallest cell were 500.

M. STOTO: I don't know that that's true, but the — well, okay. I don't think there's any point in pursuing this, but yeah.

D. JOHNSON: I'm just trying to understand the ...

M. STOTO: Yeah, but I think — but the key — the key point here is the one about the prior hypothesis.

D. JOHNSON: I agree you don't — we don't need to spend too much time with the basics of biostatistics. But, you know, the point was made that it was small numbers that limited the study, so I was trying to get some clarification as what was meant by that.

R. TREWYN: And I just want to throw in that the, you know, again, as a laboratory scientist, when you write it up for publication, you always had the hypothesis before you got the data to support it. That doesn't always mean that's the way it came about because you're going to adjust and come up with a brilliant hypothesis based on what your findings show and it always sounds better though.

M. STOTO: But there's a plausible story here that it — which I think is true.

R. TREWYN: Right.

M. STOTO: That's — yeah. Okay. I hope that this is not an hour one; the next talk will put us to sleep.

J. MICHALEK: Yeah.

M. STOTO: But ...

R. TREWYN: It's sleep disorders.

Sleep Disorders

J. MICHALEK: This one is very difficult for me to present because I'm not the author. Dr. Lynne Frame is the subject matter expert and her graduate student, Ying Liu, was the one — the person that did most of the work. And I provided the data and proofread the manuscript, so I'll try my best.

I do — can tell you that Dr. Frame has been working with dioxin and circadian rhythms in mice and rats for years and years at Texas Tech. She's been interested in this connection as it's shown effects in animals in circadian rhythm and disturbances in mice and rodents exposed to dioxin. And she was intrigued by the possibility of studying this in Ranch Hand veterans because we gave a sleep questionnaire in 1992. And so this was the only data available in Vietnam veterans on sleep disorders and dioxin because we had also measured the dioxins of course.

So that's why she became involved and she still — well, this paper — these slides have led to an article and the article's in submission to a journal, *Environmental Health Perspectives*, right now. So I'm going to just walk you through these. She has a justification for the endpoint, then using data from other studies that sleep has been an issue in plant workers exposed to dioxins. And, of course, there's many papers to show associations between sleep deprivation and other health outcomes, such as diabetes.

And like I said, this is the first study to measure both sleep disorders and dioxin in the same people.

We actually gave that sleep questionnaire in two years: 1987 and 1992. The questionnaires were derived from a survey in Los Angeles in 1979 and the questions from that survey were applied to this study and asked of all of our study subjects. The analysis is restricted to individuals who were compliant to the 1987 or 1992 physicals and they were using the same approach that we've used in most of our papers and reports, namely the so-called "model 3 dioxin category analysis." They defined insomnia using a formula taken from the literature using these components.

R. TREWYN: That's not normal?

J. MICHALEK: Insomnia?

R. TREWYN: No, all those characteristics.

J. MICHALEK: Having trouble falling asleep? I'm really sorry; I can't talk as an expert on this. It's her subject area, not mine. And defined para-insomnia this way; it seemed to me to reflect some kind of disturbed sleeping involving dreams and sleepwalking. Maybe Dr. Camacho would know something about this. I'm sure she'd be delighted to come here and give you a talk on this just as Dr. Matsumura did on his subject area.

But these were the risk factors. Here are sample reduction tables showing you the number of compliant and non-compliant with individuals with missing dioxins were

excluded. Here are the background — comparison, background, low, high categories in the rows and in the columns showing the two years of interest: 1987 and 1992. Demographic information consistent with that that you've seen in all other presentations, namely that the individuals in the high category are younger than those in the low category.

I don't see that on the slide. They look to be all roughly the same age. I wonder why that is? Bill Grubbs, can you say anything about this? They are younger in the high category, but only by about three years, four years. That's about right; it's about a four- or five-year difference. Yes, it's consistent with previous — this is what their age in 1987. This was around 45 years old, which is consistent with the average age in 1982 being around 42 years old.

So those are the rest of the risk factors of interest and they're consistent with other studies. And now we're going to see a series of findings which she interprets as adverse relating dioxin and sleep disorders in these men and that has adverse implications regarding their health. For example, in this case, sleep complaints in the low and high category, the reporting of sleep complaints was significantly increased in the low and high dioxin categories relative to comparisons: 32 percent versus 26 percent after adjustment for those risk factors that I — that I mentioned.

And in the low and high categories, the disabling daytime fatigue was increased in the — in those veterans relative to comparisons, significantly increased, and so was

daytime sleepiness. She would say that we have a pattern of significant increases here that are consistent with an adverse association, but they're not seen in all variables obviously. They're seen on a subset of the variables, but that, to her, that's sufficient to suggest there is an association.

There was at least a concern here of dioxin being related to adverse sleep disorders. And there you see an association between disabling daytime fatigue in the high category, and in the low against comparisons in 1987, and increased risk of abnormalities in '92 that don't always correspond to what we saw in '87. For example, insomnia in 1992 was significantly increased in the high category.

She looked at the trajectories. In other words, in the last row, we have individuals who experienced insomnia in both 1987 and 1992 and you see an increased of — risk of that event in the high category down there in the red in the lower right-hand corner as compared to comparisons. So they made an attempt to look at the data across time this way.

There were other findings that I'm not going to show you on the slides, but they were consistent with the ones you've already seen; that sleep complaints were adversely related to dioxin exposure category. So finally, her bottom line was that somehow dioxin targets arousal regulation and interferes with sleep. And that's consistent with her studies in animals and she's written that up in great detail in the manuscript, which is now in submission. I'm sorry about this very abbreviated and ...

M. STOTO: I guess that ...

J. MICHALEK: ... lack of expertise; that's the data. Yes?

M. STOTO: ... the concern that I would like to ask about or the concern I have and I would like to ask about is that — is the multiplicity issue.

J. MICHALEK: Yeah.

M. STOTO: I mean, it strikes that lots of different things ...

J. MICHALEK: Many different things compare. Actually, she reduced the data considerably over what was in our Cycle 3 and 4 report. She reduced it down to a small subset of the variables and still you see many variables being tested. The ...

M. STOTO: The fact — but the fact that you're ...

J. MICHALEK: Yeah.

M. STOTO: ... you know, you find this in '97 and this in ...

J. MICHALEK: But I will see — I'm not — I don't want to say anything more about that except I agree with you. I do know the paper has received — it made past the first gate at *Environmental Health Perspectives*. It made it past the editor and has been sent to the referees. and we'll know in a few months or a few weeks what the story is on that.

M. STOTO: Sandy?

J. MICHALEK: Yes?

M. STOTO: Microphone.

S. LEFFINGWELL: Do you contemplate looking at this data in the same way you looked at diabetes and SEER cancer?

J. MICHALEK: The — yeah. Well, I don't contemplate doing anything because I don't work for the Air Force anymore. But I have to say from an academic point of view that the consideration of days of spraying and last year of service in the region are important variables and that opens up the question about other endpoints in the study of which this is one. That's it for this segment.

R. TREWYN: I was going to agree. I mean, when I looked at those insomnia trajectories, they seemed to look like they're all over the place and I would hard pressed. But I agree; I think there are certainly other endpoints. I'm not sure insomnia would be a — would be a huge one, but I think there are other endpoints that are probably pretty important to look at with some of these new findings. So hopefully, the recommendations will be that that will be addressed on down the road.

M. STOTO: The other — the other issue is to what extent people know how much dioxin they've been exposed to because of having been in the study and whether they — they're more likely to report sleep problems? I mean, you know, that's not an issue. People are not likely — more likely to be diagnosed with diabetes because they know that, but I can imagine this is all based on self-report and that could ...

J. MICHALEK: Well, actually the — we told the men their levels, but they didn't learn their levels until 19 — after 1989. So the 1987 data is clean in that respect, whereas 1992 is not. They all received their dioxin levels in a letter from us.

M. STOTO: So that provides a way of looking at that issue?

J. MICHALEK: Yeah.

M. STOTO: Okay. Other comments?

RHAC Business

M. STOTO: So I think that is the last of the formal presentations and we want to come back to — we have additional unresolved issues. One point I think I'd just want to make is when we write the minutes, I mean, obviously, we're saying this now; we've said this over the last couple of hours. But I think that the last couple of presentations really showed that there's much more that can — is still coming out of these data; that despite having worked on this for 25 years, it's — that there's still new findings coming here.

And I think that needs to be reflected in the part of the — of the minutes where we — we're talking about the study about — the IOM study about what should we — disposition study. Any other issues that people want to bring up — bring up again and so on, substantive issues? Len has been keeping a list of possible discussion items for our September and November meeting. You want to remind us?

L. SCHECHTMAN: Okay. Based upon the discussions that we've had here and the ideas that have been unfolding, I — I've been trying to keep track of things that might be ready for the September meeting and might be ready for the November meeting. And the folks in the Air Force perhaps can help us determine what those are. But for September so far, I thought that possibly what I heard was we might have the Cycle 6 report ready or at least in draft form for the Committee to review?

K. FOX: It will be the final form.

L. SCHECHTMAN: Final? Okay.

K. FOX: The final report.

M. STOTO: I mean, it's in the final form already now, right?

K. FOX: It is in final form. It just hasn't been released.

L. SCHECHTMAN: So ...

K. FOX: That's the only thing that I would — that I know of.

L. SCHECHTMAN: Okay. I also caught the possibility of Dr. Michalek's draft paper or papers that you were still working on when you departed from the Air Force effort. Will that be ready for the September meeting for review perhaps?

J. MICHALEK: I will — I will be working on a draft diabetes paper. Now we have to be careful here between the Committee, and the Air Force and me. I'm not with the Air Force anymore and so any connection I have with you is either disconnected completely from the Air Force or something. I don't know how to say it, but I'm not

working for the Air Force anymore. So how we — how I interact with this Committee is a question.

K. FOX: I — yeah, that's right. Okay. First of all, the Air Force, if we have papers to present that Dr. Michalek is involved in, then we can see that he gets here if that's the question. I do not think there's really any other papers really out there. We've never really presented — we've presented this information, but we never go back and present in the past.

We haven't presented the final paper. So usually, this is all you get from us and then you get to see the paper when it gets published. So I'm not really sure what else you wanted to see on these two topics because, I mean, the manuscript is very, very basic. It's nowhere near being completed on these two and usually we don't present them. So I'm not sure where we're going with this.

M. STOTO: Well, with respect to the final report, I mean, there really — there really is nothing to discuss at that point because it's final. So I'm wondering whether we need the September meeting, right? I mean, is there ...

K. FOX: That would be the Air Force thought; that there isn't really any need for September; that there seems to be a November one when we're actually going to have some other new things to show you and we would like some interaction: the — like the "longitudinal study," which that's not the right title that we would like to be able to discuss ...

M. STOTO: Yeah.

K. FOX: ... at the next meeting, yes.

M. STOTO: Why don't we go over the list of things for the — for the November meeting before we ...

L. SCHECHTMAN: Okay. What I've captured was the NAS study report if that's ready for the Committee to review and discuss.

D. BUTLER: If it's available, I will be happy to be here and we can talk about whether it might be possible for the Committee to review it.

L. SCHECHTMAN: Okay. So that would be one and with — David's willingness to be here as well so we would have that — a presentation from you as an agenda item as well perhaps.

D. BUTLER: For November.

L. SCHECHTMAN: For November, right. The Air Force "longitudinal study," whatever we're going to call it — summary.

K. FOX: Summary.

L. SCHECHTMAN: Summary, okay. The SAIC paper on the history of the Air Force Health Study.

K. FOX: We can give you a status on what's going on with that and where we're headed, yes.

L. SCHECHTMAN: Okay, and will there be any more health study chapters coming forth for review or consideration by the Committee or we're finished with all the study chapters? Sorry?

K. FOX: We'll announce the date the report's released.

L. SCHECHTMAN: That's it?

K. FOX: But there's no more chapters.

L. SCHECHTMAN: It's over. Okay. Okay.

M. STOTO: But perhaps there might be more progress on the papers that we were just talking about by November.

K. FOX: Yes. There — we could probably give further response to that and maybe we might have something with the congeners and the further — the 106, so there are some things that might be in the working. But we'll get closer to November, we'll be able to tell you that and maybe add some more stuff to the agenda.

M. STOTO: What's the 106?

K. FOX: The 106 — the CDC where we're analyzing the ...

M. STOTO: Oh.

K. FOX: ... congeners and all that.

M. STOTO: Congeners, yeah. Okay.

K. FOX: There also — we are, by that time, we may be able to talk about where we are having samples from all six cycles, unfreezing portions and actually analyzing

them for about 100 values — chemistry values that we — and comparing what we — they get with what we had at the time of the sample to see if the samples are viable from ‘82 on.

M. STOTO: That seems pretty important and ...

D. JOHNSON: Whether it’s worth it.

M. STOTO: I don’t know whether, I mean, I don’t want to speak for the IOM, but they ...

K. FOX: They know about it.

M. STOTO: They know about it? Okay.

K. FOX: Oh yes. We have told them about that.

M. STOTO: Right, but that would — that would be important for us to hear too I think.

K. FOX: And we should ...

M. STOTO: Yeah.

K. FOX: ... be able to, hopefully by that time, the contract will be — have — and given and we will have some results back.

M. STOTO: Okay. Well, given all that, it sounds like we have a potential for a pretty rich meeting in November and a pretty thin one in September. And I — maybe we should even consider having, you know, a day and a half in November if we need it

rather than the September meeting. That puts us into a different fiscal year, so there's issues there I suppose. But ...

L. SCHECHTMAN: Well, let us worry about that.

M. STOTO: Okay.

L. SCHECHTMAN: We'll do what we can do for ...

M. STOTO: Right.

L. SCHECHTMAN: ... the Committee's sake. Right now, I don't know if any or a few of us have our calendars handy, but I was able to come up with a couple of possible meeting dates to try and get it into some time in November. And the ones that I've come up with as far as our office is concerned at least, which is the only calendar I have right now in my hands in terms of order of preference would be the 18th of November, the 10th of November and the 3rd of November based upon just how much information becomes available and when we'd want to have it. Before we were talking about as late in November as possible to accommodate the NAS.

P. CAMACHO: 18th?

L. SCHECHTMAN: 18th, 10th and 3rd in order of preference. Sorry?

P. CAMACHO: The 10th is terrible.

L. SCHECHTMAN: 10th is terrible?

M. STOTO: Yeah, I — I'm going to be teaching on Thursday afternoons ...

L. SCHECHTMAN: Okay.

M. STOTO: ... in the — in the fall.

P. CAMACHO: For those of us who teach, I don't want to speak for — Fridays are better.

M. STOTO: I think that we're all leaning to Friday the 18th now.

L. SCHECHTMAN: Otherwise, we — I'm sorry; otherwise, we have to move into December and we'd be looking at — I'm sorry? The 9th might be the earliest in December; that's a Friday and then Friday the 16th of December. We're still trying to avoid the holiday season as well, probably would be the latest in December we'd want to go.

R. TREWYN: So are you saying the — if we did a day and a half that the 17th, 18th wouldn't work? I'm just wondering if we, for example, flew in in the morning or something, if there would be possible we could meet, you know, have enough time in one afternoon so we're still only doing a one overnight possibly.

L. SCHECHTMAN: Yeah, I — let me — let me do a quick check on this at least. There is the Thursday afternoon/Friday possibility for December 15, 16 if we got into December — if we got necessarily into December. For November? Let me see what I have.

RECORDER: Dr. Stoto, can you clarify a September or no September meeting?

M. STOTO: I think that we're ...

RECORDER: Heading toward ...

M. STOTO: ... heading toward no September meeting.

RECORDER: Okay, and you're working on November now.

M. STOTO: Well, why don't we circulate calendars here.

L. SCHECHTMAN: We may only need one day, so ...

M. STOTO: Yeah.

L. SCHECHTMAN: ... then there's not a — it's less of a problem.

M. STOTO: Okay. Okay, better turn this on.

D. JOHNSON: I have a question.

M. STOTO: Please go ahead.

D. JOHNSON: The last information we heard today, these last presentations, are they — will they be part of — with the — with the — that Joel just gave us, the different using days of spraying and that sort of — is that going to be included?

M. STOTO: Why don't you get closer to the mike?

D. JOHNSON: Will the data that we just received, the last three or four presentations, is that going to be included in the final report?

K. FOX: No.

D. JOHNSON: No. This is for our information today?

K. FOX: This is for your information, yes. The final report was just on Cycle 6. The summary report will not have this because it hasn't been peer reviewed.

D. JOHNSON: Okay.

M. STOTO: Well, it's not just for our information because there — the intention is to submit it for publication, right, as in — as a journal article. And I guess one of the questions that I would like to come back to in November is, is this important enough that the — that the publication of the so-called "longitudinal report" should be held up so that it could be — it could be included or that it could be included even though it's not peer reviewed or something or other?

D. JOHNSON: So the — now the answer is it may be included is what you're saying?

M. STOTO: I said I think that it needs to be considered.

D. JOHNSON: Okay.

M. STOTO: Because, I mean, this strikes me that this ...

K. FOX: We will try to consider it, but we also have a contract and it needs to be closed out. But there's nothing saying that we cannot mention that it's — at least at the end of the report — that there is something else in the works.

M. STOTO: Well, I mean, let's ...

K. FOX: So that ...

M. STOTO: ... go back to that in November, right. I understand you've got the contract and it's not easy to do that, but ...

J. MICHALEK: And this, I think, is very likely that the diabetes material I showed you will be in submission to a journal at least before we see you again or before the Air Force sees you again and it might even be published.

M. STOTO: Yeah.

J. MICHALEK: It's likely because ...

M. STOTO: So it may become a moot point?

J. MICHALEK: Yeah.

M. STOTO: It may be ...

J. MICHALEK: It might be published before November.

M. STOTO: So I don't think we need to resolve it now, but I ...

J. MICHALEK: It's too early to talk about it, yeah.

R. TREWYN: I want to go back though to a point that Paul made early on because again, the arguments we made in the past regarding the Cycle 6 report, the things with this "non-longitudinal study" — whatever, the summary thing — the more open about positive findings that are out there, the more one can set the table with the fact that the data has shown other things and that you somehow come across that it's in addition to the history, but there's valuable information coming out of this, the more that is put out for general use. And certainly in the summary report and ...

P. CAMACHO: The better off you are.

R. TREWYN: Yeah, the better off you are. And truly, I mean, you know, we all have, in the university environment, we have lots of research contracts, and grants and — but contracts as well. And okay, there are certainly ways you can incorporate at least some of this information in a way that would be valuable, I think, and again, without maybe getting into all the detail.

But because this isn't going to give detail anyhow, that at least one could set the stage in a way that it's going to be a positive for all concerned, again, if the — if this "longitudinal" whatever, if it comes out as just a regurgitation of we looked, we found nothing, then it doesn't help. I mean, it's not accomplishing, I think, the important component that there's valuable information that's coming out of the data that we've got, so ...

P. CAMACHO: We've already beat this point.

D. JOHNSON: Well, I ...

M. STOTO: And we'll discuss it in November. Yes?

D. JOHNSON: Well, I think for the data that we had, you know, we had a prolonged discussion about the limitations of it. I think if that's included in the summary report, that needs to be a little bit clearer than the way it was left today because I heard that it was limited because it was stratified and I heard, well, it doesn't — no, it wasn't because a p value is a p value.

So and I think that limitation, it would need to say that there's an — there's an association of the increased overall cancer is significant enough to explain it pretty clearly what the limitations and the strengths are — strengths and limitations are of that.

M. STOTO: Okay. Any more?

D. JOHNSON: No.

Closing Session

M. STOTO: Okay. Then I think we're ready to adjourn. Let me thank everyone from the Air Force and the colleagues who made presentations today. It was a very interesting day. And I thank all the Committee members, and of course the staff, including our note taker. I look forward to seeing you all again in the fall. Thanks.

[ADJOURN 2:15 P.M.]

CERTIFICATION

State of Georgia)
)
County of DeKalb)

I, Nadine Rivera, do hereby certify that the foregoing transcript, consisting of pages 1 – 183 in total, was personally typewritten by me and is a true, complete and accurate transcript of the proceedings recorded by me.

I further certify that I am not related to, employed by, or attorney of record for any parties or attorneys involved herein. I further certify that I have no financial interest in this matter.

WITNESS MY HAND AND OFFICIAL SEAL BELOW.

This 12th day of July, 2005.

_____
Nadine Rivera

[Seal]