DEPARTMENT OF PESTICIDE REGULATION

METHYL IODIDE

EXTERNAL PEER REVIEW PANEL

WORKSHOP

THE PAGODA BUILDING

429 J STREET

SACRAMENTO, CALIFORNIA

THURSDAY, SEPTEMBER 24, 2009

9:00 A.M.

REPORTED BY: ESTHER F. SCHWARTZ
CSR NO. 1564

ATTENDEES

PANEL MEMBERS:

JOHN R. FROINES, CHAIR
PAUL BLANC
KATHIE HAMMOND
DALE HATTIS
EDWARD LOECHLER
THOMAS MCKONE
RONALD MELNICK
THEODORE SLOTKIN

STAFF:

ELINOR FANNING
SARAH KOBYLEWSKI

DPR STAFF:

MARYLOU VERDER-CARLOS

PRESENTERS:

ROGER COCHRAN
TERRELL BARRY

RANDY SEGAWA

LORI LIM
NU-MAY RUBY REED

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SACRAMENTO, CALIFORNIA

THURSDAY, SEPTEMBER 24, 2009, 9:00 A.M.

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DR. FROINES: I just wanted to tell you that we have one Review Committee Member who is not here yet. The choice is to start on time or to wait for a full complement of participants. We are going to wait five minutes and hope she arrives shortly.

We have a very well defined way of holding our scientific review panel meetings. One of the things that we feel that is very, very important is that the panel of the scientists who are the review committee can actually talk to each other. So what we have been fiddling around with while you have been patiently waiting is to try to make sure that we have an environment where people can feel comfortable communicating with one another. So that is what has been going on. Just to keep you informed.

MS. VERDER-CARLOS: Good morning, everyone. Before anything else, I want to give some housekeeping announcements. Bathrooms are out there on this hallway, right outside of the elevator. There is disabled access as well. If you get through the elevator and all the way down, there is

an exit on the P level for disabled access. And in case of an emergency, the stairs are around the corner from the elevator. There is stairs going all the way down to the plaza level and you exit to the plaza level.

Coffee, water and soda are available in the central level, on C level. If you notice the elevator has no numbers. It has levels. We are on CV and then to exit to J Street is C level and the P is Plaza Level.

And there is an ATM machine, if you need any money, on the fifth floor, the Sky Level.

Welcome to the Department of Pesticide Regulation risk assessment workshop for methyl iodide. I am Marylou Verder-Carlos, Assistant Director for the Programs Division at DPR and project manager for this workshop. This public workshop involves the External Peer Review Committee we have here today charged to evaluate DPR's risk assess of methyl iodide.

As you know, methyl iodide is one of the fumigants proposed to replace methyl bromide and is also proposed for registration in California. DPR opted to conduct a risk assessment of this fumigant after preliminary toxicological evaluation of its

health effects. The External Peer Review Panel, comprised of nationally and internationally renowned scientists, is here today to listen to presentations by DPR, OEHHA and several interested parties who have sent comments to DPR regarding the risk assessment document. They are published on our website as well.

The agenda for the two-day workshop is available on the table in the back and also in the entrance downstairs.

Before I introduce the Chairman of the Peer Review Panel, I would like to introduce DPR and OEHHA scientists who will be presenting today: Dr. Roger Cochran, Dr. Lori Lim, Dr. Ruby Reed, Dr. Terrell Barry; and from OEHHA, Dr. David Ting.

At this time I would like to introduce Chair of the Committee, Director for the Center of Occupational and Environmental Health at the University of California, Los Angeles, among his other duties, as he said, he has also been the Chair for the Scientific Review Panel for California.

Dr. John Froines. From this point on, he will be presiding over the meeting.

Thank you.

DR. FROINES: Thank you.

Let me tell you how this process of reviewing methyl iodide is going to occur. What we decided to do was to have a session on the first morning where DPR and OEHHA presented their risk assessment. And so that formed the basis for getting started on this process. Following that, tomorrow, we are to hear from interested parties. We are going to hear from the manufacturer, Arysta. We are going to hear from USEPA. We are going to hear from the Pesticide Action Network, and then we will hear from the public.

And I left out one thing. One of the important things we are going to do this afternoon, and I suspect it won't take long, but what we want to do this afternoon is for the panel, having heard the DPR and OEHHA presentation, we want to in the sense identify tasks for panel members. So that when they go back to their respective homes and work on methyl iodide, that they're working in specific areas of expertise as well as, obviously, looking at the overall document as well.

And so I should tell you, which may come as no surprise to anybody, but there is a massive amount of literature and materials to read. We have the primary documents. We have responses. We --

(Mike problem.)

DR. FROINES: So that there has been a massive amount of information. And so the panel is charged with a very difficult task. Tomorrow we will, as I said, hear from interested parties, and then we will hear from the public and then everybody goes home. And there will then be a third meeting sometime when we can get everybody scheduled together. And the third meeting will be a meeting in which the panel will meet. In other words, we will be talking with each other; and that's it, pretty much. We can ask questions of DPR. We can ask questions of people that we think have relevant information, but basically it will be an evaluating process of the panel. And from that will come our written report to DPR on our scientific findings to methyl iodide.

We anticipate a three-meeting process. We think we can get the final report done without a fourth meeting, but if that were necessary we could do it. But, hopefully, we can do the final report with three meetings. So that we are going to get started and we will hear from DPR.

I should tell you that what I would like to do first, though, is we have a group of extremely

distinguished scientists on this panel, and everybody in the audience should rest assured that you're going to get the best science that we can provide, and that you should feel confident then in the findings that will emerge. At least I hope so. I don't want to overstate it.

So what I would like to do at the outset -- for the panel's purpose, when DPR presents their risk assessment, what I would like to do is, if there are major issues, the panel should ask questions. If there are issues of clarification, the panel should ask questions. But we shouldn't get into lengthy discussions that disrupt the presentation by the DPR folks. So that it seems to me, that only in the case where something is particularly important or where there are clarification issues, we should give DPR a chance to make a presentation that has a certain degree of continuity associated with it.

What I would like to do at the outset is to introduce the members of the panel -- have them introduce themselves. Describe where they are from and a little bit about their background, and we can move ahead with the presentation by DPR. The two people sitting next to me are staff at UCLA and

they're providing support, and they're not members of the Review Committee, but they are essential to the Review Committee because they are the people that make sure everything goes well.

Let me go to Ted and he can introduce himself.

DR. SLOTKIN: I am Ted Slotkin from Duke University Medical Center, Department of Pharmacology and Cancer Biology and the Integrated Toxicology Program. My expertise is developmental neurotoxicology, particularly as it pertains to neuro active pesticides.

DR. BLANC: I am Paul Blanc. I am professor of medicine at the University of California, San Francisco. Chief of Parnassus Heights Division of Occupational Environmental Medicine, and also Associate Medical Director of the San Francisco Division of California State Poison Control center, and member of the Scientific Review Panel for the Toxic Substances for the Air Resources Board.

DR. FROINES: Did everybody hear Paul?

DR. BLANC: My name is Paul Blanc. I am professor of medicine at the University of California at San Francisco and chief of the Parnassus Heights Division of Occupational

Environmental Medicine there. And also Associate Medical Director of the San Francisco Division of California Poison Control Center, and a member of Scientific Review Panel.

DR. LOECHLER: I am Ed Loechler. I am a professor of biology at Boston University. And my research interests are mechanisms of mutagenesis of chemical carcinogens.

DR. MELNICK: I'm Ron Melnick. I've been associated with the National Toxicology Program almost since its inception, which is now located at the National Institute of Environmental Health Sciences. My area of interest is obviously in toxicology, as well as chemical carcinogenesis, the identification and characterization in relation to human risk.

DR. HAMMOND: I am Kathie Hammond from the University of California, Berkeley, School of Public Health. I am a professor of environmental health Sciences. I am in the area of environmental and occupational health, and participate in exposure assessment for epidemiologic studies. I also serve on the Science Review Panel for Toxic Air Contaminants.

DR. MCKONE: I'm Tom McKone. I am senior

staff scientist at the Lawrence Berkeley National Laboratory where I have an exposure and risk assessment group. I also am an adjunct professor of environmental health science at Berkeley. My research is in exposure assessment, particularly as it relates to risk assessment and risk assessment methodology. I've been involved in risk assessment since 1982 when I attended the first initiating meeting at the National Research Council. I've been heavily involved with risk assessment methods and commentary through the National Research Council and National Academy, including serving on the committee that recently I issued the report Science and Decisions, Advancing Risk Assessments.

DR. HATTIS: I am Dale Hattis. I am about three decades into risk assessments. And I'm originally a geneticist and educated at Berkeley and Stanford. I moved out to the George Perkins Marsh Institute in Worcester, Massachusetts and Clark University. I'm a specialist in mechanistic modeling, including physiologically based pharmakinetics, variability among people and uncertainty.

DR. FROINES: So that gives you a thumbnail sketch of the participants. So I think we can get

started. Ron Melnick had a question for me when he came in, and I wanted to give him a chance to raise it for DPR.

DR. MELNICK: Actually, I have two questions. One was: Although we have seen a lot of material, there is a lot of material that we haven't seen, particularly original study reports, so that we can actually look at the data as opposed to just summary data. Is one.

And secondly, if we identify the need for additional analyses, is that something that can be requested or alternative analysis by DPR?

DR. FROINES: Mary Lee, the question, this is a really quite a fundamental question which is there, obviously, the DPR document is the secondary document. It doesn't use primary literature. And, obviously, it is very beneficial to scientists to be able to look at the primary literature, because there you are looking at the actual quality of the studies that have been undertaken. And so as we go forward between this session and the next session, I would hope that DPR could provide primary literature to the panel, and we will see how easy it is. But hopefully having the primary literature is, I think everybody on this panel would agree, is really quite

essential.

So do you think that works okay?

MS. VERDER-CARLOS: Yes.

DR. FROINES: Ron, what was your second question?

DR. MELNICK: Further analysis might be helpful or alternative analysis.

DR. FROINES: I am about to blurt out, "Of course we can do that." But since I am not a DPR person, I won't blurt it out. I will ask if there are other approaches that people want you to take a look at, I assume that would be reasonable?

MS. VERDER-CARLOS: Yes, it is reasonable.

DR. LOECHLER: It's possible in some of my questions that I may need a white board, blackboard or some kind of large piece of paper to write some figures on. Can we have that by at some point?

MS. VERDER-CARLOS: Here, yes. Poster paper?

DR. LOECHLER: Probably won't happen until tomorrow, but just in case.

DR. FROINES: So these are two really important issues. And I think that this issue of the quality of the science, especially of science and academic studies, there is a very good paper in

environmental health perspectives that looked at Bisphenol-A and looked at FDA's evaluation of it, and came to the conclusion that the evaluation was not effective using their criteria for good laboratory practices.

And so that I think the panel should be proactive in terms of asking for additional information that might be of value and particularly looking at some of the alternative approaches to the issues.

On my left is Sarah Kobylewski, who is a Ph.D. student in toxicology at UCLA. And on my right is Elinor Fanning who took her degree, her Ph.D., in toxicology with Martin Smith at U.C. Berkeley. So we have a very skilled staff of people to help the other panelists. And now I'm buying time.

Is the mike working there?

DR. COCHRAN: Start at the outset by apologizing to the panel. I have a slight cold. I have a cough drop. So my voice at least will try to be level as we go through this.

My name is Roger Cochran. I'm in the worker health and safety branch. To my right is Dr. Terrell Barry. What we are going to be talking about today is the potential exposures of human

population to methyl iodide. And the reason that we are considering potential exposures of the human population to methyl iodide is because methyl iodide is being considered as one of the replacements for methyl bromide as a preplant soil fumigant.

DR. HAMMOND: Excuse me, do you have copies of his slides? Some of us don't have them.

DR. FROINES: Again, panel, feel free to ask questions as we go along. I want to reiterate, the panel needs to feel comfortable asking questions during the course of the presentations, but don't over do it.

DR. BLANC: We will look to your feedback on that score. How about that?

DR. FROINES: That is good. This is an issue which has come up where sometimes the important people presenting the material can't get a word in edgewise because the panel is talking so much. It makes for a poor communication, and so I'm just trying to make sure we don't have that problem.

DR. LOECHLER: Can I suggest if we are going to far --

DR. FROINES: I think that's what Paul meant.

Okay let's go ahead. I'm sorry. I apologize

to the audience for the delay.

DR. COCHRAN: If I might, I've got on the screen now a comparison of the chemical and physical properties of methyl iodide and methyl bromide. Again, methyl iodide is being looked at as a replacement for methyl bromide because ozone considerations. Methyl iodide is about one-one-thousandth as effective in converting ozone into something else as is chlorofluorocarbons. So that is the basic measure that we are looking at here.

As you can see, methyl iodide is much heavier than methyl bromide. It has a specific gravity and at room temperatures it tends to be a liquid. It has less vapor pressure than methyl bromide. However, in the studies that we are going to be talking about later, it tends to come out of the field faster, which is different than what the chemical physical properties seem to suggest. Does seem to evolve into the air faster.

DR. BLANC: Roger, clarification. On a day like today in the Central Valley, it would be near boiling point?

DR. COCHRAN: Yes, if it were above soil. But -- so would methyl bromide.

DR. BLANC: Methyl bromide boils at four degrees.

DR. COCHRAN: That's correct. All that I am saying is that it comes out of the soil faster than methyl bromide. Then chemical physical properties would predict it would come out slower, but it doesn't.

DR. FROINES: There is quantitative data available to demonstrate that? Or is that a -- cause it sounds a little like a supposition rather than --

DR. COCHRAN: We have actually measurements from the field.

These are the USEPA registered products that contain methyl iodide that are proposed for registration in California. And this one right here -- you will notice that they all contain chloropicrin. This is just the warning agent. This exposure assessment only deals with methyl iodide. There is a separate exposure assessment that will be dealing with chloropicrin. That is not going to be talked about today.

The different types of applications that you have for preplant soil fumigation ---

DR. FROINES: Roger, can I say -- I want to

say one thing to the audience. The Scientific Review Panel that I chair, that Paul and Kathie are members of, are going to take up chloropicrin in the next two months. And so, we actually have an interesting situation where the evaluation of a toxicity of chloropicrin and the evaluation of the toxicity of methyl iodide will, in fact, be coupled, and we'll have to see how one handles that situation, because it's obviously a very, very important issue.

Sorry.

Tom.

DR. MCKONE: I have a question about chemical properties and this issue of why it volatilizes faster. Soil is three-phase, not two-phase. Do you have the Kow? I didn't see it on the actual water or the organic --

DR. COCHRAN: We actually do, but it is not on this particular slide. It is in the document.

DR. HATTIS: You talk about vapor pressure, those are partition factors. The rate constant controls, and it's also the three-phase partitioning that would play along.

DR. COCHRAN: Correct.

DR. HATTIS: So they actually could be

quite consistent with observation of a three-phase partition as opposed to two.

DR. COCHRAN: That's correct.

Now I was talking about the different types of applications that can be done for preplant soil fumigations. These are the studies that we received. One was drip irrigation with tarped raised bed fields. The other was shallow shank injection of the methyl iodide into the soil as the tarped raised bed or as a tarped flat fume. This means just without the raised beds in the field.

To make things easier to understand, this is a picture of the tarped raised bed field being prepared for drip irrigations. You can see the bags on top; these contain soil, and they are there just so that the tarps don't blow off in the wind. That is the only reason they are there. When you are all set to do an experimental field supply like this, you want to make sure you can do it. That's what's there. Sometimes they don't have those things.

The application of methyl iodide comes from these cylinders. It is fed into the water line that you see that carries the irrigation fluid out into the field. This individual here, you can see is wearing -- these are the air samplers that are in

his breathing zone. He has on his back pumps that are drawing air through the air samplers. So the entire time that he is working there, they are drawing at a fixed rate. Knowing that, we know the volume that goes through. And after we determine the amount of material that's on the resins in the sampling devices, we can come up with what the air concentration is based on, divide the amount by the amount of air going through.

This is the shallow shank injection.

DR. LOECHLER: Is that in real time? In other words, is there an alarm system or is this after the fact?

DR. COCHRAN: The determination in the resins here is after the fact. There isn't an alarm system. I'm not aware that there is currently a real time detector for the levels of methyl iodide.

This is the shallow shank injection. And what you have here is, this is a tractor driver who is driving the tractor along. This is methyl iodide here in the front that is being injected into the soil. Behind him, there is tarp unrolling. This is the tarp monitor making sure that it is going down properly. Walking adjacent to the tractor is the shoveler. Now in this particular instance you can

see all three of them are wearing half-face mask protection. But in others that you saw, they weren't.

Initially we don't know what the air concentrations are. They are not doing the maximal applications. It is a limited time that they are out there. They are required to have safety equipment present, even if not wearing it during the experimental use trial.

DR. FROINES: Should they be wearing the protective --

DR. COCHRAN: During it?

DR. FROINES: Should they be wearing it?

DR. COCHRAN: Well, it is required on the label now. It was not at the time.

DR. LOECHLER: You just said this and I should have written it down. I didn't. There are names for these different individuals, and I would like to know --

DR. COCHRAN: It is in the document.

This is a tarp monitor here. He is sitting here. This a tarp that is being unrolled as they are going down the line, and it's being applied to the raised bed.

DR. LOECHLER: And the person walking

behind him?

DR. COCHRAN: This guy is a shoveler. Carries a shovel.

DR. LOECHLER: I'm sorry, shoveler. Obviously, the other one is the tractor driver.

DR. COCHRAN: The tractor driver is up here hidden. I should say these pictures come to us from Arysta. They are allowed to be in the exposure assessment document for clarification. When you're writing about what jobs these people have, you at least have a picture. You can see what they are doing.

At the end of the row, the shoveler cuts the plastic tarp and covers the end with the soil so the gas will be trapped underneath the tarp.

Now I have to state at the outset that the exposure estates that we're basing -- that we are doing this on were based on measurements that we got. But we also modify them based upon what is on the label. This is a federally approved label, so this sets the law that we have to follow. All of the handlers, including the shovelers, are now required to wear respiratory protection or -- the tractor driving can work with engineering controls, which is generally a fan that blows air, so a

dissipation of the gas. And the level of protection that is assigned to the different types of respiratory protection that they use are set by OSHA and CAL/OSHA. So when it says it is 90 percent protection, that is what OSHA and CAL/OSHA says, and that is what the law says.

DR. HAMMOND: I am not sure whether I should pursue this questioning.

DR. FROINES: Yes.

DR. HAMMOND: I have a concern with that. As you may know, the OSHA also requires an extensive respirator protection protocol, a whole series of things you have to do. Like fit testing and a series of that. Are those actually also required?

DR. COCHRAN: Yes. They are in the regulations.

DR. HAMMOND: I know they are in OSHA regulations.

DR. COCHRAN: In our regulation, also.

DR. HAMMOND: That would also require facial hair?

DR. COCHRAN: Yes.

DR. HAMMOND: To your knowledge, has anyone done any testing of these respirators with methyl iodide?

DR. COCHRAN: There has been some testing at the national level, at federal level to see whether or not the canisters actually filter the methyl iodide out of the air. They do.

DR. HAMMOND: They are a couple of levels of testing. We will talk about that. What's the change-out rate for those?

DR. COCHRAN: I can't tell you, offhand.

DR. HAMMOND: Those are critical things, and most often they are not available. Is that information available.

DR. COCHRAN: If you E-mail your question, I'll see that you get your answer.

DR. HAMMOND: The expectation is that all the various people who apply would know how institute a full respirator protection program that is involved. It is very complex.

DR. COCHRAN: They won't be licensed to do it unless they have gone through the training for it.

DR. HAMMOND: Has anyone ever tested the actual protection factor for these in terms of these respirators?

DR. COCHRAN: You would have to ask somebody at OSHA or CAL/OSHA.

DR. HAMMOND: You were relying entirely on OSHA and CAL/OSHA for this?

DR. COCHRAN: Right.

DR. FROINES: Why would CAL/OSHA test protection factors?

DR. COCHRAN: They have industrial situations as well?

DR. FROINES: I was at OSHA. I understand that. The question is, they look at the issue from compliance with standards. They are not a research agency. So the questions that Kathie is getting at is: Has somebody explored some of these issues in a noncompliance context? And I presume the answer is no, as far as I can tell.

Does that answer your question?

DR. HAMMOND: I think of information that I can get right now. I will probably --

DR. BLANC: Also, Kathie, there was a back and forth on this question because the very same critique was raised by OEHHA. And in the responses to OEHHA's comments on respirator fit use there were similar statements made. So you might want to review that carefully, but I would share your skepticism in that regard.

DR. LOECHLER: Can you gave us a sense in

California of how many tractor drivers there are, how many of these people are doing this kind of work?

DR. COCHRAN: I don't know offhand myself.

DR. LOECHLER: A ballpark?

DR. COCHRAN: I can't tell you.

DR. COCHRAN: If you want to E-mail me, I will get the information for you, but at the moment I don't have it at my fingertips.

DR. FROINES: Are there any further questions at this point?

Go ahead.

DR. COCHRAN: The label also says that no more than 40 contiguous acres in a day could be treated. So we consider that to be what is possible. Whether or not they actually treat 40 contiguous acres is questionable. We make the assumption that the label permits it, that is how much they could do. We are always looking at the max that the label permits. The same is true in terms of the application rate, which is 175 pounds of active ingredient per treated acre.

All of our calculations are based on use that maximum application rate. There is a buffer zone that is required on the label, and since it's near a

40-acre field, that buffered zone is 490 feet or about 152 meters. You are not allowed to go into the buffer zone without respiratory protection until 48 hours after the application is done. In addition to which, the buffer zones between treated and fields that are treated cannot overlap. As a consequence, you'd end up with a thousand feet between each of the fields that you treat. It is unlikely that they are going to leave a thousand foot zone of untreated land on their properties. So what they generally tend to do is they treat it in one corner, then go down treat another corner until they get the entire thing treated. As a result of this particular factor, we did consider people that are doing the application as having additional exposure from a previously treated field. That is not likely to occur because of this particular thing in the labeling.

DR. HATTIS: Are these treatment limitations similar to what was the practice for methyl bromide?

DR. COCHRAN: Yes. This was the practice for methyl bromide, also. They don't do adjacent fields. They tend to do one quadrant, and then they go down and do a different quadrant for the next

application, if they have an area that is larger.

DR. HATTIS: Working an eight-hour day, they have plenty to do with 40 acres.

DR. COCHRAN: Yes. That is true.

DR. FROINES: I'm having a little trouble because of having spent time in the valley and other places in California. And are we talking about now buffer zones per farm?

DR. COCHRAN: You are talking about buffer zones per treated field. There could be more than one field on a farm.

DR. FROINES: There could be one field on the farm. So we're talking about -- we'll keep adding the material until we have dealt with that geographical distribution?

DR. COCHRAN: Correct. You aren't going to be able to do more than 40 acres in a given day. That's an awful lot.

DR. FANNING: The next farmer could be doing --

DR. COCHRAN: Yes, but he can't do it so that the buffer zones between the field that he is treating and field that was treated will overlap.

DR. FROINES: I'm glad you have that point on your slide because your slide says buffer zones

between treated fields and fields being treated may not overlap. I think that is a very good goal. I think it's potentially a very difficult goal to achieve effectively.

Kathie, would you agree with what I said?

DR. HAMMOND: I am not a farmer, but certainly seems like that would be.

DR. FROINES: It's --

DR. HAMMOND: I guess they have a procedure they follow with them. The same as methyl bromide.

DR. COCHRAN: Yes.

DR. HAMMOND: They had some procedure that they developed?

DR. COCHRAN: Yes.

DR. FROINES: The characteristics of methyl bromide and methyl iodide are different, so it is not --

DR. HAMMOND: It's following these procedures is something.

DR. FROINES: This is worth thinking about further, I think.

Go ahead, please. I'm sorry.

DR. COCHRAN: So when we're looking at acute exposures to the workers, what we are looking at is upper bound air concentration. The number of

individuals that we had in the study are not that great. So we didn't want to rely on just the highest measured value. We looked at the upper bound, 95th percent of the distribution, and this is the method of calculating it based on the arithmetic, which is what the Office of Research and Development at USEPA recommends we use when looking at the upper boundary exposure.

We also needed to consider potential repetitive exposures. Since methyl iodide is not currently used in California, but is slated to replace methyl bromide, we looked at the application profile for methyl bromide as a guide as to what we might expect in terms of repetitive exposures. There is a three-month period of application. So there is a seasonal application that you see.

DR. LOECHLER: What was the label, 600,000 pounds.

DR. COCHRAN: Yeah. These are 600,000 kilograms.

Now in our document we also calculated the absorbed dose. We do that by calculating the concentration of methyl iodide in micrograms per liter times the inhalation rate, which is given there. Protection factor that we're using for the

required respiratory protection is 90 percent. That is what CAL/OSHA and OSHA says. And the absorption factor using for the -- this is retention absorption of methyl iodide by the human body, is a hundred percent. This is a default value. There is actually a human study, and their was variability in there, anywheres between 53 and 92 percent of absorbed dose. Because the number of individuals was small and the conditions there were different conditions that they used, so we couldn't predict what the conditions were going to be. We couldn't pick a different number, so we fell back on the default number. Se we are probably overestimating the absorbed dose.

DR. HAMMOND: On the inhalation rate, how did you choose the inhalation?

DR. COCHRAN: This is a standard inhalation rate that we have come to agree on between Work Health and Safety and federal toxicology there is policy memo to that effect.

DR. HAMMOND: For people working in the field?

DR. COCHRAN: I think it is stated in the document. You're asking is this an increased rate of absorption of whatever?

DR. HAMMOND: Not the absorption rate, the inhalation rate.

DR. COCHRAN: The inhalation rate. You mean because they're working and exerting themselves, they should have a higher respiratory rate?

DR. HAMMOND: Uh-huh.

DR. COCHRAN: No. This is just a standard rate. This is an average rate.

DR. HAMMOND: Right. It is an average rate. These people are not doing average work.

DR. COCHRAN: I agree with you. I also think that, and you can play around with that as much as you like, because when you get to the actual assessment of risk that the absorbed dose is not considered. It is simply air concentrations.

DR. HAMMOND: I know that. But I assume you have to deal with it, each of those things.

DR. COCHRAN: I understand what you are saying. We also have some other problems that I will get to in terms of assumptions that we have to make as we go along.

DR. HAMMOND: I understand that, too. But I guess I am saying I want to put, make a mark here that I think the inhalation rate is underestimated

seriously.

DR. COCHRAN: Underestimates the amount material that can be absorbed? It's possible. That's an uncertainty.

DR. HAMMOND: It's not an uncertainty; there is more information to pick a better number.

DR. COCHRAN: That again is possible.

DR. LOECHLER: Maybe they have rats working in the field when they --

DR. HAMMOND: No, no. There is information about breathing rates at different work levels.

DR. LOECHLER: I was just kidding.

DR. HAMMOND: Usually, you want to look at some estimated.

DR. COCHRAN: If we went back to the original picture, the guy that is driving the tractor is he going to have the same breathing rate as the shoveler? Is the guy riding as the person that is as the tarp monitor, is he going to have the same breathing rate as the shoveler who is walking along side. Do we change the breathing rate for each of the various individuals who is there and how do we do that?

DR. HAMMOND: I guess if you find that very confusing, I would suggest to you that you might

think about who is likely to have the maximum rate of all those people and --

DR. COCHRAN: I think you will find as we go through we have taken into consideration maximum exposure.

DR. HAMMOND: If this the inhalation rate -- I don't know. I defer to you, John. Too much time --

DR. FROINES: That is fine.

DR. HAMMOND: But I want to mark that as an issue.

DR. FROINES: I think this, we should not -- if we are at a point where we can resolve this to some extent, we should do that rather than having to remember to come back. You don't have -- you may have notes, and but it's not always -- Elinor has notes. But ask your questions if you think they would be appropriate.

DR. HAMMOND: I think I have the answers to my questions. And I guess I am going to say -- but my comment and answer is that at this level I think that the inhalation rate being used is inappropriate. I don't know if we to go beyond that.

DR. BLANC: I think that will also be just

as with the protective factor of 90 percent and the assumption underlying that. I think in both the OEHHA presentation and EPA presentation, actually, the EPA, federal EPA, attacked, critiqued, Department of Pesticide Regulation for using a higher respiratory rate than federal EPA in their exposure assessments. Actually, I think the topic will come up again. There will be opportunities to explore that.

DR. HAMMOND: I guess I was trying to figure out -- I was just trying stay in that world. Maybe that is how we are supposed to.

DR. PAUL: I just validate that you hit on a question which is not at all trivial, which will, in fact, come up in several other places in the discussion, just as the other -- and I had mentioned that and I would refer you to the document that is the responses to OEHHA from the Department of Pesticide Regulation, the last two pages of that document which you have among your other documents, is entirely devoted to back and forth about the respirator and use, with OEHHA asking the same questions you asked, and with the response from the Department of Pesticide Regulation being that because the label says you should use a respirator,

therefore, they will follow the respirator fifth guidelines that are not on the label, but trailed along with other state regulations. And because they will be using that regulation, therefore, they will implicitly have to follow the other regulation about cartridge changeover.

DR. HAMMOND: I guess I am just trying to express my own view.

DR. BLANC: You should. You should.

DR. FROINES: That is why we are here. We don't need you if you are not going to express your opinion.

Tom, you were going to say something.

DR. MCKONE: More methodological. Although I'm sure there is some implicit opinion in here. The concentration was taken at a 95th percentile?

DR. COCHRAN: Right.

DR. MCKONE: That one actually makes a statement about variability, but the other ones, you try to set a value. Has anyone thought about actually taking each -- taking the range of concentration, the range of inhalation and the range of protection and then doing the 95th percentile with respect to all the variabilities instead of just picking one?

The danger of this is you are assuming you are at upper bound because you picked one parameter at the upper bound. Another way that somebody might do this is put all the parameters in the upper bound, and then, of course, we don't know where we are. Then we are upper, upper, upper on everything.

Or the other thing you could do is explore how far apart everything spreads. We could say what is reasonable upper bound and what is the expectation with respect to all the variations. Just end up with -- you have to do this for multiple parameters. You end up doing the same thing and you have more insight into where the variation really is.

Right now all we see is the explicit treatment of variation of concentration, but no explicit treatment of the question Kathie raised. Some workers may not be breathing much at all. They are sitting on the tractor.

So how do we actually -- I don't think we can pick a representative individual because there is nobody as the average. One person is here. One person is there. Maybe doing this with some bounding analysis. Even though you say later on the risk is actually based on concentration, not on the absorbed --

DR. COCHRAN: Air concentration.

DR. MCKONE: Air concentration. To translate that into an effect, there is always going to be something explicit or some level of breathing, like the animals were breathing. We just don't want to assume that the animals are a model of humans breathing at the same rate. I think this suggests some need to kind of bracketing instead of arguing about what the best number is. Everyone is going to have a best number. Maybe take Kathie's values and really show where they fall. It is just a thought. You are doing variabilities. Expand it to a little better treatment of variability, variability concentration.

DR. BLANC: There is one other issue in the breathing rate we should come back to at some point. I think that the issue of looking at combined chloropicrin effects sort of beyond the scope here, by and large. But since chloropicrin is acute respiratory irritant, it is likely to increase people's respiratory rate also. That is something that somehow we need to grapple with or theoretically not in your equation, but in recognition of some of the limitations. So if you had co-exposure, for example, you might stimulate

breathing in exposure itself, breathing rate.

DR. COCHRAN: I would ask, you increase the breathing rate through respiratory irritation, what happens to the tidal volume?

DR. BLANC: The tidal volume would -- it does depend because dead space can increase. If you don't have pulmonary edema, pulmonary fibrosis, then dead space to tidal volume ratio should fall with increased respiratory rate. It is a complex factor.

DR. COCHRAN: I agree. In the study we are looking at where we are looking at human respiratory uptake of methyl iodide, that is one of the complications that was in there. So, again, we are doing the best that we can because we understand that there is a variability, and it is discussed in the appraisal section of the document and the uncertainties that were there in terms of our estimate. But there are some things we are kind of stuck with. We have to come up with an answer, regardless. But it would be nice to have a number of years to investigate it and whatever. We have to come up with an answer.

DR. FROINES: I think this is a very good point that we need to keep in mind as we go forward. Because in general -- as far as I'm concerned, in

general, the toxic that we're dealing with here really do need careful evaluation because they really define what ultimately ends up as an MOE. So we need to be careful. I just want to say that a couple times you said that there are regulations from CAL/OSHA and from federal OSHA for respirators. And that's -- I consider that a very controversial topic. It's not a given, that just because OSHA says something that, therefore, we an assume that that is what we are going to find. Telone went from zero to, what, 4,000,000 pounds a year and I would argue that it may be that the exposure between zero and 4,000,000 pound may not be trivial in terms of the exposure assessment, and that in terms of respirators we need to be very concerned about that.

I have been in textile mills where workers cut holes in their respirators so they can put cigarettes through. So this issue -- we shouldn't be Pollyannish about the respirator issue because it's really quite -- there is the real world and then there is the world that -- and then there is the world we would like to live in. And believe me, when it comes to respirators, they are not the same.

DR. BLANC: We should go on.

DR. MELNICK: Just real quick. On the

inhalation rate, if you have to pick a value why don't you use the value that federal OSHA uses?

DR. COCHRAN: We have a document which is cited. I have to use that policy.

DR. FROINES: Go ahead, I think. Everybody is looking down.

DR. COCHRAN: Which is what we come up with when we looked at short-term, intermediate-term, long-term exposures and lifetime exposures for handlers and reentry workers. In the top portion we are dealing with -- this gives you an idea as to the number of individuals that we have data from for each of the various estimates that we had to make. And the top number that you see is in micrograms per kilogram per day, and bottom number is in equivalent ppm's that we get to get you to that concentration.

This again is a upper bound. This is the average. This is amortized dose because, clearly, you don't have air concentrations of methyl iodide all year-round. You won't have air concentration of methyl iodide.

The dose is amortized for the full year. There was a conference at USEPA that dealt with intermittent exposures. Basically, they came to two conclusions. You can consider something for a

longer period of time if the chemical stays present in the body and can build up over time, which isn't the case for methyl iodide, or you can have damage that occurs from the first exposure and carries over to the second exposure and can accrue over time. Since there is an oncogenicity concern associated with methyl iodide, we provided medical toxicology branch with estimates of both chronic and lifetime exposures of methyl iodide so that they could go ahead and estimate what the risk of cancer was.

DR. BLANC: Clarify one thing. In our pictorial walk-through the techniques, we didn't really talk about the whole punch list, whether at a certain point people come along and punch holes so the plants could come through. Right?

DR. COCHRAN: Right. It's about a week to ten days afterwards that we people coming through to punch holes in there, and those are the hole punchers. They also have that planters going in at approximately the same time. Now what I had to do in this particular instance is include both the hole punchers and the tarp covers and removers in that group to get a sufficiently large group. They are all coming in at approximately the same time, but not doing exactly the same thing.

DR. BLANC: There is something about tarp cutting and tarp removal that seems to be high exposure of something because what your pure hole puncher is there, they have much lower estimate.

DR. COCHRAN: You up above here?

DR. BLANC: Yes.

DR. COCHRAN: Yeah, I would say that is the case. In the case here what you have is also, this is a flat fume included with the raised bed. Because of the variability between the two when you're looking at the upper bound, that is why you get, because of the variability of different tanks and whatever, it is probably an exaggerated level.

DR. BLANC: In your view, is this physical property of the coming out of the soil at a higher rate than you might have thought partly why people, who become dazed later as they punch holes, have relatively high exposures compared to some of the people who are actually applying the material in the first place? Not the shallow shank applicants, but the drip applicants, for example.

DR. COCHRAN: The drip applicators up here?

DR. BLANC: Yes.

DR. COCHRAN: The purpose of the tarp is to retard the evaporation of methyl iodide coming out

of the soil. So, yeah, if you got it trapped in a pocket underneath the tarp, you would expect when you cut that it's going to come out.

DR. BLANC: One further clarification, regulatory clarification, would a hole puncher still be considered an applicator in terms of the regulatory process?

DR. COCHRAN: Well, no. He wouldn't be considered an applicator. He is not making an application. This is a week to ten days after.

DR. BLANC: Would he still be covered by all of the --

DR. COCHRAN: He is not required to wear the respiratory material. Was not factored in.

DR. BLANC: What about the tarp cutters and removers, are they required to wear a respirator?

DR. COCHRAN: The reason you probably are seeing this is so much lower, the applicators here and the applicators here and the shovel men and the tarp appliers --

DR. BLANC: Is because of the 90 percent?

DR. COCHRAN: Because of the 90 percent protection factor. Whereas, the other people coming in later don't have to wear a respiratory protection, so we didn't have to factor that for

them.

DR. BLANC: I think that that was not sufficiently clear in the document. And since there are probably going to be a fair number of people that might be doing the activities, you might want to consider insertion of several sentences that clarify who would and who wouldn't be covered in that way. It wasn't said in the response to OEHHA, by the way. Well, yes, we recognize there is some people who won't be wearing respirators at all.

DR. HAMMOND: I actually think a more transparent way to express that would be actually to have a column of just the actual measured values, and then to have the respirator, the measured concentrations which were in the breathing zone, and then to have a value that represents the -- they're not really breathing zones. As I looked at them, they're personal samples, but the measured personal sample and then the estimate from a respiratory protection factor as that factors. A lot of that we know what it is.

I was deducing that some of these are really different numbers in the same column, and we really want to have same kind of numbers in the column.

DR. COCHRAN: I thank you for the

suggestion. We'll take that strongly under consideration.

What you were seeing at the hip was a pump, the actual --

DR. HAMMOND: I saw the pump.

DR. COCHRAN: The white tubes are the samplers. Those are up in the air zone.

DR. HAMMOND: I understand about the pump. Is there only one pump?

DR. COCHRAN: Each person wore two pumps. They also wore two samplers on either side, just in case one burned out. Then you would have some measurement.

DR. HAMMOND: When you have an N and a six, is that counting two for one per person?

DR. COCHRAN: That is counting one. It's the average of the two considered as a single number.

DR. LOECHLER: If we saw the standard deviations of these numbers, would they be huge or small?

DR. COCHRAN: In some cases and in other cases small.

DR. LOECHLER: Would you actually put that in?

DR. COCHRAN: I can provide you with that information. Again, you E-mail me. I don't think it would make the document really cumbersome.

DR. LOECHLER: It is a nice table. The table could be included, this table.

DR. BLANC: The table isn't the exposure.

DR. COCHRAN: This table is not in the document.

DR. LOECHLER: That is what I am saying. The document is worthy. The table is not a succinct way of presenting the information. This table could be included. I'd also like to have a picture -- I don't know what a shallow shank applicator is. Does everybody else?

DR. BLANC: They showed a picture.

DR. COCHRAN: I think back there on a slide seven or eight.

DR. MELNICK: Some of those ends are extremely small values and I assume a N represents one person not assessed multiple times?

DR. COCHRAN: We had a number of tests, and so you combined everybody from all of the tests. But everybody that was involved in the drip irrigation studies included in this. You don't have that many applicators. You are looking at --

DR. MELNICK: For example, that is a hole puncher. Three people on one-day's work.

DR. COCHRAN: You had one hole puncher throughout the three studies.

DR. MELNICK: It is essentially three measures. Are geographic or weather conditions impacting on this? For example, temperature, when the application is done, they must vary under the conditions - environmental, climate change, climate factors.

DR. COCHRAN: I am not sure what you are getting at.

DR. MELNICK: If you have a cold day versus a hot day it's going to be different in terms of exposure. What was the condition under which each measurement was taken?

DR. COCHRAN: There is different places that this is being applied. It is being applied along the coast. It is being applied in the Central Valley. It is applied in a number of different places. Obviously, the climate conditions are not going to be the same in any of the situations.

DR. MELNICK: Where were these taken?

DR. COCHRAN: It is in the documents. I can't tell you.

DR. FROINES: I actually think that this, what appear to be a small issue of the hole punchers, tarp cutters or removers, is a very important issue, and I think Ron is absolutely right, that temperature is a factor that is going to influence the potential for exposure, especially if you have clouds underneath the tarps that are kind of trapped. You may get the potential for an even greater inhalation exposure and, quite frankly, this will come up later, I would argue at that point even a potential for dermal exposure. So it's -- this particular -- these job titles deserve a little more evaluation as we proceed.

DR. COCHRAN: So if we move on to consider potential bystander exposure, we had a number of studies in which fields were fumigated, and we had monitoring stations at different positions around the field to collect samples. And my colleague, Dr. Barry, is going to talk about how that data was used.

DR. BARRY: Chairman, good morning. We are going to talk about the estimated air concentration associated with bystander exposure. And we used an air dispersion model to estimate those bystander air concentrations associated with various scenarios

that Roger showed you, application methods.

An air dispersion model links emission from one or more sources - we looked at single fields at a time in this case - and estimates air concentrations associated with those applications. We used the Gaussian Plume Model. The inputs are field volatility, which is the flux rate as mentioned in the documents. We also input dimensions and orientations of treated field.

You can estimate air concentration of various distances from the field. We did look at the USEPA labeled buffer zones specifically, but we have a range of concentrations at different distances. You can have different dispersion, atmospheric dispersion, categories. We used rural because these are agricultural areas, and that tends to give you higher concentrations, everything else being equal. We used the Gaussian Plume Model in what is called a screening mode for risk assessments.

In this case the model will predict reasonable worst case downwind, ground level concentrations conditions. We discussed in the document and I'll talk about further. We have a set of screen level worst case that we used. Going to go back to this figure that Roger showed you couple slides ago just

to give you a context of where the flux estimates came from.

This a diagram of a field study. The applied area is shown in green, in this case square field, and these studies were square field for the most part. The off-site air sampling location are the numbers in circles. We have 12; in this case 12 samplers surrounding the field at different distances. Those measure air concentration over time. The sampling intervals are structured anywhere from two hours to 12 hours, depending on where you are in the application process. And they are structured so they do not span sunrise or sunset, because those are times when the atmospheric stability is changing rapidly. We don't want a sampling interval to be in the middle of the two or three or four hours that span sunrise and sunset.

The measured off-site samplers can be used to estimate flux by back calculation method. That is the first one listed here. That's a method that DPR developed and we published in peer review journals and has been very thoroughly reviewed, peer reviewed, and we have used since 1992 to estimate flux estimates, to obtain flux estimates.

An alternative method that we also accept is

the direct method. They are several of those. It is not shown here, but this was a study that only used calculation. But in a direct method, you would have a mass in the middle of the field, and it would have air samplers and censors at different levels, typically five or so, starting at just above the ground and going to high enough to capture the top of the plume, basically. And then there are analyses that you do to estimate the flux.

Data from either method to estimate flux is acceptable to DPR provided the step is there and the quality of control and all those sorts of things.

This speaker illustrates off-site movement, off-site movement of a plumb. The move is away from the field and it's affected by wind speed and direction.

This a view, obviously, from above what, you would see looking directly down on a field. And in this case you are downwind center line is directly this way.

Next slide.

So the fumigant volatilizes mixes with air and moves downwind. Shown here, the wind location has changed and the center line has changed. And also this is a larger application from the previous

slide. Also get a sense of what happens to the plume structure, both in terms of size of application and how the wind interacts, the geometry of the field.

DR. MCKONE: The sunset is the street.

DR. BARRY: Yeah, I know. That is the name of the treats. Good question.

DPR uses the ISTCST3 Gaussian Plume Model. It is a study state model. So what that means is it is assumed that the atmospheric conditions do not change within the time. That is typically an hour time step for Gaussian hours, but it can be different. The Gaussian Plume Model has a form that the air concentrations peak at the center of the plume and taper towards the edges of the vertical and crosswind directions, so it is a bell-shaped curve in vertical and horizontal crosswind. Although the speaker shows a staff, which is a point source, the same basic propositions hold in the shape of a Gaussian Plume for the sources of the ISCST3 Model will handle. We are using air resource for our model.

Now it's been suggested both in the methane reviews and also other fumigants that DPR should consider switching to a model called Air Mod, which

is the next generation Gaussian Plume. We have taken that under consideration. It needs to be noted that we are using an area source for these analyses. The area source algorithm using Air Mod is the same as the area source algorithm in ISCST. So all of our vetting, all of our -- since 1982 use of this model has been with the ISCST software. We have chosen to say consistent with what we've been doing and what has been reviewed thoroughly. And for this time for area sources at least we don't plan to go over the Air Mod Model. And it remains consistent with methyl bromide.

DR. BLANC: To clarify, this is one of those areas where the EPA comments went on and on?

DR. BARRY: Not about Air Mod.

DR. BLANC: It was something else?

DR. BARRY: It was not about Air Mod.

DR. BLANC: This wasn't the one that all of the lines of computer programming hadn't yet been reviewed?

DR. BARRY: That is Perfum, and that is a different issue. Air Mod is the next generation Gaussian Plume Model that EPA has shifted to. ISC is still on there website. You can use it as an alternative model, but we continually had

discussions about shifting to the next generation. Perfum has as its center -- its center kernal is the ISC model. It has a front end and back end.

DR. BLANC: We will we have to come back to that in the exposure assessment?

DR. BARRY: Not necessarily. Possibly

DR. BLANC: Will you highlight where that will become an issue?

DR. BARRY: That will be coming up in the session. Good question.

DR. HATTIS: It must be a little tricky to model the source because that is effected by whether the tarp is on the field and the temperature buildup might be.

DR. BARRY: That is true. That is one that Arysta has provided us with a really good set of flux estimates. They have done quite a few field studies. We've got replicates of the same application method that they have done in separate applications. So that we have what I would consider, short of methyl bromide, we have a very good set of flux estimates.

So with that, that relates to that question that we need to have that flux function characterized. That is what I will be talking about

in a second.

DR. FROINES: Does this question go to the -- does this go to -- would you like to see the Arysta flux estimates from which she is talking?

DR. HATTIS: Most likely the idea is that because temperature is important to the volatilization as well as the air flow. Then you got to study the effect of that. Yesterday was a pretty hot day. I imagine it is hotter out in the middle of agricultural fields. And particularly under the tarp, it will make big temperatures and that will create its own, changes the flux. But if you got some empirical information, that is helpful as long as the information is collected in a fair way.

DR. BARRY: Yes. I think that that is an important point, and I agree with you.

One thing on that subject, we have for methyl bromide 32 studies of flux estimates. We did look at whether we could tease out effects of flux of meth conditions. Different application, different soil type. And what we found was that tarped or no tarped, bedded, not bedded was all that we statistically pull out.

I agree those differences are probably there,

but the question is: Can you measure it above various background variations? That is the yes we're actually discussing.

Next slide.

I mention, of course, ISC is the primary model used by DPR since 1992. We are very familiar with this model. We did go through in an extensive review of our entire methyl bromide program, and our model was part of that review by the National Academy of Sciences. Since that time, we have gone forward and used this model and methods with confidence.

The Gaussian Plume Model was developed by USEPA Office of Air. This is just a simplified version so I can explain how the air concentrations are estimated by this model. There are a lot of software and other equations associated with this, but this is the kernel of the model where air concentrations are estimated using flux. And then times a more complicated function that incorporates meteorology and distance, crosswind and vertical away from the source.

As you can see, air concentrations are directly proportional to flux. So it is an

important component of these air concentrations. And the meteorological functions are more complicated, but it's affected by the meteorological variables of wind, speed and atmospheric stability. As I said before, we use screening methods in order to produce reasonable worst case air concentrations. And under screening conditions the averaging time of the air concentrations is directly related to the averaging time of flux estimates.

So one of the central things we do in our analysis is obtain a flux estimate that we are comfortable with is worst case for our averaging period of interest. For example, eight hours or 24 hours, whatever toxicology really says at the end of the day. The meteorological data is considered the predominant consideration for that average time. The thing also to remember is that even though you're screening met conditions, they can and do occur in the environment. Actually regularly.

The wind direction is interpreted as a predominant or average direction for that averaging time. So you don't say for 24 hours the wind went pinpoint in that direction. It is a predominant average direction, and you need to interpret is as such.

For example, our night screening conditions are one meter per second and at stability; and, basically, you can't get any more stable with a Gaussian Plume Model that is upper bound concentration. It is a highly stable atmospheric condition.

DR. MCKONE: The Gaussian Plume Model is a dilution model; it takes you from here to there. And actually looking at the pictures, they're very interesting. They show you off-site locations get dilution of about half. So if your model is getting that, we should be comfortable with it.

F stability in agriculture area probably getting a mixing height of three meters.

DR. BARRY: Possibly.

DR. MCKONE: It is not really -- when you've got a few meters, there is no normal distribution. It's trapped. Did you do then the second worst or probably the daytime when you established the stratification or just that sunset-sunrise lots of turbulence in the air, really unstable. Would be the best time to release chemicals. The worst time is in the night. And so do you do the eight-hour worst time?

DR. BARRY: Yes.

DR. MCKONE: Average at night, second worst at daytime.

DR. BARRY: I understand what you are getting at. What we have done is take a rolling eight-hour average flux, and then find out what the maximum flux is. But can't stop there; you have to look at what the air concentration is because the flux --

DR. MCKONE: Do you match.

DR. BARRY: Is matched in time of day. That's important. You have to keep in integrity. I will show you a flux profile a little later. You have to keep integrity of how the flux profile was developed. So if it's about 8:00 in the morning, that has to be start time of where your rolling average is. Then look for the maximum eight-hour flux. Then you estimate an air concentration using the Dallas [phonetic] center line worst case for that time of day. So the daytime is going to be one meter per second D stability. But then you have to look at nighttime flux, too, because even though it is numerically lower than the daytime maxing hour --

DR. MCKONE: It is substantially worse.

Dr. BARRY: You have to find the critical

time period, and we did do that.

DR. MCKONE: Do you have a random -- I know many years ago there was a study of a nuclear power plant. They actually did random thousands of thousands of random simulations, sort of like when they got the worst conditions. Not to use the worst, but to basically map out what is the range. And in this case actually two things that really matter, the dilution and emission. And one gets worse at night, but the other gets better. It would be interesting to see these tracks, where they are, kind of trade-offs, how the map out.

Have you done it?

DR. BARRY: That the sort of analysis would be characterization, more thorough characterization, of scenarios that we do in the mitigating phase, we haven't done that for methyl iodide.

DR. MCKONE: The purpose of this, as I understand it, is to give us a sense of what is a range high to sort of medium high range of exposures at the first off-site occupied location.

DR. BARRY: We --

DR. MCKONE: Really interested in just the relationship between aeration and dilution.

DR. BARRY: Yes, yes.

DR. MCKONE: You're probably doing that dilution in a range. And I agree it doesn't matter whether you use Air Mod. You can sit down with a calculator.

DR. BARRY: Yes.

DR. MCKONE: Dilution is not a hard thing to do. It is really going to be difficult to getting the right emission to match up to that dilution. We all know that at night, these numbers are fairly standardized. Gotten to where the models have credibility. Anyone who works what model knows what the answer is going to be --

DR. BARRY: Yes.

DR. MCKONE: -- in F stability with one meter and know what sunset with A stability and high wind speed.

DR. BARRY: Did I answer your question?

DR. MCKONE: Yes. I'm kind of feeling out where -- the idea where the critical points are for the key sensitivities.

DR. FROINES: Given what the two of you said, it sounded to me as though they have adequately addressed the questions that the two of you were asking. And so I want to make sure that you don't -- you are not asking for additional

information that would help you and your consideration?

DR. MCKONE: No. I just want to understand the level of detail that has been done or could be done.

DR. FROINES: You are happy, Dale? Good. Go head.

DR. BARRY: The last point I would like to make on this slide is that we really are following at this phase of our analysis, this assessment phase, something that is stated in the USEPA Office of Air screening procedures document, and that is the simple screening procedures are applied to determine if the source poses air quality risk. Conservatism is incorporated into the screening procedure to provide reasonable experience that the maximum concentration will not be underestimated. What we are interested right now is that we're capturing the maximum concentration.

Now here is flux profile. This gets to what Dr. Hattis was asking. This only shows the first three days. Because the scale gets really -- I wanted to show the actual function on the original measurement scale. What happens as you go out here to two weeks it just trails off. It pretty much

stays very similar to concentrations and then trails off to zero in some cases.

DR. BLANC: This is presuming a discrete period of application.

DR. BARRY: Yes.

DR. BLANC: And that is when the release is? Or is this based on also on sampling that you did following a whole bunch of hole punching going on and tarp changing? Where is that in this model?

DR. BARRY: What I will do is explain this. This is okay right here. And typically in a tarp application the air concentrations during the application are actually lower. And then I have seen this in the flux studies from idomethane and I have seen it in other fumigants. Typically the flux goes up in the second sampling interval. My feeling is because they are flushing the lines with water and it is kind of pancaking things out and causing a plume of flux. That is what you are seeing here; this is the second interval.

If this was 8:00 in the morning, this might be a couple hours that the application takes place. Arysta is very good at capturing the application period and then starting the next interval. A very nice progression of flux estimates.

This is a second interval, that it just starts to drop off. The flux profiles for all methods were relatively similar. There is going to be a peak. There might be a second peak that is smaller when you hole punch the tarp.

DR. BLANC: That is not until day five.

DR. BARRY: For this particular day five it would be a blip. It just trails off to a couple micrograms per liter per square --

DR. BLANC: Did they measure on those days?

DR. BARRY: Yes.

DR. BLANC: How much days out did they measure?

DR. BARRY: Two weeks.

DR. BLANC: Based on real measurement?

DR. BARRY: Yes.

DR. FROINES: Excuse me. It is Elinor's and my impression that what we are talking about now is not in your document; and that if that is the case, then we think it should be.

DR. BARRY: It might be a table or in one of the appendices.

DR. FANNING: It is sampling times, sampling interval, duration; that kind of time.

DR. BARRY: It is in my memo which is an

attachment.

DR. FROINES: We may been wrong.

DR. BARRY: It's a lot -- as you mentioned, there is a lot of paper. We have summary tables in actual documents, but the memos that I developed air concentrations, they're attachments, they're appendices. It might not -- it is probably not graphed, but it's -- all the flux estimates are in tables.

DR. FROINES: Do we have that?

DR. BARRY: I think so. I think they are appendices to the report.

DR. FROINES: Well, there are appendices and appendices.

DR. BARRY: We'll make sure you have it.

DR. FROINES: I think it is quite useful to have. This is the using --

DR. BARRY: It gets to what you are looking at, looking at the original data, too. I used Arysta's flux estimates. I didn't change them because they were good estimates. They were reviewed. I reviewed for quality. And they are in a table in my memo. So you just look down at see the flux estimates. It doesn't answer your questions about seeing the original data. It does

summarize flux.

DR. FROINES: You might check and either send us an E-mail. Go through Marylou, however you guys wants to do it.

DR. LOECHLER: I'm totally ignorant about this. Are these points where a value has been determined by collection for ten minutes at that particular point, or is this some kind of collection that went over three or four hours and this is just the average point placed at a single spot on this curve?

DR. BARRY: The flux estimates is made over a period of from two hours to 12 hours, depending on where you are on the flux profile. What happens is --

Can you go back to 18?

So the samplers here are going to be run. The application takes two hours. Samplers are run for the entire two hours and then sent to the lab. And you get the values in each one of the samplers. Then if you're using off-site method, back calculation method, you calculate the flux using those off-site samplers. It is a two-hour number or a 12-hour number. The flux is a integrated sample. So when you get the flux profile, this is considered

to be two hours. In the this case a two-hour flux. So for two hours you consider that that is a hundred micrograms per liter squared per second. That is mass you live with at a uniform rate over that sampling interval.

Does that make sense?

DR. HATTIS: This is a number that is calculated by taking a sampler one height or samplers from several heights above the ground and measuring the wind speed made. Therefore, inferring what might have been the flux in concentration profile.

DR. BARRY: There is two methods. The first one is the off-site calculation. They are all at the same height. You also got off-site met conditions, and the regression procedure that you used to get the model and measured values to agree. And then the direct flux, you are also talking about with the different heights. Direct flux is one mass in the center and both met conditions and air concentrations are measured. And it takes the effect of the field and calculates based on that profile of how much mass is lost and it is averaged over your sampling time. Ten minutes, nothing is going to be as short as ten minutes in these

studies, because it is the mechanics of making flux estimates that is too difficult. It is changing the samples out that is quite a task. So I think we might have some one-hour estimates in one study. Most of them are two hours, which for these purposes of bystander exposure has worked fine for us.

DR. FROINES: Go head.

DR. LOECHLER: I am just looking at this high point. You said something like the highest point, something like they're adding water at that time or something --

DR. BARRY: The mechanics of the application, this is a direct method. What I was saying is that we have three drip studies for idomethane, and each profile looks like this. The numbers along here, the magnitude, may be a little different, but the functional form looks very similar for those three drip studies. If you look at chloropicrin or look at metam, the functional form is similar.

I was reviewing the studies, and I'm realizing all of a sudden I'm seeing the same shape over and over for drip. What is really important with drip is when does this occur. If it occurs after sunset, you're going to get higher concentrations. If it

occurs in the morning, you're going to get that nice mixing and air concentration are lower.

DR. BLANC: Is there anything in the regulations that require applications at certain times of the day?

DR. BARRY: On the federal label? We don't have a regulation here yet. I am not familiar with federal level to know that.

DR. BLANC: You're quite -- these were done -- just technically, perimeter sampling studies, were they done concomitantly with the worker exposure? They were test field applications so they were carried out by the --

DR. BARRY: Some of them the early ones, that were put together and the worker exposure and the off-site were done at the same time. But others, they were separated.

DR. BLANC: One thing I would like to be assured about would be that test data from which the flux values were drawn included standard practices that always include the hole punching p activity. You usually do not have access to that. But if these came from the proposed registrant. When they speak, I would want them to be prepared to clarify them.

DR. BARRY: I think the two initial studies were overlap studies. I am not sure about after that, whether you had workers and off-site.

DR. BLANC: Roger, coming back to something you said, this ties with the same issue. The presumption that you made in your modeling was that because of the requirements for buffers between applied areas, somebody wouldn't be exposed at a time from another field at a time when they were working on their field, their area.

DR. COCHRAN: Yes.

DR. BLANC: But does that presume that it would be enough days out that somebody wouldn't be hole punching? There is no buffer. The buffer zone, what is the period of reentry, or the period for the buffer requirement?

DR. COCHRAN: Forty-eight hours is the requirement.

DR. BLANC: So isn't it possible, therefore, that I could be working here and exposed from my application and also simultaneously be exposed not by a neighboring application because there is a buffer zone, but by somebody hole punching right next to where I am, or tarp changing? Because they were not trivial exposures based on

your --

DR. COCHRAN: You're asking if the hole punchers could be out there while something is being applied next to the field that they are punching the hole; is that what you are asking?

DR. BLANC: Or vice versa. Yes. I guess it would be both ways.

DR. COCHRAN: Technically that is entirely possible.

DR. BLANC: Should there -- would it make since to have some kind of worst case scenario since you have the exposure data for them, or that would be such a small blip in the --

DR. BARRY: I think it would be important to look at the flux profile and see if someone in a field next door, whether it would been enough mass to make a difference in the exposure. I haven't done that yet.

DR. PAUL: I would suggest that as a sort of -- at least to reassure yourselves.

DR. FROINES: I think it goes to a fundamental question of one can develop a perspective on what is likely to happen. But in terms of issue of uncertainty, one should also look at the questions of where might there be adverse

effects that could occur that we should think about at least in terms of guesstimating whether or not those are likely or unlikely, because in the end it does affect your estimate of exposure.

DR. BLANC: That is why I bring it up. This is such an inherent part of how these things are used, that is going to be -- it is not going to be a rare thing. If you are applying and moving around your plots in an area, you're obviously going to be at that period, a critical period of time, where you have to punch holes so the plants come through or start fiddling with the tarp or whatever you do. And that is going to be happening in a big area. It is going to be happening next to some other area. You are limited in the period of time when you're doing all this fumigation work, right, a period of a couple weeks in one or another place. So you're going to have to maximize it. It is highly likely there are some people doing that work within -- closer than the buffer zone.

DR. BARRY: I think that the odds are we would look at what we've done with methyl bromide. There are extended discussions there. I wasn't familiar with it because it wasn't something I did. That is where we look at how they handled that with

methyl bromide. That is a very good point.

DR. FROINES: There are some differences between methyl bromide --

DR. BARRY: The structural, doing the analysis. Kind of how to lay that out.

DR. LOECHLER: For those of us who are a little bit ignorant in this area. We go back and forth a lot between micrograms per meter squared and parts per million, ppm. And I get lost when we do that. Is it possible to always put them both in or something?

DR. BARRY: Flux is normally presented micrograms per liter squared per second, which is why I left it that way. I understand what you are saying.

DR. FROINES: The point that you are making is one that is a problem. As far as, since I have be on the Scientific Review Panel since 1983, I can tell you that this issue has come up for those many years and that trying to get consistent milligram per kilogram per day versus parts per million. What we would like would be everything to be consistent so we can always make comparisons. Otherwise it drives you nuts.

DR. LOECHLER: It's starting to drive me

nuts.

DR. HAMMOND: Just as a quick thing.

DR. LOECHLER: Do I multiply by six?

DR. HAMMOND: You multiply ppm by six to get the number of square feet, roughly.

DR. MELNICK: From your models you should be able to predict the percentage of applied methyl iodide that has come off the fields over this amount of time. What is that approximate percent?

DR. BARRY: Depending on the application method, it varies between about 45 percent and 95ish.

DR. HATTIS: That is a useful number. That means that you can't be wrong by a couple folds in the overall integrated flux.

DR. BARRY: Yes. We do check that we are not predicting more coming off than was put on. We do that all the time. That's an important question, actually. We have some discussions about that it, and it actually will come up in the next slide because we are talking about seasonal exposures. So, yeah.

DR. MELNICK: Will your later models account for the hundred percent eventually? It has to go somewhere.

DR. BARRY: Mass balance. We haven't modeled mass balance, and I'm really only on the air part. That is a valid question. My main concern in my part, the air part, is that I am not producing air concentrations from flux estimates with more material than was applied.

DR. MELNICK: We need to know where the other 50 percent goes.

DR. BARRY: You want mass balance. There were some studies that Arysta did. There was an early study where they did measurements and looked at mass balance.

DR. FROINES: Can I say, speaking from the Chair, that the mass balance issue to me is an extremely important issue. And if we can get some further information, I think that would be great, valuable.

DR. BLANC: Chair. We are sort of coming close to the two hour point.

DR. FROINES: We are in contact with each other. Are you asking about taking a break?

DR. BLANC: Yes.

DR. FROINES: We are due for a break. How long do you have to go?

You do one more slide and then we can go back

to Roger.

DR. BARRY: That is actually a good break, I think, if you are going to.

So the flux profile that I showed you in the previous slide, coupled with our screening level met conditions can be used directly to estimate air concentrations up to 24 hours in duration. You start doing anything more than that, then we need some other alternative methods.

So based on the flux profile, we wanted to -- Roger asked for two-hour and 30-day air concentrations, average two-week air concentrations. So based on the flux profile, the average 24-hour flux was calculated for each of the 14-days over that two-week period. Then 24-hour flux that was an average for those days was calculated, so you get a smooth 24-hour flux.

The thing is that we need to account for variations in met conditions. You can't use that number as a two-week average. You need to adjust the 24-hour air concentration that was estimated with a time scaling factor. It is a screening method, so we are using a time scaling factor. We followed the methods in USEPA Office of Air screening procedures modeling documents. And the

time scaling factor, to get a 24-hour air concentration to a two-week average air concentration is a number, is adjustment of .48. And that comes from peak to mean theory. The relationship between 24 hours and hours in two weeks and that is how we produced that number.

So time scaling factor accounts for the affect of meteorological variation on the air concentrations over that longer averaging time, basically. And the details of these calculations, because it is a series of equations, are given in my memo on development of subchronic air concentration estimates associated with a single fumigant application. I steps through all the calculations we did and values that we obtained from the EPA document.

DR. PAUL: Basically discounted by half?

DR. BARRY: Yeah. Going from 24-hour to two-week average is a discount of about half.

DR. BLANC: What is confusing me is you said you have the data for two weeks.

DR. BARRY: We have a flux profile for two weeks, and we have air concentrations for two weeks. What you want to do is to be able to get that screening level air concentration for two weeks. So

each day of that 14-day period it's got an average flux. If it's nighttime, one meter per second, that's stability. You get that air concentration. Do that for each day. Take that average, that is the average 24-hour air concentration, not a two week concentration.

You need to stretch that. If you were at an air monitor running over two weeks, it would be lower than what that number is. Just about half.

DR. BLANC: Again, I'm not I may be -- you have a series of sampling times, but they are not throughout the 24-hour day.

DR. BARRY: No, no. There was 24 hours a day.

DR. BLANC: Then for two weeks?

DR. BARRY: Yes. But I don't have one air concentration at the distance and under the screaming met conditions. I used the model to get that.

DR. BLANC: I see. You have them from different sites.

DR. BARRY: Exactly.

DR. BLANC: This acts like a smoothing.

DR. BARRY: It is a smoothing based on peak to mean theory.

DR. MCKONE: Just to clarify. The observation is a single event. The model allows you [inaudible]. Basically, what you're saying is that you have an observation, provides ground proofing but it is only done -- you can't see the variability that you need to without extending, using a model properly, assuming based on a peer review, that the observations are four limited set of variations. You can't do a thousand different observations, but the model can be run 10,000 times. So really explore different conditions and variations. So hopefully the observation provides calibration or ground crew that you can say, "Okay. We were okay on these conditions, but you need more variation. You need to propose different scenarios that you can't do experimentally."

DR. BARRY: That is a next step in the analysis. What you are saying there is running a model with, say, five years' weather data. That is not what we did here.

DR. MCKONE: Even if two weeks. I don't know how many fields you monitored.

DR. BARRY: I think eight or nine. I realize I should have counted.

DR. MCKONE: That is eight or nine events.

The model will allow you to -- the range of variability does not happen in eight or nine events.

DR. BARRY: That's true.

DR. MCKONE. The range of variability, especially high end conditions, they may not happen. You may not get the really severe eight-hour, two-meter mixing height. Really, you want to explore that. This is the part you may not want to rely completely on. Trying to articulate what is going on. It makes sense. Sort of a reason we do the models, to enhance the observations.

DR. MELNICK: As a follow-up to that, do you also -- you create your model based on a certain set of data. Do you then test your model against another set of data that wasn't used to create the model?

DR. BARRY: We did that with methyl bromide. We don't have enough data to that with idomethane. We are using the same model, the same types of studies. We are making the same assumptions that the same sorts of processes hold. The model and the measure for idomethane match well.

DR. MELNICK: That is calibration built in?

DR. BARRY: Yes. And the other thing I should say is, we have one study where direct flux

and back calculated flux at same field were done for idomethane, and they matched quite well. So the two flux estimation methods matched well.

DR. FROINES: That is raisng a fundamental question that I want to make sure that we are on top of. One of the things that you always have to worry about is not the data that you have, but the data that you don't have. And, therefore, you're not sure how that data would affect the way you look at this particular issue.

Understand what I am saying?

And so I think this is a very important question and it goes to something I want to say before we take a break. We have had lots and lots of questions and questions about information sources. And what I want to be sure, Marylou, is that one will rely on people's notes for what we can have. But what we really will need, get the script, transcripts, and we need to -- and people need to make notes so that they are remembering what questions they're asking so that when we get around to it, Paul hasn't forgotten everything he got to because time has passed. This is an extremely important issue because so many questions raised in this particular presentation.

MS. VERDER-CARLOS: I will make sure you have the transcript.

DR. FROINES: We'll take a break, but I wanted to compliment Terry because I think that's been a really excellent presentation.

DR. BARRY: Thank you.

DR. FROINES: I don't think Roger is finished, so he doesn't get a compliment before he's finished.

(Break taken.)

DR. FROINES: Can we get started again? I think Roger is going to finish up; is that correct?

DR. COCHRAN: Yes.

DR. FROINES: At the break, there were people who had sat in the back of the room who said that they had not been able to here soft discussions. So anybody who is in the back of the room, my friend Baker here, if you can't hear, don't not tell us. It helps if I know that there is a problem. I think there is some logic to that. So please let us know because some of the discussions -- Dale and Tom are soft spoken. Paul goes up and down, as we know.

So, Roger, you are on.

DR. COCHRAN: Do you want to respond?

DR. FROINES: We've been friends for approximately 40 years, so don't worry. He'll have to take whatever comes.

DR. COCHRAN: So what we are going to do now is move into what kinds of exposures these flux and air concentrations translate into. And what we are looking at here is assuming that we have workers adjacent to a field that has been treated with methyl iodide, and what we want to know is that -- we have the different types of applications - the drip irrigation, the raised bed shank and flat field. And you had the three different types of application techniques, and the air concentrations that are associated with them are all different. So what you have here is the air concentration and the absorbed dose that is expected from somebody that is staying at the edge of the buffer zone. This is the 150, two meter buffer zone that is near all of the application sites.

The problem that I have is the people, obviously, are going to be moving around, either during the eight hours that they are there or during the week. But I don't have any way to quantitatively adjust that value. So I am using as a worst case, a reasonable worst case value, that

which they would get at the edge have that buffer zone during that entire time.

So here is what you would expect from the workers in terms of drip irrigation field or raised bed or flat field shank injection. This is what the seasonal exposure would be.

DR. BLANC: Before you move on, I have a call questions. The first one is if: You look at this in a relative way and you compare it to the worker application exposure data that you have, the irrigation worker exposure level was about 100, the shank exposure level for the worker. So yet this is even higher drip irrigation. We go back to your previous table. Is that because of the flux phenomenon that we were shown before is an order of magnitude for the irrigation?

DR. COCHRAN: As Dr. Barry indicated, the air concentration over the field at the time of application itself is much lower. It starts to come out of the field afterwards.

DR. BLANC: It must have to come out of the field afterwards much, much more for drip irrigation than for the other ones. Is that the point?

DR. COCHRAN: That is correct. It did in these studies.

DR. BARRY: In this particular case, this the drip irrigation study, the fluke was quite high in that second averaging interval. That is where that higher concentration is coming from. With raised bed it tends to come off immediately as it is applied. You don't see that low and that high number in the flux profile; and the same thing with the flat field, although it is a little more attenuated.

DR. BLANC: I am comparing it to Slide 15, the data. On the ADT for the workers and if you look there, there is an order, there is two orders of magnitude difference.

DR. FROINES: Paul, people in the back are still having trouble hearing.

DR. BLANC: There is a two order of magnitude of difference in the other way, so the shallow shank applicators have values of 120 micrograms per kilogram per day, and drip irrigators have a value of one. So it is a hundredfold difference the other way. Yet here you are saying it's because of the area of flux?

DR. BARRY: Yes. Because drip irrigation workers are on the edge of the field, and there is very little come out during the application itself.

With the raised bed and flat field shank they are fully walking in the field. So you're getting exposure, and it tends to come back out as it is being applied although there is controls on that, too. The fluke is higher during the actual application of the shank.

DR. BLANC: My second question is: Given the values are different - 800, 325, 530 - why is the SADD all the same?

DR. COCHRAN: The SADD is based on the two-week average. So what you are looking at is the average for all the various fields. That is what that is.

DR. BLANC: This is -- again, you know it would I guess to help at some point to see what the curves look like for the other ones you showed. This is then indicating that not only is there a big peak but the drip, but then it falls to a lower level. Whereas, for the other ones it's maintained at a higher level over a bit longer period of time in order to get exactly the same number.

DR. COCHRAN: The last column is actually an average for all different types of applicators, separated out by the different types. It is a little misleading.

DR. BLANC: Why did you do it that way?

DR. COCHRAN: Perhaps a mistake, but that is what that is. It is a little bit misleading. It is an average for all the different types for two weeks.

DR. FROINES: Don't you think you need to look at distribution?

DR. HATTIS: It would certainly help to have the distribution. If we are going to do calculations on a consistent basis, we can calculate populations, averages and various sets.

DR. FROINES: I didn't want to cut you off, but what you were saying -- we'll come back to Paul next.

DR. MELNICK: There is a difference between the Slides 26 and 15 in that one is a method and one is a worker. What you are describing in this slide is really the method notes on the drip irrigation worker?

DR. COCHRAN: Correct. This is just a worker that happens to be near a field.

DR. MELNICK: Did you remove the protection factor from the worker or is that built in?

DR. COCHRAN: There is no protection factor?

DR. MELNICK: That may account for that.

DR. BLANC: It shouldn't account relatively. I understand, but the relative irrigation to the raised shank in the other calculations that had both workers. So --

DR. COCHRAN: This is a bystander worker. This is not somebody doing an application or is involved in the field itself that is treated. This is somebody outside. Maybe picking strawberries in a field adjacent to a field that has been treated.

DR. FROINES: Is there a conclusion that the three of you think is appropriate?

DR. BLANC: One thing I would say is minimum. I haven't been going back and forth to the document itself to see what tables are tables you prepared for slides that aren't in the documents or are similar to this. Because if there is something similar to this in the document, then I think it is a bad idea to present in one column the methods specific data and then in the second column to present the average of all the methods.

DR. COCHRAN: I agree with you.

DR. BLANC: It is a moot point if there is no such table in the document. But you should double check it, and, if so, correct it, I would

say.

DR. COCHRAN: Again, what we have here is looking at an adult who is not a worker. And in this case we are looking at a resident bystander, somebody who lives adjacent to the field. You are not looking at a simple eight-hour exposure. This is a 24-hour exposure. This is a summation of all the seasonal exposures. I didn't break it out by the different types of fields, so that is probably misleading and should be changed.

As you can see, the exposure for child would be greater than that of an adult on acute basis. And on a seasonal basis, the assumption is that the person will be on the edge of the buffer zone the entire 24 hours. I don't have any way to adjust for indoor and outdoor air concentrations because there is nothing on the label that requires that the house be closed up. I don't have any way to adjust for dimensions of the house, where people are going to be as they move around.

So, again, this is a reasonable worst case exposure that you are looking at. This is maximum air concentration that we can possibly get.

DR. BLANC: Is it that on Slide 27, the previous one, the value of 473 is just an arithmetic

error because it is supposed to be -- the difference between 473 proportionally to 882 versus 278 to 325 isn't the same, but you are prorating over 24 hours. Is that because of, again, because the flux curve? Is it driven by the flux curve over 24 hours.

DR. BARRY: It may not be the same flux. It might be -- there is three replicates, for example, for drip. It would have been the highest 24-hour flux. It may not be the same study as eight-hour.

DR. BLANC: Again, it reflects these flux phenomenon are different.

DR. COCHRAN: That is correct. Again, the last one here is of the infant. You can see they get the highest exposure in terms of [inaudible] distance. The air concentration that you're seeing at the bottom is simply the air concentrations that they were exposed to next to those fields. In the document we use the highest air concentration that you would find, which would be next to the drip irrigation field, in estimating what the 24-hour absorbed dose would be for resident, adult, child and an infant. The seasonal exposure and an annual exposure.

DR. BLANC: Another question. What is

driving mostly the higher child levels? Is it their body weight or their respiratory rate?

DR. COCHRAN: It is a combination of the higher respiratory rate and body weight for the child. The relative absorbed dose tend to be greater for them.

DR. BLANC: That comes back to Kathie's question. What affects would it have if the respiratory rate would increase? Even in an adult it would tend to increase the delivered dose because the inhalation would be higher?

DR. COCHRAN: We have different rates for infants and children than we do for adults.

DR. HAMMOND: Maybe I could follow up on that. Perhaps it would be a little more transparent - I'm trying to go back to what is the table in the report as opposed to there - is if you have at the boundary what the actual air concentration is. Although the inputs to the dosage models are, you could have what the air concentrations are of the boundaries and what you assumed the breathing rates. The various assumptions that have gone into this. At least have those very transparent.

DR. COCHRAN: I believe that is in the document.

DR. HAMMOND: Okay. Just trying to see that again. Thinking about that.

DR. FROINES: Look at Table 29.

DR. HAMMOND: I was trying to see what is in the document. This is micrograms per kilogram per day, which has buried in it an assumed inhalation rate. That is what I am saying. What I want to see is the air sierra concentrations at the boundary, all the inputs. Is that .3 ppm, is that the air concentration?

DR. COCHRAN: That's correct.

DR. SLOTKIN: The child inhalation rate is based on resting respiration?

DR. COCHRAN: It is based on the 24-hour average.

DR. SLOTKIN: Anyone who is a parent of a kid that age knows that they spend most of their awake hours running around and breathing hard.

DR. COCHRAN: Three to five, yes.

DR. BLANC: Looking in the document, I'm confirming, in fact, that problem of the averaged among the methods number is what is used for the SADD. I think you want to go back and fix it. Not you, but somebody needs to go back and fix it.

DR. COCHRAN: I need to go back and fix it.

DR. BLANC: Pages 40, 41, 42.

DR. COCHRAN: That's correct.

DR. HAMMOND: I know the other question.

DR. FROINES: Ted's point about children and their level of activity raised an issue with respect to children in general in this. That there are circumstances where children may be at higher exposure than we're even estimating at this stage.

DR. SLOTKIN: Certainly, an ill child will have a higher respiratory rate for a maintaining period. One of the things that bothers me here is when we go from an acute exposure to a seasonally adjusted to an average exposure for an adult, that has a very different meaning for a child because they are going through specific critical periods of development where the high exposure for a very short period of time, may have devastating consequences and it sort of dilutes the affect to treat seasonally adjusted and average things the same way you do for an adult.

I'm just wondering if somehow the assumptions here need some explanatory information about the assumptions that are made and their limitations, particularly as they reflect effects on infants and children.

DR. MELNICK: You think there's a peak value as well?

DR. SLOTKIN: I am thinking that maybe because of issues like neurotoxicity, which I can get to eventually, that for kids the ADD maybe relatively more important than the seasonally adjusted average. The peak concentration rate -- whop them upside the head with a two-by-four and that might be more worrisome than acute exposure in an adult.

DR. COCHRAN: You would be correct. Remember what we are dealing with are intermittent exposures. You might be looking at damage that carries over from the previous exposure to the endpoint.

Again, my function in this is simply to come up with the air concentrations and the exposures. It will be up to risk assessment to deal with it.

DR. SLOTKIN: I understand that. The point I am trying to make is when a table is presented like this, with adult and child and infant, the natural implication is that there is an exact parallelism as you can down the column. I am just wondering if in terms of medical impact, if splitting the child and infant information away from

the adults in these tables might be more psychologically accurate in the way people assess them.

DR. COCHRAN: That is a possibility. It is something to consider.

DR. BLANC: Roger, would the age categories that DPR uses, are those mandated or just traditional?

DR. COCHRAN: The age categories that you are looking at in terms of body weight, respiratory rates, et cetera, we have a number of different categories, not just these. I picked these. They had the greatest differences that you are looking at. We have for a number of different ones. It is in policy, cited in the document.

DR. BLANC: One observation, now that we have the data from the Air Resources Board funded childhood asthma study, what thing we have learned is that exercising adolescents are perhaps a group that are at higher risk of inhalation exposure to selective air contaminants.

I wonder whether we are not just a sensitivity analysis or something. You may want to do some quick calculation, not necessarily include in every table, but these would be adolescents with a fairly

high respiratory rate because they are our on the soccer field, basketball court, of whatever, and just sort of -- in other words, since we have a precedent for it now in epidemiology from California.

DR. COCHRAN: Interesting suggestion.

DR. BLANC: May turn out that is not so different than the adult.

DR. HAMMOND: Something was a little less than clear to me, but going back. Starts within the worker exposure section. There is a section in Manteca where they used engineering controls. And so there was a dividing of the worker's exposure by ten to get to be comparable. When those things are done, it is not clear to me in the table when the number -- I would like to have a table of the actual measured values. I think it is along of what I was saying before. Without respiratory protection, without engineering controls. One goes up. One goes down. And if one changes these assumptions, you can work with it.

My question becomes taking that into the bystander area, like in Manteca they said the workers were exposed. To make it comparable you would have to multiply by ten to compensate for

engineering controls. If I understand what you wrote. Is that correct?

DR. COCHRAN: The question that you are asking refers to one of the -- each of the studies that the registrants did were different. And in one of cases -- what they are trying to do in the process of doing their studies is not just provide us with data, but also testing various other things. In other words, does engineering controls provide them with a level of protection that they wanted. So they ran that test in there. So they had engineering in it. Those people were then exposed to -- the tractor drivers were then exposed to less.

So we took the protection factor off them. So that we ended up, when we combined them with the others who didn't have engineering controls, that they are all on a level playing field and we then look at that. At then apply the protection factors to everybody.

DR. HAMMOND: I understand the reason to do that. I am not saying not to do it. But I would have at some point the data as actually measured.

DR. COCHRAN: The data is there for each of the studies.

DR. HAMMOND: Maybe I misread it. But the

data I thought had already been multiplied by ten to compensate for the fact of engineering. This was actually observed data? In some of these tables there is the protection factor from respiratory protection that has been applied.

DR. COCHRAN: If the individual study descriptions, that's the data that was in the study. We haven't manipulated it.

DR. HAMMOND: It is the data on the charcoal two divided by the volume of air samples.

DR. COCHRAN: Correct.

DR. HAMMOND: Without any correction for --

DR. COCHRAN: We correct for recoveries. They had field spikes that were down there.

DR. HAMMOND: Is that what they meant, they didn't call it recovery. They call it something else.

DR. COCHRAN: Those are field spikes. They assumed that everything that happens to a field spike happens to the samples that they bring from the field.

DR. HAMMOND: They have a thing called trapping efficiencies. That was confusing to me.

DR. COCHRAN: There is that, too.

DR. HAMMOND: Is that something different?

DR. COCHRAN: Is a little different.

DR. HAMMOND: I don't know if we should take the time to go through this analytical stuff right now. There are issues. Maybe we should stay within this.

DR. COCHRAN: If you shoot me an E-mail, I will help you with that.

DR. HAMMOND: Thank you.

So these tables as I -- in Table 8 when there is an air concentration, that is actually what was measured before you do anything about the engineering controls or respirator controls?

DR. COCHRAN: Essentially, what you are looking at in the document itself is that is unmanipulated air concentrations. All that has happened with that individual. You see the individuals across the line. All that has happened there is an adjustment to the field spike; in other words, recovery.

DR. HAMMOND: Say Table 7, which is Manteca where they had the engineering controls, right?

DR. COCHRAN: Correct.

DR. HAMMOND: That is what's actually measured, and then later, when you want to make a comparable, that is when you multiple it by ten.

DR. COCHRAN: Correct.

DR. HAMMOND: They didn't have any bystander control measurements done at the time of that Manteca. Do we have any idea what the -- I don't have an answer. It is a real question. Do we know the affect of the engineering controls is on -- what happens at the boundary lines.

DR. COCHRAN: I don't think it has very much affect on it at all. What you are looking at is a fan on the tractor. All it's doing is blowing air so that the tractor driver is not getting the methyl iodide concentration coming his way.

DR. HAMMOND: A kid standing right at the boundary fence and looking in gets the --

DR. COCHRAN: I don't think the fan carries that far, ma'am.

DR. HAMMOND: Right, true.

DR. BLANC: My question is in a different direction. When we do these estimates for the eight-hour exposure that someone has at the edge of the field, it's reasonable to assume that they could only be at the edge of one field at one time. When you do the seasonal estimate of their exposure, are you assuming a certain amount of multiple exposure from multiple fields? Or are you assuming zero

other sources of exposure? How many sources of exposure can one bystander have?

DR. BARRY: The two-week average and the 30-day average that we calculated are for a single field. Just a single; we didn't address.

DR. BLANC: So if I live in a farming community and I happen to have the bad luck of being downwind from field X for two weeks and then I have a week respite, and then I am two weeks downwind from a different field because of prevailing winds change or because the five days or two days have passed so that the farm is now doing the adjacent fumigation plot. Is that anywhere handled in the exposures?

DR. COCHRAN: Yes, it is.

DR. BLANC: How?

DR. COCHRAN: We did a comparison between the two-week average that we had without methyl iodide with the two-week average that was done by ARB when measuring seasonal exposure in communities with methyl bromide. What you find is they are not different. The values are just approximately the same. So I don't think that --

DR. BLANC: Walk us through that. In other words, what ARB found in their limited sampling of

methyl bromide was that almost all of your -- if you live in a community, that the actual measured exposure that you have that was estimated from a single field exposure is pretty close to what you got from integrated exposure to all the fields?

DR. COCHRAN: It was not done with a single field. ARB was looking at a community. The highest two-week average that they were able to find at various communities near the fields that were treated with methyl bromide during the season was approximately the same as the two-week average that we get from methyl iodide from these various fields from being at the buffer zone.

DR. BLANC: You assume the rest of the week there isn't exposure, do you? You don't say that that two-week exposure, you don't multiple the whole season and say that the two-week exposure -- for 12 weeks of the season they are exposed to what they are exposed to in two weeks? Does your model assume it is zero?

DR. COCHRAN: Your two week exposure is assuming that that is the average air concentration for the whole season.

DR. BLANC: It does assume that?

DR. COCHRAN: Yes. Average air

concentration, and that is what you're going to get for the whole season.

DR. BLANC: That is very helpful. Let me just say again so I am sure I understand it. Do you estimate two-week exposure and you extrapolate that and say that average two-week exposure continues on, and that for 12 weeks you're actually exposed at that level throughout the 12 weeks?

DR. COCHRAN: Is assuming you have that air concentration for the whole 12 weeks. That two week air concentration is for the whole 12 weeks, yes.

DR. BLANC: Not divided by six. It's actually multiplied by --

DR. COCHRAN: It's what a person would get in a 24-hour period. We are assuming that air concentration does not change.

DR. BLANC: Doesn't go down?

DR. COCHRAN: During that period of time. So you're looking at a person's 24-hour exposure is simply that air concentration for 24 hours. Average air concentration for 24 hours. They are going to get that day-in-day-out. What changes -- the only adjustment that you ever make in terms of the seasonal exposure would be for -- when you go from, not what you're looking at here. If you're looking

at the worker, you are looking are -- again, you're doing the same thing. You're basically saying, lets look at the average concentration, not the upper boundary. That is what gives you the seasonal.

DR. BLANC: If there was a fourth column between 24 hour and seasonal adjusted dosage, it would be exactly the same as seasonal, it would be 19.

DR. COCHRAN: If you had a two-week value, yes. It would be the same.

DR. BLANC: Because that is, in fact, what the seasonal is, adjusted based on a two week.

DR. COCHRAN: That's correct.

DR. BLANC: Anybody else other than me for whom it was not obvious?

DR. HAMMOND: Like you, I was not clear, right.

DR. BLANC: I don't know what, this may be one of those cross-disciplinary things where it is so bread and butter to what you guys do that it's obvious and, therefore, it doesn't need to be stated. But it may help to have a sentence that just would say were we to have had a column that was the two week, of course, it would be exactly the same as seasonal because the seasonal assumes that

the two-week estimate is continued on through the season.

DR. COCHRAN: You are not amortizing anything; you are looking at average value.

DR. BLANC: And applying it to the whole season. That should take into account repeated exposures. In fact, it should assume what it assumes is that the season is three months long.

DR. COCHRAN: Correct.

DR. BLANC: It assumes on average you have six similar exposures. It would be as if every two weeks you start another exposure period to the new application.

DR. COCHRAN: Right. Essentially what you're going to be doing is gauging the risk of that against an animal study of comparable length and time of seasonal exposure.

DR. BLANC: I understand. But one of the reasons I think we've all been harping on some of the exposure estimates is that we realize that down the road there is an exercise that is carried out that is not in these documents, where you're going to do a ratio of what your estimated exposure is to the risk levels that are determined. So I know earlier you said that none of this in the end is

going to affect the risk assessment, but it will affect that ratio because this goes into that. Right?

DR. COCHRAN: In the end you're only going to be concerned about the air concentration. You are not going to be concerned about the absorbed dose. That is where the human equivalent concentration is going to be. It's simply going to be the air concentration and absorbed dose is not really dealt with there.

DR. HATTIS: If you were doing a carcinogenesis risk calculation that in some way integrated over population, then you may want to do that.

DR. COCHRAN: I don't want to speak for medical toxicology. That's their bailiwick, not mine.

DR. FROINES: But, in fact, that denominator becomes quite crucial. Isn't that what you're implying?

DR. BLANC: Yes. However it is, you get to it. It will have an effect. The exposure half of equation does come in. Maybe the units are different and there are different exposure considerations for children, adults, et cetera, et

cetera.

DR. FROINES: We are going to get that, but the difference between an MOE of ten versus 4,000 changes one's attitude towards what the circumstances are. And so that denominator number becomes fundamental to the whole determination.

DR. HAMMOND: I am agreeing with you. Totally agree with you.

DR. FROINES: Let's go.

DR. COCHRAN: We are done.

DR. BLANC: You promised you would tell him he did a good job when he finished.

DR. MELNICK: One question.

DR. FROINES: Roger, thank you very much for a very well open presentation.

DR. MELNICK: We are only focusing on air exposure, but we still have another 3,000 pounds of methyl iodide. How do we eliminate water as a ground exposure? Not all of the methyl iodide dissipated from the field, by the flux data. Where did the rest go and how do we eliminate water contamination?

DR. COCHRAN: You've got somewhat of a variability there. My colleague indicated it's anywheres between 45 percent and 92 percent. And

you are looking at 175 pounds per acre. Where is the thousands of pounds?

DR. MELNICK: We still have 50 percent.

DR. COCHRAN: If 92 percent come out or 45 percent, then there is probably some residual there. I don't know.

DR. MELNICK: That is a thousand aces, 45 times.

DR. HATTIS: Is a good chance that some of it hydrolyzes, but there is also the experience with dibromochloropropane and some other compounds in the past that people didn't expect would show up in water and it did. But we don't know exactly what that mass balance is going to look like eventually.

DR. MELNICK: We have dealt with water soluble chemicals that have gotten into the water in California, such as MTBE. What you want to share is that this is not that scenario.

DR. FROINES: What was just said I think is problematic and deserves intense scrutiny. Because, yes, methyl iodide can hydrolyze. But that is one of these things that happens a lot in documents like this, where somebody makes an explanation based on some notion for which they have no objective information whatsoever, but you say methyl iodide

can hydrolyze and, therefore, that solves all my problems of what the exposures are.

Well, it is doesn't solve all the problems of what the exposures are. It actually says we need better and more information to come to grips with this issue because of the fact that we do MOEs and we have to divide by exposure. And I think this is going to come up around dermal exposure, not just groundwater. We have some topics that are yet to appear on our radar screen that I think, Dale, you would agree that we can't simply assume the hydrolytic pathway.

DR. MELNICK: There is an assumption.

MR. SEGAWA: There is a lack of data regarding --

Randy Segawa. I'm with DPR's environmental monitoring branch. And my group is the one who did the fate portion of risk assessment, and we did evaluate the ground water potential. And I do have some slides if you did want to go through that. Take me about a minute.

DR. FROINES: Do we want to take up groundwater contamination at this point? You're opening up Pandora's box when you do that.

DR. LOECHLER: Once it's in the

groundwater, it's still going to be hydrolyzed.

DR. FROINES: Groundwater contamination is a very complicated issue. And at the hearing before the Legislature there was very extensive testimony from a professor of organic chemistry at Davis who talked about the varying likelihood for groundwater contamination. So that the question is how and when do we address that issue because it is not a trivial question. And Dr. Shore from Davis argued vociferously for there being groundwater contamination.

So I am not sure we want to kind of wave our hands and fly by it in five minutes.

DR. BLANC: The question, what time are we scheduled to break for lunch? I was going to say if the next presentation after this the health effects? Doesn't make sense to start that for ten minutes and then break for lunch. If this truly is -- at least get this on the agenda now. We can come back to it later. It would be a nice way to use a small piece of time before we break.

DR. FROINES: We have 30 minutes before lunch. So, okay, Randy, go ahead.

DR. BLANC: Was it otherwise scheduled on the agenda at all, the water stuff?

DR. FROINES: No. But I assumed that it was going to be raised by DPR. That was my assumption. Let's face it, we were all at the hearings at the State Legislature and heard the testimony. And so this is an issue that can't just be put by the wayside.

DR. BLANC: I am not trying to put this on the wayside. I thought this was a good way to try to get it up further up on the agenda.

DR. FROINES: I think this issue will come up again at some other point. Is this equivalent, Randy, to DPR presentation on environmental fate?

MR. SEGAWA: Yes. It turns out that the only real issue regarding environmental fate is the water issue unless there are other issues you want us to discuss. In terms of water or our evaluation of the water contamination potential, we did look at both surface water potential and groundwater, and we determined that contamination of surface water was very unlikely. Groundwater contamination by the parent methyl iodide was also unlikely, but that the groundwater contamination potential by the iodide and ion breakdown product was uncertain due to lack of data.

In terms of surface water, the reasons why we

feel it is unlikely that it would be contaminated is because volatilization is a primary route of dispassion. The labels do require for all applications to have tarpaulins be laid down so there is a barrier to prevent the water contacting the soil. In addition, in California the surface water runoff issue is primarily a wintertime phenomenon. That is, during summer there is little runoff. And fumigation would occur during the wintertime period. Most fumigation occurs during summer and fall. In addition, there is low runoff potential in toxic soils that are normally fumigated.

And the groundwater, contamination by the parent compound. Again, volatilization is a primary route for dissipation. There isn't a whole lot left in the soil. We did conduct some empirical modeling under some extreme irrigation conditions for some of our other fumigants. One of our mitigation measures is to actually apply water following fumigation to help suppress the emissions. So we have concern with other fumigants as well as with methyl iodide as to whether or not these additional irrigation would cause problems.

And so we did run this model. I used some

extreme irrigation conditions. We compared that modeling scenario with some known groundwater contaminants, for instance DBCP. In this scenario, we way overestimated the concentrations of DBCP. The model predicted concentrations in the parts per million range, and we only detected them in the parts per billion range.

Under this same scenario, the model repredicted essentially zero groundwater contamination, zero concentration of the parent compound.

DR. LOECHLER: When you say detected, is this a simulation or actual measurement?

MR. SEGAWA: This is a simulation. There is extensive monitoring done of groundwater for certain contaminants, including DBCP. We compared the model results with those measured concentrations.

DR. HATTIS: The model must have a certain reaction rate of the methyl iodide with the soil. You'd have sort of an effect of being a half life of that soil.

MR. SEGAWA: Exactly.

DR. HATTIS: What was that half life? What was it based on?

MR. SEGAWA: I don't recall offhand. I have to look that up.

DR. MELNICK: Does that mean more than 50 percent?

MR. SEGAWA: In this exercise I think we did assume that 50 percent went in the air and 50 percent was left in the ground.

DR. MELNICK: Still have to get rid of the 50 percent.

MR. SEGAWA: Correct, yes.

DR. FROINES: What is the basis of that assumption?

MR. SEGAWA: Based on the flux data.

DR. LOECHLER: I was confused by that. In your document you have T one half for soil, and there are three different values. This is one of the documents. Was five days, two hours or 13 to 43 days on different pages. Not something that I want to clear up now. But I was just confused because it was so variable in the different pages.

MR. SEGAWA: Yes. I don't recall the numbers exactly, but it is probably due to different conditions, different soil types, different temperatures, and things like that.

DR. FROINES: Wait, wait. I want to ask a

question. In terms of your confusion, if you could say something more given what you just said. Are you now satisfied that you understand the basis of what -- basis of the conclusion?

What worries me about these documents is where we have found vacuums as opposed to -- we have data that we make determinations from. And we all know that. But there is also this funny feeling sometimes we get where you feel like you're operating in a vacuum, and I think this committee has to feel confident that they are understanding what has led to the conclusions the way Terry was talking in terms of fluxes, for example. And without that confidence, we are in a vacuum.

DR. LOECHLER: *I'*m a chemist and know something about mutagenesis, carcinogenesis. I don't know anything about flux. I don't understand these equations, never seen them before or anything like that. I try to get a feel for them, and I try to get a feel for a bunch of the numbers. I noted what is the T one-half in a river? It is in the document so I recorded that. And I don't know if I will ever need that number, but it's like I felt like I need it. It's like I ask a question, how many workers are exposed to this? It's like I don't

know if I am going to need that. I kind of want to have that kind of in the back of my mind as I think about these things.

So one of my questions: What is T one-half for hydrolysis? And so I got these three different numbers. I look for them. And so now I'm going to go back and try to figure out what you said, and I'm going to look to see if it mentions three different kinds of soils. It would be great if all have these things could be compiled in some kind of master table of: How fast does it volatilize at some temperature? What is the photolysis of it? What is the hydrolysis rate of pH 7? What is the hydrolysis rate in this soil? In that soil? Kind of a huge table with all of that kind of background data, not just what is the molecular wait. Maybe it is in the documents.

DR. FROINES: I would just say, I think we should go on and not prolong Randy's presentation. But the reason I put together people like Kathie Hammond and Tom McKone is theoretically they actually know something about the subject that you don't know anything about it. And if they hear something that perks their ears up, I think we are going to hear it from them.

DR. MCKONE: I will say something briefly. This is very qualitative discussion and has a lot of logic to it. But I think it is out of character with the rest of the document where we see things quantified.

In the field of environmental fate analysis there are these wonderful handbooks that Don McKy [phonetic] has written where you take a chemical and you do your fate mass balance. Because it basically says here is what goes in and here is how much what volatilized and here is how much goes nowhere, appears. And I am struggling how to translate this into not just unlikely, but just say: What would be the mass balance under different conditions? How much you -- put a ton in, whatever you put on a field, 45 acres time 175. That is a lot of mass, and 50 percent if it may go to the atmosphere. How of it much degrades before? It is a moving front. When we asked how much degrades before it hits groundwater.

Again, there is wonderful literature in one of these papers where we talk the probability of penetration. We have a penetration down. We can calculate probabilistically the likelihood that something gets to a water as a function of its

chemical properties. Vapor pressure, water solubility, and degradation. It is very sensitive to the degradation rate. If you use one degradation rate, the penetration depth may be a meter. Which means it is unlikely the chemical will disappear before it goes much further than a meter. You switch to another degradation rate, hydrolysis rate and it is ten meters; and you switch to another one and it is 30 meters. It's very sensitivity, this penetration front. It is very sensitive to what you know about the basic chemical properties. It is not a single number. Not something that we say it is unlikely if you do one calculation. The fact that the numbers -- degradation rates are among the most variable and uncertain parameters that we use in fate studies. It is always uncomfortable when somebody says, "Well, we looked at the data and we picked a single value. It is not going to hit, unlikely to hit groundwater." Actually, I think we need a little more characterization what that means.

DR. LOECHLER: Let me step in here. Because I am just going to quote. Here is Page 8. It says the aerobic soil metabolism half life calculated was two hours. I assume the compound is dissipating with a half time of two hours in soil

that is aerobic. On Page 5 it says half life raging from 13 to 43 days in unsterilized soil. Those are differences of factors of 500, something like that. And so I'm just kind of scratching my head, what that is and what it means. We don't want to answer that now. But it's certainly something that struck me as dramatic, curious and important in terms of these concerns.

DR. FROINES: I think you're right. I think you're playing a very important role. Obviously, everybody on this panel isn't an expert on every topic in these documents. Obviously, there is some division. For example, it is not just Kathie and Tom who raised some of these issues, but Ron Melnick raised the mass balance question. And I am a chemist and every good chemist knows you have to deal with mass balance. So that we've got basically five people who are raising issues.

But the question that I think Paul is very good at is to try and take the questions to someplace where you actually learn what the relative significance of the questions are. And that seems to me to be our job. And so I think we have to keep working at basically the points that Tom was making prior to that.

Pardon for me making such a generality, but you understand what I am trying to get at, I think.

DR. MELNICK: I love models, but I also like to see data that validate the predictions. And that is something that, if it hasn't been done, should be done.

DR. FROINES: That message has actually come up a lot today. And so it is what it is.

So, Randy, you want to go ahead?

MR. SEGAWA: Couple more slides here. There is so far a high uncertainty as to what happens with the iodide and ion breakdown product. It is one of the initial breakdown products from a methyl iodide along with methanol. We don't think methanol will be a problem because it degrades rapidly in soil. And normally we would have some field dissipation data for the compound. Unfortunately, the date we have currently does have some short comings. Number one, the iodide was not able to be measured for the first seven days of the study. The test location where the study took place is not one that we will consider vulnerable to groundwater in California. And the amount of water that they applied with this study wasn't enough to actually cause downward movement of the chemical.

So, basically, we don't have a good enough field dissipation study in order to evaluate the groundwater contamination of iodide. And so we did some worst case calculations as to what the concentrations might be. We assumed that the maximum application rate of 175 pounds per acre was applied. We assumed that 50 percent of it went into the air, leaving 50 percent in the soil. That all 50 percent of the methyl iodide in the soil gets converted to iodide and ion. So that would leave 8.8 grams of iodide and ion per square meter on the field. We also, since without the field dissipation study, we assumed there was no soil absorption of that iodide and ion, and it undergoes no further transformation.

Based on the mean groundwater recharge rate in Fresno, half meter per year, we calculate very simply worst case groundwater concentration of 8.8 grams per square meter divided by .5 meters per year and arrive at 18 milligram per liter or 18 ppm as our worst case groundwater concentration.

This calculation does have a number of uncertainties. We are uncertain as to whether the iodide is, in fact, a major breakdown factor or something else, and the rate that that occurs. We

are uncertain about the mobility, how much of it is absorbed into the soil does not reach groundwater. Since this compound is not registered, we are not sure how it would be applied to vulnerable areas and also the amount and timing of water after fumigation is uncertain. We do think that additional field dissipation data is needed to answer some of these questions.

DR. FROINES: I am assuming that organic compounds in the soil are going to be relatively small. And so we are not talking about thiol industry with methyl groups which is going to be a major issue later. So I am assuming that methanol, you would assume that the methyl group is primarily -- ends up as methanol?

MR. SEGAWA: Correct.

DR. HATTIS: For comparison with your water concentration, 18 milligrams worst case per liter. What is sort of the normal dietary intake of iodide?

MR. SEGAWA: That is a question you can ask the --

DR. HATTIS: We will talk about it.

DR. BLANC: So if I understand what you are saying, is that there are substantive groundwater uncertainties that should be clarified before one

could adequately determine whether or not this chemical would pose a potential risk to groundwater? Is that a fair characterization of what you just summarized?

MR. SEGAWA: I think that is a fair characterization. However, let's assume that fact we do register this compound and it is used in California. We don't think that we would need this data prior to making a registration decision.

DR. BLANC: Why not?

MR. SEGAWA: It would take several years, not decades, to use that concentration. We do think that we can obtain this data in the next year or two and then decide if, in fact, it is a problem and mitigate if so.

DR. FROINES: I was actually talking to Elinor. I didn't hear your question.

DR. BLANC: My question was if it was a fair characterization of what was presented to say that we do not have sufficient data at this time to appropriately characterize the groundwater risks; and you said, yes, that that was a fair characterization. You went on to say something that I hadn't asked you specifically, which was you said it would take a couple years to get those data, so,

therefore, we could theoretically put the toxin into wide use and figure out afterwards if there is a problem because there wouldn't be enough time to mitigate the problem afterwards.

And what was your basis for saying that? I understand the basis of the first part; it would take a couple of weeks to get the data. What is the basis since you don't have enough data to quantify what the groundwater risk is? Why is it that you think you could mitigate after the fact?

MR. SEGAWA: We can -- we have quite a bit of experience in terms of groundwater contamination by other pesticides in the state.

DR. BLANC: You mean like our great mitigation efforts with DBCP?

MR. SEGAWA: Yeah. I mean after the state passed laws regarding potential groundwater contamination by pesticides and we managed to mitigate many of those based on different -- changing cultural packaging, changing irrigation practices and things.

DR. BLANC: You just used the word "agricultural." Did you mean agricultural?

MR. SEGAWA: Yes, agricultural.

DR. BLANC: That was -- it is a small

point, but I have to say in your documents it presumes a certain jargon of the reader. Most normal people would not read the word "cultural" as a short form agricultural.

MR. SEGAWA: You are correct.

DR. BLANC: Well, I think it is important to separate out things which are presumptions versus things which can be said solidly. Seems like you are on very solid ground saying we don't have enough data to characterize the groundwater uncertainties. What the policy implications are of that, I think are open to discussion. Because you don't have data to support a statement one way or the other about --the policy decision is a different kind of question.

DR. FROINES: I have been saying that repeatedly today. And that is that we always have the problem of, in science of negative results or result that are aside -- they are negative because we don't have the data. Those are two different ways of looking at it. And the vacuum issue of where we make decisions that are negative because we don't have the data is quite problematic. And MTBE had to deal with this for years, of lack of data. And so this is an issue of some significance, I

think.

And, Randy, not to be critical, I would like, if we could, to not use the world "registration" over the next two days. That is a political, social, whatever you want to call it decision. And this panel should look at science, and we don't -- I would rather that registration wasn't an issue in the back of our minds, although it's obviously impossible to not have been aware of the issue. But let's leave the registration issue to another venue.

DR. BLANC: It is another area of groundwater uncertainty or soil residence uncertainty the interaction between this chemical and bacteria resident in the soil? Or is that data well elucidated?

MR. SEGAWA: In terms of whether the bacteria would serve to degrade or transform the compound, yes.

DR. BLANC: Yes what?

MR. SEGAWA: It is a certainty.

DR. BLANC: Is one possibility this methylating agent is that it would accelerate the mutagenesis rates and bacteria would potentially lead to the selection of different strains?

MR. SEGAWA: I don't know the answer to

that question.

DR. FROINES: I would just say it's not just, quote, mutagenesis rates. This is an issue of thiol chemistry and so we are talking about sulfur and not just DNA basis. And so we will come to this issue in great detail.

DR. LOECHLER: Just one other comment. Again, as O looked at these data, I saw hydrolysis rates in soil. And I was seeing numbers like half time of 43 days, a hundred days, something like that. Such that in a year you've gone through half lives of four half lives, something like that. You are left with 5 percent of the material hydrolyzed. And 5 percent of numbers like 600,000 kilograms is a really big number that is still in the water a year later. So it's those kinds of concerns. I don't know how much groundwater there is and how fast it spreads and whether it ends up in a well or not or anything like that. But those are the kinds of concerns that someone ignorant of the details is left with.

DR. FROINES: Do you have more slides?

MR. SEGAWA: That's it.

DR. FROINES: What time.

DR. SLOTKIN: I have one more issue.

If I recall correctly that you're calculating worst case, 18 milligrams of iodide per liter.

MR. SEGAWA: Yes.

DR. SLOTKIN: The recommended daily dietary intake of iodine is 150 micrograms per day. And there is, according at least to the information I just pulled up on PubMed, there is cause for concern when the intake level exceeds three times that value. So at 18 milligrams per liter, if you drink one liter of water, you're orders of magnitude above the upper limit of recommended iodine intake. So I think the issue of groundwater is perhaps, even if the calculation is off by a factor of ten, we may have problems here.

DR. FROINES: We'll break for lunch.

Do you think we can eat in an hour rather than hour and a half?

Come back in an hour.

(Luncheon break taken.)

---oOo---

AFTERNOON SESSION

---oOo---

DR. FROINES: Are we ready to go?

I think we have our speakers. We have a committee. It's just that we have no audience. So that it seems -- I am not criticizing the people who are here; I am criticizing the people who aren't here. We can start.

So welcome. Hope you enjoined the morning. And it's all yours.

Does everybody have your PowerPoint slides?

DR. SLOTKIN: Can I make a general statement? It would be really helpful if we got electronic copies of these PowerPoints instead of printed ones. Not just these, but this morning's as well.

MS. VERDER-CARLOS: You want it on your computer?

DR. SLOTKIN: Not now. For when we are doing our writings and that sort of thing.

MS. VERDER-CARLOS: I will send it to Sara or Elinor.

DR. FROINES: Please introduce yourself.

Dr. LIM: My name is Lori Lim and Dr. Read is on my right. And we both will be presenting the

health risk assessment part of the whole document.

On this opening slide I also included the scientists - John Corlett, Tom Moore, Harry Green, Charles Aldous and Joyce Gee - who actually did the study reviews of each one of these studies. The panel talked about getting the actual raw data. These are scientists who did the actual data review. We added this slide that is not in your handout. During the break we talked to Elinor, and I said maybe we should give you an overview of the entire framework of the big picture.

This morning you heard the exposure assessment being presented, and so Dr. Reed and myself get the other three bubbles as hazard identification, dose response assessment and the risk characterization. And the risk characterization will go into what is called the risk management, which the managers make decisions to whether accept the risk and no action, and unacceptable risk, then a risk mitigation, which was also mentioned this morning. And then if risk mitigation goes back into the exposure assessment to somehow reduce the exposure and then comes back to us as risk assessors to see if that reduction would now be acceptable or not. That is an overview slide.

DR. BLANC: Is that actually correct in the situation were are in? Isn't that more a model of a pesticide that was already approved?

DR. LIM: Yes, that's already approved.

DR. BLANC: That is not what we are dealing with. That is a huge difference in that box, because what we're talking about is you should have sort of a crossed line that doesn't go out of the box.

Dr. LIM: I think USEPA risk assessment, their document included mitigation before they actually registered the product. That was together in a single document.

DR. BLANC: That is not what we are contemplating here.

Dr. LIM: We are at the risk assessment portion, yes.

DR. BLANC: We shouldn't ever presume that it is ever going to get out of the box.

Dr. LIM: We promise, we won't say the R word.

DR. FROINES: I would say one thing. And I think Dale Hattis, who is on the committee, but the National Research Council released a new document on risk assessment, and that documentation takes the

old red books pictures that you showed and expands it rather dramatically and raises lots of new interesting issues.

And you might actually look at that because it doesn't go to Paul's question, but it does go to how the NRC is now looking at risk assessment methodology.

DR. FROINES: You and Dale.

DR. HATTIS: I was a reviewer.

DR. MCKONE: He came to several of our meetings.

DR. HATTIS: I approved what they did. They did a wonderful job.

DR. FROINES: It's the densest reading I've ever done in my life.

Dr. LIM: This part of the presentation focuses on the toxicity of methyl iodide and the risk of human exposure to methyl iodide. The two factors that determine the risk are exposure, which you already heard this morning, and toxicity. The exposure comes in as the risk characterizes right here.

First, I will discuss the identification of methyl iodide to establish the critical no observed levels, the NOELs, and the toxicity endpoints from

laboratory animal studies for the toxicity part of risk equation. Dr. Reed will then talk about the quality exposure human equivalent concentrations, HECs, from the animal NOELs using physiologically based pharmakinetic modeling. She will also discuss the application of uncertainty factors. I would then come to talk about HECs with repeated exposures, followed by presentation of the risk estimate of modular exposure and the cancer risk probability and how to evaluate these estimates.

In the selection of the NOELs and toxicity endpoint, duration of exposure and population subgroups exposed or considered. From the exposure assessment and toxicity study four exposures duration agency are identified. Acute, subchronic, chronic and lifetime. There are two groups with potential exposure to methyl iodide. The workers, those involved in fumigation and those working nearby, and the general population. Includes bystanders and residents living in the application area. In the application of toxicity endpoints the effects observed in adult animals have to go through all ages, including children. However, effects in fetuses and in young animals as a result of parental exposure, only go to exposure in areas which include

women of child bearing age.

DR. SLOTKIN: I don't understand why applicable groups doesn't include children as a subdivision in light of what we saw this morning with children receiving a higher effective dose at the time environmental exposure.

Dr. LIM: What this means, if, for example, we have a fetal death in which the pregnant laboratory rats exposed to methyl iodide and we have fetal death. So we apply that endpoint at NOEL to the pregnant women. Then you would protect against any fetal endpoint.

DR. SLOTKIN: I understand that. But in light of what we saw this morning, shouldn't test groups include juvenile animals as opposed to fetuses?

DR. LIM: General population, we include that. Different age groups. That is exposures with less than one incidence.

DR. BLANC: Let me just clarify further. I think the point here, let's leave the exposure aside. Let's say that we have taken into account with our modeling, we put a different exposure factor for children. Suppose within the general population there are sensitive or susceptible

subpopulations. This slide which reflects actually how you approach the data in the document, actually never really considers susceptible subpopulations.

Dr. LIM: This is the identification of the NOELs and endpoints. I think subgroup's ability comes in when we decide how much the factor needs to be for the acceptable modern exposure. That -- it comes later.

DR. BLANC: So let's revisit this and then we talk about --

Dr. LIM: This endpoint.

DR. BLANC: Let's come back to it when we talk about uncertainly factors. Make sure it didn't get lost.

DR. FROINES: I want to emphasize this as a point for this committee to deal with during it's process. And that is that we need to address quite specifically the issue of susceptible subgroups. So we should be making lists of topics that we are going to need more information or more discussion on, as we go through.

Dr. LIM: For the acute inhalation toxicity of methyl iodide three endpoints have been identified. Acute neurotoxicity in rats. A port of entry effect olfactory epithelial degeneration in

rats. And developmental toxicity has increased late absorption in rabbits exposed to methyl iodide during pregnancy. This endpoint is applicable to women of child bearing age. The data for each of these endpoints are presented in the following slides.

DR. HAMMOND: Just for clarification, go back to the previous side. When you say that the developmental toxicity in rabbits is applicable for women of child bearing rage. That is only one of those endpoints, that is? So neuro toxicity is not?

DR. LIM: I think that is not what I meant. It means I will not apply this endpoint to children exposure.

DR. HAMMOND: That is my question. You're saying that neurotoxicity, that endpoint would not be applied to children?

Dr. LIM: No, no, no. I think we will see it as we get down later.

DR. HAMMOND: Okay. I'm sorry.

Dr. LIM: All three endpoints apply to adults. Adults have women of child bearing age. These two endpoints were applied to young children. Because the developmental toxicity was not a result of young -- direct exposure of young animals to the

methyl iodide.

DR. HATTIS: For the second point of developmental toxicity in rabbits, there was also another endpoint in that study; that is the fetal growth image, which is another point for consideration.

Dr. LIM: So I will start with acute neurotoxicity study. The adult rats were exposed to methyl iodide for six hours by whole body inhalation. They were evaluated before exposure, on the day of treatment and after treatment. The treatment related effects were detected by functional observation battery, FOB, and motor activity assessment, when the treated animals were conducted within three hours after treatment. At 93 and 401 ppm the effects observed were reduced body temperature, chronic convulsion and decreased motor activity with a NOEL observed effect level at 27 ppm. When animals were tested against seven and 14 days after the initial acute six-hour exposure, there were no treatment related finding in the FOB or motor activity tests. No histopathology was detected in the CNS, or central nervous system tissues of control and high dose groups after the acute six-hour exposure.

DR. SLOTKIN: I have a number of questions about this, if I might. I notice from the data you supplied, and you're only going to go through a little bit of it, you restricted the analysis to male rats. Is there a reason for that?

Dr. LIM: Let's go onto the next slide.

DR. SLOTKIN: I have other questions about this as well. Is there a reason?

DR. BLANC: Because it would have been higher in NOEL if they had done the same approach with female rats.

DR. LIM: The female data is in Table 7 of the volume. This overhead is only in male data. Just to make our presentation shorter.

DR. SLOTKIN: Let me ask you several other questions. Why did you focus on acute neurotoxicity as opposed to what you had in your earlier slide, which was acute, subacute and chronic?

DR. LIM: Because this is a six-hour single study exposure. That's all they got.

DR. BLANC: They're going to come to the chronic later.

DR. SLOTKIN: Is there any chronic neurotoxicity study?

Dr. LIM: No chronic neurotoxicity study.

DR. SLOTKIN: That is my perception. It seems to me that is really not representative of anything accept acute poisoning. And in that case damage doesn't appear immediately from the case studies that I've seen, but rather emerges much, much later. In fact, even with in vitro studies where they showed toxicity to neural cells in a culture dish, the damage takes days in a culture dish to appear, which amounts to really weeks or months for in vivo events. So in this particular case it would seem to be me that any LOEL or NOEL that you might come up with is grossly above what the likely LOEL or NOEL is for any realistic exposure scenarios.

The second thing that I want to ask about histopathology. When did you look -- what did you look at and where?

Dr. LIM: One thing to remind the panel is that we did not conduct this study. This study was conducted by Arysta.

DR. SLOTKIN: The studies that Arysta reported, which I haven't seen the original data, what did they look for? When did they look and where in the brain? The brain, after all, is not just a hunk of matter. It is discrete regions with

differing vulnerabilities.

Dr. LIM: This is one case where you would like to see the actual study with the raw data?

DR. SLOTKIN: Yes, absolutely.

Dr. LIM: That would be probably the best way to answer the question.

DR. SLOTKIN: For a great many of the industrial neurotox studies, it consists of things like weight of brain, region and thickness. And they didn't look to see whether neurons have been destroyed or replaced by glial. Under those circumstances, you might even miss Parkinson's disease.

DR. LIM: I think the issue will come up when Dr. Reed talks about the PBPK modeling, too.

DR. FROINES: I have one.

DR. MELNICK: Can you define NOEL for me? If you see a trend, but that dose is not significant, does that mean it is NOEL? Can you tell me the definition of NOEL as applied to your studies?

Dr. LIM: In this case this is the male data for acute neurotox study. And I wrote here that the reason I wrote modified, I have taken actual table with the document and simplified it so

you should be able to find the same information in the same table number. And in this case the NOEL was defined by statistically significant decrease in the body temperature. And in this case here we decided that there is a positive trend in terms of the number of animals showing the repeated jaw and mouth movement which we define as chronic convulsions. In this case a positive trend was enough for us to say that this was no effect level and these are the facts.

DR. MELNICK: In some cases you used logic and some cases you used statistics.

Dr. LIM: Right.

DR. SLOTKIN: I don't understand either the logic or the statistics for the convulsions. So a study designed with only 12 animals, and you get 25 percent of the animals convulsing, and that is not statistically significant, which also means that it is not distinguishable from a measure of zero. Basically, the study has no power to distinguish anything short of 33 percent of the population showing a response.

So I don't see how you can pick a no effect level at zero out of 12 when zero is no different from three. I could also pick zero as no effect

level based on the same data.

DR. REED: I agree with you. I think, if I get it right, Dr. Lim was saying that maybe this is not a good example, but later on we will show you an example in that actually where the -- we need the panel's decision on where the NOEL is for that rabbit neuro developmental study.

DR. BLANC: We can come back to that, but I am willing to give you input here because, actually, here is just as good an example, frankly, as your implantation absorption. In fact, 27 parts per million is your low effect, lowest effect level, not your no effect level. It is incorrect scientifically, in my opinion, for you to decided this is a LOEL. The reason why this is NOEL is because -- why this a LOEL and not a NOEL is because it's quite obvious, for example, even for this very crude outcome measure of motor activity it's going down linearly with exposure. Even beginning at that dose. That is not a no effect level. You go from 100 percent to 80 percent to 25 percent to 13 percent. And, similarly, for mean ambulatory motor activity counts you go from 100 percent to 75 percent to 22 percent to 3 percent.

So I think what you need to do here is, with

the data that you have, either to call this a LOEL and use the safety factor below that or to attempt some kind of dose response benchmark approach, assuming they will allow it. It is certainly not correct and there is not public health protective to call the 27 parts per million a no effect level based on data you have.

DR. FROINES: I think if one does a statistical analysis, one will find that a trend test will be statistically significant. And so to use it sort of traditional P test, some simple minded statistical test, when you can actually do a dose response -- identify a dose response relationship, you can't go that way.

DR. BLANC: It comes back to what was raised before. If you have insufficient power to do a series of paralyzed comparisons of the doses with any kind of assurance of not making terrible beta error, which is what you're really concerned about. You really aren't as concerned about an alpha error from a public health. You need to go back to the blackboard and either treat this as a LOEL and use a safety factor, or, if you wish, attempt some kind of dose response modeling.

DR. HATTIS: You can do a benchmark dose

calculation. That might be the more straightforward way.

DR. SLOTKIN: Again, I think this is a strategic issue here. This is neurotoxicity based on acute exposure. And to me, the ability, no matter how you determine whether the LOEL or NOEL is, to extrapolate that to the neurotoxic effects of repeated or chronic exposure is highly questionable.

DR. BLANC: That is not what they are trying to do from a regulatory point of view. That is not what they are doing. When they get to chronic exposures, you're critique could very well be, but there is not chronic neurological study here. But in terms of the very narrow questions they are asking, what acute effect can we see, if they see a neuro effect acutely like sedation or whatever, they can use that as an endpoint, if they want. They are not pretending that that is a chronic.

DR. FROINES: What Paul is doing, for those of you who don't know him so well, he is identifying a major problem area and making sure that that is on the record. And will be one of the issues addressed as we go forward. It doesn't -- Ted's issue is going to come up, appropriately. But I would also

add to that that I don't see any of the case studies in here, and that is going to be a major issue, at least from my standpoint. And there is clear evidence of chronic, irreversible neurologic disease from case studies, and that goes to the point that Ted Slotkin was raising that this is -- here we are looking at an acute effect, but there is obviously examples of long-term irreversible effects that need to be addressed as well.

DR. SLOTKIN: The point I want to make is that what we have is a vacuum of some of the essential data that would be needed to make a judgment about how to use animal values for human safety, and that the acute may get at calculating some kind of safety factor, but the dose effect relationship for chronic effects may be completely different.

The other question since you reviewed the primary Arysta data and I haven't seen it has to do with data quality. If we look four lines from the bottom of pretest, I presume those are essentially controls for each of the will values that are below that. And it looks to me as though they can't get reproducible measurements from control populations at the VARIABILITY of the controls is bigger than

biological effects. Which then means that the uncertainty as to where even the LOEL is becomes even larger.

I guess we are on the record. If one of my students brings in stuff like that, I would just say that is crappy data.

DR. HATTIS: Just as a point of information. Are your plus-minus values standard errors or standard deviations?

DR. LIM: Standard deviation.

DR. HATTIS: Essentially, the standard errors are much, much tighter.

DR. SLOTKIN: The mean value of the controls alone floats around by a factor of 50 percent.

DR. BLANC: I do want to also say one other thing. I realize, having read the EPA comments, this will come -- I think, this is why you said you'd like our feedback on the other. That you were actually under a lot of pressure to choose higher LOELs than you did in certain instances. I do want to acknowledge that I think you went part of the way there and should be commended on not simply putting on blinders and going straightforward with this sort of pairwise comparison and if it is not at point .05

on a pairwise comparison between two doses, there is nothing going on. So my comment is sort of meant for you, to encourage you, you should go even farther same direction. But I realize that you received criticisms, which I don't agree with and I think the OEHHA comments were supported of the general thrust. But I think you actually need to go further in the same direction you are going. I commend you for doing that.

DR. MELNICK: I would like to see the panel go on record for recommendation on how this should be approached because I think the argument whether it is a NOEL or LOEL still does not include all of the data. Benchmark dose analyze to use all the data. I'm not arguing. I'm just saying it would be wise for the panel to go on record of the appropriate approach to analyze the data.

DR. MCKONE: Speaking of the science and decisions. That was a strong recommendation. NRC report is to avoid trying -- because of what we are talking about, a NOEL and a LOEL. There are studies right that show that as you increase the number of animals in the study, the NOEL and the LOEL keep dropping. It is not a statement of value. So the argument in favor of point of departure is that it

is something that you can statistically analyze, you can merge multiple data sets. I am also of the sense that we should really push, if possible, and stay away from this and try to get to a robust point of departure, which then can be argued.

You do a margin of exposure, you are much better off working with point of departure than NOEL or LOEL. They are not a stable number. It is something that changes. Every time you get a new study you get a different LOEL. A point of departure tends to be more robust. What you do is you lower your interval of uncertainty about it. You don't really change your expectation.

DR. HATTIS: One of the advantages of recommending going to the benchmark dose framework is the fact that it rewards the responsible firm for doing a more extensive study. Whereas, the tendency for the LOEL and NOEL framework is giving incentives in the opposite direction. That is a good reason why we should want to get better --

DR. LIM: I can certainly go back and look at the data and do a benchmark dose analysis. But I would like to ask the question: Would the benchmark dose response be 5 percent or 10 percent?

DR. MCKONE: That is a good question. I

1 think the conventional thing at this stage is to
2 give 5 percent unless there is some good reason.
3 Otherwise, other choices are to look at some number
4 of standard deviations to the control value. I
5 think I would go better with the -- since this is a
6 qualitative parameter that could matter, I think I
7 would do that. Actually, the guidelines that are
8 evolving is you go where you can get the most robust
9 result. If that is 10 percent, go to 10 percent.
10 If you can push it and really get reliable and
11 repetitive results at 1 percent, but it affects your
12 -- then that relates to the guideline you are going
13 to use for MOE. If you are using an EU 10, you are
14 not going go with a low margin of exposure. You are
15 going to do with a larger margin.
16 DR. HATTIS: Defining the benchmark
17 response, how big a change in activity level do you
18 think is important enough --
19 DR. LIM: For this?
20 DR. HATTIS: -- for this kind of endpoint?
21 That is why it's not at all a trivial question. It
22 is a matter of applying your toxicological inside of
23 your values in some sense. And, of course, we are
24 completely innocent scientists here. You guys,
25 you're acting for the people. You to apply your, to

some extent, your policy judgment in selecting that.

DR. LIM: We should go back and look at 5 percent and 10 percent and see what it looks like for a start.

DR. HATTIS: Well, I think it would be reasonably transparent to do that, and see how much difference it makes. You and your risk managers can go from that for this particular type of endpoint. It's not likely to be as sensitive as some over endpoints within the neurotox --

DR. SLOTKIN: Even in that case, the study design has to include sufficient power to pick up anything. So, for example, what is the biological import of any incident of convulsions in the population?

DR. HATTIS: That is another endpoint. That is a serious endpoint.

DR. SLOTKIN: In this particular case we begin with a study population that is insufficient to pick up something where 2 percent incidence would be biologically important. We can argue, and people in behavioral science do argue, that ambulatory motor activity counts in rodent and what it means for humans.

But there are certain endpoints that are unequivocal. Parkinson-like outcomes, cognitive defects, convulsions. These have all been noted from case studies in humans. What bothers me in the data that you've been provided with to make your assessment is that from the point of view of someone - I am not a regulator. I am developmental neurotoxicologist - these data are totally inadequate to make sound conclusions from a scientific standpoint, and, as we'll get to, there aren't developmental neurotox studies. You've got damage to the brain in adults, in areas of the brain that are known to be most vulnerable in the fetus. And yet there is not a single even preliminary developmental neurotox study. That seems to me to be weird. And I don't see how one could rationally set a safety limit for exposure of pregnant women absent any data about what is probably a very much lower threshold for developmental neurons.

DR. BLANC: Another advantage of your benchmark approach is that I think you will be able to show that there isn't heterogeneity between the male and female of the test animals in terms of the two endpoints, and that you will be able to combine them for the purpose of the benchmark. I think you

will be able to show there isn't heterogeneity, and you can combine the males and females in terms of endpoint. It looks to be almost identical.

DR. HAMMOND: There are seven females. The number seven --

DR. BLANC: I meant for the two endpoints you can look about.

DR. HAMMOND: We are talking convulsions, also.

DR. BLANC: That's at the highest level. I am talking about the endpoint for motor activity.

DR. LIM: We can do a benchmark for each one of these endpoints. Combining them and separating them. So we will have some better idea.

DR. FROINES: As I understand, basically, that there is the consensus of the panel with respect to the benchmark dose, that Ted is raising some related issues that he wants to be part of the record.

DR. BLANC: Which we should come back to when we talk about. The problem is the way this is structured is that it is not by organ system. They are not talking about toxicity of the brain. What they are talking about, for better or for worse the way this is structured, is acute toxicity, subacute

toxicity, chronic toxicity. Most of what you are referring to we should revisit when we get to the level when they talk about the chronic toxicity. But there aren't any chronic toxicity studies for the endpoints, the ones we care about, for chronic. I think that is how I interpret your comments.

DR. SLOTKIN: I think it is just an organizational difference. I see it as neurotoxicity.

DR. BLANC: That's not how the organized their documents. That is why --

DR. FROINES: Let's move on. We have a long record of Ted's comments. And so the fact that they're are here now, means that they are going to be dealt with here as well as further along.

Dr. LIM: The next acute endpoint is the nasal toxicity. In this study the rats were exposed to methyl iodide; 0, 5, 21 or 70 ppm's six hours per day, five days per week, for 13 weeks. The primary finding was that we considered as an acute endpoint is olfactory epithelial degeneration, with NOEL at 21 ppm. And we considered this as an acute effect that I will show on the next slide.

DR. BLANC: Can you refer to what table that would be in the main document?

DR. LIM: I will show in the next slide.

DR. BLANC: Doesn't tell us what table it is. Is that -- it's not Table 11.

DR. LIM: Table 11 and 12. Combined -- again, this is a modified table, trying to make the data --

DR. FANNING: Table 42, 43.

DR. LIM: Highlight the data and make our points. Got it right? Great.

So the reason we consider this acute is that if you compare the four week to 13 weeks, those two time points measured. There are only slight increase in severity. And, also, the effect is consistent with a published study in 1995 where rats were exposed to a hundred ppm for four hours or six hours. And they show a moderate or marked degeneration, and this is a single exposure study. Compare these results with the 70 ppm results, we see that is probably an acute effect.

DR. FROINES: I have a question about the data. And that is as I look at the table on Page 42, it looks to me like we are back into the same issue that four cumulative mean body weight changes, that that looks like a LOEL to me rather the a NOEL.

DR. LIM: That will come up when we talk

about the subchronic toxicity, I believe. That endpoint, that was measured after 13 weeks. Is what I am going to talking about.

DR. BLANC: Your cutoff for acute effects is four weeks or less?

DR. LIM: Acute we put less than one week.

DR. BLANC: This is a four-week exposure.

DR. LIM: Exact total is 13 weeks. And here is four years. What we have seen, for example, on this level, the histo of the tissue, this level here is, four out of ten. They are showing the minimal degeneration. And your exposure, extra nine weeks. You also get the same incidence, although there is some increase in the number showing mild. And so I would just, in this case, six out of ten and five out of ten, there is no dramatic increase in the severity or incidence. So we consider this, each one of these daily doses is an acute effect causing degeneration.

DR. BLANC: That is where you lost me. I mean, it seems you have this one study, which is actually going to have a lower final endpoint, considerably below the one we just talked about. Right? Because we've just already determined that what you have is a LOEL is not only -- not only not

going to be a NOEL, but you are going to do benchmark assessments. So it is going to come out considerably lower.

Now you have this weird study where you are calling four weeks acute because you are saying there is not a big change between four weeks and 13 weeks. So four weeks is like one week and one week would be acute.

Is that what you're saying? It seems really stretching it to try to use these data for acute exposure effects.

DR. LIM: We're using it as acute portal entry effect. So that we have some idea of what the irritation aspect of it would cause. So, again, we are not excluding any of the endpoints. We are saying there are three endpoints for acute exposure that we looked at. So that we are covering different parts.

DR. BLANC: What I would say, you don't have an adequate database to look at portal of entry acute effects. Rather than trying to make a silk purse out of an sow's ear.

DR. LOECHLER: Can I ask one question here? Dose it matter if you call this acute or subacute? It is an effect. Does it matter which category we

put it in in terms of how we assess this? If it doesn't matter, should we? I don't know.

Dr. LIM: It does because it translates into PBPK modeling. It gets carried forward.

DR. MCKONE: Can I make a comment about the structure of the organization? Part of it that is causing the confusion. This is really your hazard assessment.

Dr. LIM: Yes, it is.

DR. MCKONE: And in hazard assessment you are kind of bringing in what we call a dose response. You are trying to find a LOEL and a NOEL. You shouldn't be doing that yet. You are doing a hazard assessment. The goal is to define the range of diseases that you are concerned about. And, again, it is confusing to do chronic, subchronic. It is kind of moving into where we want to look at dose rates and dose times.

The first thing to do is to define the portfolio of diseases that the literature reveals and some of the mechanisms. And to make the argument that these are the things we have to worry about, these are the things that are some day going to look at data. I think we make -- this is just jumping back and forth between a preliminary dose

response in the sense of trying to find no effect. You don't have to find a no effect level to demonstrate the possibility of harm. And a hazard assessment is about the possibility of harm, not the likelihood of harm. That is a dose response assessment.

If we get this kind of boundary set up, then we can focus the hazard assessment on the plausibility argument and the dose assessment on the probability or likelihood of harm at what dose level and whether there is evidence of no effect or low effect. That all belongs in a later part of the risk assessment to help us focus on -- we are all struggling with this, too. Because some of us are jumping ahead to dose response argument, and really right now it should be how well can we understand the evidence of disease. And that, actually, I think, it would be better to organize by disease category. And take off chronic and subchronic as opposed to starting with chronic and subchronic, and try to figure out what disease.

Again, I am having trouble with some of the framework organization and how we sort this out in a way that is very transparent.

DR. REED: I think there is probably more

than two ways to approach risk assessment in terms of hazard identification and dose response, whether they should be going to or not. I certainly understand how -- the way we approach it is confusing. And so I appreciate that comment.

What we do, we just pick a study and we take individual study, and we try to identify the toxicity of it. We are trying to, from each study, draw a threshold, if it is assumed to be a threshold approach. At the end, when we have individual studies listed, we are going to list them all together. Then start considering which one could be used for what.

I think what Dr. Lim was trying to present is while she is presenting a study and because it is our practice to also write at the point of departure or threshold, and so that part is confusing. But in a sense, if perhaps you can wait until the end when we put all the endpoints together, then you will see how we for this, of course, we approach risk assessment. This is not the only way to approach risk assessment.

I apologize for the confusion. If you could bear with us.

DR. LOECHLER: I want to ask my question

again. This is where I am confused. To me it looks like you've got an effect, and in the end you're going to say, well, with 70 parts per million we got some bad stuff going on in a certain population of the animals. And so we got to worry about a level ultimately that we're going to decide on given this endpoint. Will we get a different number of what this threshold is going to be if we define this as an acute effect or subacute effect? Will that give us a different number?

Dr. LIM: Yes. Because the way you amortize -- if we look at it as a subchronic effect, being for 13 years. Then you would amortize it with some duration and different factors. So it becomes a lower number.

DR. LOECHLER: So the more conservative approach would be to call this subchronic rather than acute; is that true. Is that what you just said?

Dr. LIM: Yes.

DR. LOECHLER: Conservative meaning?

DR. LIM: Make the NOEL lower, yes. If you use as endpoints subchronic.

DR. MELNICK: One piece of information that is missing on your tables is the actual instance of

animals that have olfactory epithelial degeneration. Because you've broken into severities, and what is actually more important, for example, the Level IV you have four, five, one.

Does that mean you have ten animals?

DR. LIM: Yes. That is denominator. One of ten.

DR. MELNICK: No. Does every animal in that group or is it a maximal? The number should reflect ten animals were affected. Nothing. Not the numerator. Were ten animals affected? Because an animal can have both tox lesions, have a minimal in one location or a mild. What is its total incidence of animals that are affected?

Dr. LIM: I understand. So I think I looked through the data and the four animals, four, lower four, the four animals that minimal did not have mild or moderate.

Is that what our asking?

DR. MELNICK: All ten animals had Level IV degeneration.

DR. LIM: Yes.

DR. MELNICK: Why not include that at least as an entry, the total incidence of animals with a lesion.

DR. FANNING: Can I add to that? Because my understanding is that there were only ten animals assessed at four weeks so that not only do all the ten of those animals have Level IV lesions but most of those animals have lesions at multiple sites.

Is that right?

Dr. LIM: Yes.

DR. FANNING: So this is called a LOEL, but you have a huge response.

DR. HAMMOND: You scored on the maximum degeneration. If they have one site a moderate and another site it's mild, they're only entered as moderated. They don't enter the moderate and mild, both.

DR. FANNING: I'm talking about across models. There are only ten total animals that were assessed for Level II, III, IV and V.

DR. MELNICK: The reason I raise this is because the next dose group where you don't show the data here, but it is in your --

DR. LIM: Table 11 and 12, yes.

DR. MELNICK: There is one animal in ten with a Level IV, and one animal with a Level V. Are those the same animals or different animals? The number ten or two out of ten, or one out of ten with

an incidence of lesions. This is in female rat, Table 12, female rats.

Dr. LIM: In the male, all the -- the five and 200 ppm were all zero out of ten. The female is one out of ten on Level II, and one out of three in -- one out of ten in Level III.

DR. MELNICK: Is that the same animal or different animals?

Dr. LIM: I cannot.

DR. MELNICK: I can't tell either. What I want to know is it two or one animals.

Dr. LIM: I understand. It is like counting tumors. Would be benign and whether you add them together or not. Some could have both. I understand that.

DR. BLANC: Just to bring us a little bit to closure. I think that whatever you do, certainly would make more sense to consider these data as subacute, but not acute.

DR. LIM: As in subchronic, repeated exposures?

DR. BLANC: Right. I think that is more conservative and public health protected.

DR. REED: May I interject a little bit. Maybe there is something that, an explanation. I

1 think that in risk assessment - I think, Lori, you
2 can tell me if I am wrong - you use this for acute
3 endpoint, but you always use this for the -- as a
4 chronic endpoint so --
5 Dr. LIM: Is a different endpoint from this
6 study.
7 DR. REED: Is it because the subchronic
8 endpoint is lower than NOEL?
9 Dr. LIM: Is actually the same.
10 DR. REED: She used for both.
11 DR. BLANC: That doesn't make any sense to
12 me.
13 Dr. LIM: Is a different endpoint, but the
14 same ppm as NOEL. Numerically, it would be the
15 same, but your point is that this endpoint should
16 belong on subchronic. I understand that, yeah.
17 DR. FROINES: Elinor and I are talking, and
18 it looks to us, and for example with female rats,
19 that the LOEL is 21 parts per million. But the
20 question that goes to Ron's question is that there
21 is a one and a one out of ten at 21 parts per
22 million. We don't know whether they're the same
23 animal or not. But it is clear that there is very
24 significant response at 70, and the fact that you
25 are getting some response at 21 doesn't mean that

the world's getting very excited. But it does appear as though there is something happening at 21 that is not happening at five.

Dr. LIM: There is one out of ten for the female control at Level IV at four weeks. But not at 13 weeks.

So the question is: Is that one out of ten a significant finding for it to base it as a LOEL?

DR. FROINES: Is is one out of ten or two out of ten?

Dr. LIM: The female Level IV after four weeks is one out of ten.

DR. FANNING: If you sum cross levels, then it is two animals out of ever ten.

DR. LIM: That is something I need to straighten out. Is to see whether these are individual animals, separate animals or same animals. I got that point.

DR. FROINES: Let's go ahead. Some of the issues are similar to what we have talked about earlier on. But let's go ahead.

Dr. LIM: Here is the big one. The developmental toxicity study. To describe the sturdy, the pregnant rabbits were exposed to methyl iodide for 0, 2, 10 of 20 ppm, six hours per day,

during gestation day six to gestation day 28. They were sacrificed on gestation day 29.

The primary maternal effect observed was body weight reduction with a NOEL at 10 ppm. The more important endpoint is the developmental effect which we set the NOEL effect at 2 ppm, with the LOEL 10 ppm. And the key findings are reduced fetal body weight, increased late resorption, and dead fetuses, which combined to cause fetal death. And there is some concern about whether NOEL should be because of the data variability.

And the next slide will show what I meant by - as an example of data variability. And this is not in your document packet. Can certainly be added to when we revise the document. I think it be helpful.

So this is this data for late absorbing. The doses are 0, 2, 10 and 20. The number of litters per group are pretty similar - 23, 20, 20 and 21. Know that the number implantations in each litter is a range from 2 to 11, 1 to 11, 2 to 10, and 1 to 10. And that's quite a range. This shows the affected litter with 2, 2, 6 and 11. Clearly there is an increase at ten ppm and 20 ppm.

Now of the two litters that affected, what I'm showing here is the percent of fetuses affect in

the affected litter. So in one litter 10 percent of the fetus were affected, and in the other litter 20.6 percent was affected. And the same way with the next dose. You get to the 10 ppm and 20 ppm, even though the base seems to be the same, it goes up to 45.5 to 71.4 to 87.5 percent. And then if you putting -- this not all the litters affected. Here is 23, only two affected. You could have a range, quite a wide range in controls from 0 to 28.6 percent here, 0 to 45.5 and on the other ways. At the highest dose we have 0 to 87.5 percent because affected litter is 11 out of the 21. But when we add up all the numbers from all the litters expresses percent in fetuses per liter is 1.7 for control. Goes up to 3.1 to 11.1 and to 21.5. And because of the wide range statistically, the significance doesn't appear until the 20 ppm. And I will go into this data on the next slide, also.

But also I want to note that we looked at the historical data at 36, bracketing when the study was conducted in 2002. So we took 1999 to 2004, and the average range or the mean percent fetuses affected for litter was 1.1 with a range from 0 to 3.7 percent. So the 3.1 was the right here and these two are definitely higher than historical

range.

DR. FROINES: Somebody want to comment?

DR. SLOTKIN: So how is two a NOEL if the number of fetuses affected is twice that of the controls at the upper end of the historic controls, which I don't necessarily believe are valid. Against the matched group, you are getting a doubling of the incidence of affected fetuses at 2 ppm. So isn't that a LOEL?

DR. BLANC: That will be clear from your next slide.

Dr. LIM: Let's go to the next slide.

This is from Table 34. We can probably skip the body weight business and come down to the most important of this slide, where we exclude the litters 100 percent. Fetal death due to early absorption. So if we lost the fetuses, we don't count those litters. What we have here, what we are saying is if you just look at affected litter, for total litter, there is no change at 2 ppm. There is threefold increase at 10 ppm and a fivefold, sixfold at 20 ppm.

DR. BLANC: That's not actuall1y correct. Let me weigh in right now. Talking about fold increase. If you do the Chi-squared test for trends

on this data, Chi-squared test for trend has an absolute value of 54 with a P that is less than .00001 or something like that. Even if you have excluded the 20 part per million category, just use 0, 2 and 10, the Chi-squared test for trend is highly significant. And odds ratio for an affect for two part per million is 2.57. It is 9.2fold risk for the ten part per million and it's a 20fold odds ratio for the 20 part per million.

I understand that you were criticized by EPA, federal EPA, for identifying two part per million as a LOEL -- as a NOEL. They actually identified ten part per million as a NOEL. I understand OEHHA wrote that they supported your decision to choose two parts per million as a NOEL, but this example is even more blatant than that first one we talked about, in which two part per million, clearly, at best is a LOEL. And, once again, I think these data should be able to be examined in a benchmark dose way, and that is what you should do. In no way should you consider two parts per million a no effect level because your data doesn't support that interpretation.

DR. REED: Thank you. We actually from the very beginning looking at this set of data, we saw

benchmark does approach was best, so I did analysis for this particular data set. In the 2 ppm, the extra risk is about 4 percent. At 10 ppm, the extra risk is between 17 to about 20 percent. So if I were to find a benchmark response, if were to define it at 5 percent, the quote-unquote, NOEL or something equivalent to NOEL, the point of departure would be greater then 2 ppm, slightly higher.

DR. BLANC: I think the --

DR. HATTIS: I think that's the best estimate. What about the lower confidence limit?

DR. REED: I'm looking at the lower confidence.

DR. BLANC: I would have somebody double look at that. It doesn't make sense to me, mathematically, looking at the data you have.

DR. MELNICK: Alternative way to do that is to model the data and get within the range of experimental data and look slightly lower than that. I wouldn't use 5 percent. In that case I would use 2 percent or 4 percent or something like that. You don't have to pick 5 percent and say that is the level.

DR. REED: I totally understand, and it is something that we have to think about. We do not

have definitive percentage of responses with benchmark responses. Usually when we do benchmark response, we consider the severity of fetal effects is certainly severe. So it is possible for us to bring it down below the 4 percent. Yes, I totally agree with you.

DR. SLOTKIN: I want to comment. The comment you just made, we have to keep in mind in looking at these numbers that fetal death and growth impairment are the most extreme forms of affects. Because fetal growth is spared at the expense of the mom. It is only when you're pushed off the cliff that these things happen. So one of the basic questions, and since our objective is protection of human fetuses, one of the basic questions is whether the data which you been provided are really adequate to give an index for where this safety level is for human fetal exposures.

I think there are an awful lot of more sensitive endpoints that people in developmental biology would be using short of death and growth impairment.

DR. HATTIS: I want to growth impairment. I have a slide here, but I will spare you the slide in favor of telling you what it says. Essentially,

if you look at that fetal growth response, that is more or less linear for both males and females. Females are a little more sensitive. So that the 2 ppm result lines up almost perfectly or a little bit worse than what you would expect from plotting the two higher doses. So there is no evidence, and this is not at all uncommon for fetal growth impairment responses. It often happens that, essentially, what is happening is that the toxicant is acting as a text on the limit and sources that are available for the fetus to grow and develop. And that can be important because fetal growth restriction is an important phenomenon for environmental health exposures to all kinds of air pollutants. So it is important because it can help predict things like infant mortality and possibly some neurological impairment at doses where you can't make these direct observations based on human --

DR. SLOTKIN: I'll go beyond that. If I recall, the rabbit is an altricial species. That is born immature compared to humans. The human fetal growth spurt is a third trimester event period. That is when the fetus puts on its weight, which it will need in order to survive the transition from life inside to life outside. These studies all stop

in utero with the rabbit, which means that, in fact, it may be missing the major and most important phase of growth impairment in humans.

DR. FROINES: I didn't understand what you just said.

DR. SLOTKIN: In other words, if you want to protect human fetus growth, you want an exposure paradigm that encompasses the stage of development that corresponds to the third trimester which for the rabbit is postnatal. This is equivalent to stopping the exposure during the second trimester.

DR. HATTIS: This is a sensitive parameter and one that can be used for other kinds of benchmark doses that you might choose.

Dr. LIM: Should I move on?

DR. BLANC: What are you moving onto.

Dr. LIM: Good stuff. I think the point is clear that, if nothing else, 2 ppm cannot be the LOEL. I think we made that point clear, but it cannot be the LOEL as USEPA did in their risk assessment. The fact that we study as NOEL could even be the NOEL should even be lower.

DR. BLANC: Just clarify. You didn't organize this by starting with FIFRA data and not looking at sort of somehow look separately looking

at over acute exposure data, did you? You took the universe of submitted and published acute studies to look at, to answer your questions about endpoint. Right?

Dr. LIM: That is why the toxicity part is such a huge part in the document. And this has been distilled down from all information.

DR. BLANC: To the study that you chose for critical endpoints.

DR. HATTIS: This is not a published study. This is a study that is in the registrant's material, supplied to you by the registrant. Or am I wrong about that?

DR. LIM: I think this study may be published in the *Inhalation Toxicology* issue in 2009.

DR. HATTIS: There is new follow-ups to that study, but the 2002d reference that you have, I believe is to something that we don't have all the raw data points.

DR. BLANC: That's correct. You don't have a peer review publication.

DR. HATTIS: I assume this was part of registrant's supplied material.

Dr. LIM: It is registrant's supplied data,

but many of the studies that registrant supplied have been published. This one is published in 2009 that I cited. It should be in your references.

DR. HAMMOND: 2000 -- the Nemec 2000d is listed as a research lab DPR report.

DR. LIM: If you look on Page 83, where I summarize the study. I cited 2002d plus the 2000 --

DR. HATTIS: Just as a follow-up to establish the time, the active time. You think these data --

DR. LIM: The 2002 data was submitted, actual raw data in which we do all calculations on. So it would not be correct to cite the 2009 paper which is their summarized data. This is a case in which we have the actual raw data, where with the published data you are getting the summarized data.

DR. BLANC: I gotcha.

DR. HATTIS: I would like to have these data, in particular, accessible so I can do better analysis than I have done already.

Dr. LIM: I think a lot of these, because there is a study of individual animal data, and you have -- could be a lot of analysis on them.

A related issue to development toxicity is the window of vulnerability. This is important in the

PBPK modeling of the data. In this study the pregnant rabbits were exposed to during different times during the gestation. Group two exposed to six to 28 and then group three, six to 14; and the last group was exposed on GD 27 to 28. And they were exposed to only one concentration of 20 ppm, six hours per day and they are all sacrificed on GD 29.

So what we're seeing here is the fetal affect expressed in three difference ways. And when they are exposed from GD six to 28, they're is increasing the late absorption, as you would expect from the previous study. And if you look down to groups five and six, these animals were exposed only two days. First six hour on 23, and then they were rested. They were not exposed for the rest of the day and then they were exposed the next day at GD 24, and they were sacrificed on GD 29.

I think we can appreciate the timing is kind of interesting. Just looking at the data, what you see is already a late resorption with just two days exposure. And also if they were exposed on GD 25 and 26, you also getting increase in late resorption. The standard expression for developmental toxicity is that appears as fetus per

liter. If you look at it, it is not statistically significant, but mathematically we consider the affects significant. And this result is used to define what the window of vulnerability between GD 23 to 26.

That concludes all the acute end points.

DR. BLANC: Now I have a question for you, then. Because going through the literature, one of the really fascinating papers I came across is Buckle's 1950, acute inhalation study. And it is not cited in your document. Do you know why that is?

DR. LIM: I could have missed it.

DR. BLANC: I think it is relevant. He actually does -- it's more a lethality study. It was interesting in that he does have something which in terms of lethality is no effect level, and he has -- he shows -- it is acute exposure. And he shows considerable effect as 175 parts per million and there is no effect levels are between 85 and 90. And it differs a little bit in some of your other acute data. Suggests that levels higher than that have a no acute affect in terms of lethality.

I thought it was, first of all, relevant because there aren't that many inhalation studies,

as you know, and I think it is always interesting because the reason that he did this study in 1950 is because at that time they were considering the use of methyl iodide in fire extinguishers. And so instead of carbon tetrachloride. So it has some historical interest as well. I think his conclusions are quite interesting.

His summary point number one is methyl iodide should be regarded as at least as toxic as methyl bromide and about ten times as toxic as carbon tetrachloride. The point number two is there is often a lag time between exposure to methyl iodide and the onset of symptoms. To his acute lethal model shows that there is very little acute irritation in these mice and then the next day they are all dead.

DR. LIM: I think we see that in human case study with the delayed --

DR. BLANC: That is why I think these data are quite interesting.

DR. LIM: I have to get the reference.

DR. BLANC: *British Journal of Industrial Medicine*, 1950, Volume 7, Pages 122 to 124.

DR. LIM: Thank you.

DR. HATTIS: Are they suffering a

neurotoxic death?

DR. BLANC: It doesn't appear to be pulmonary edema because they don't have any -- well, just let me read you this:

For the longer exposure experiments a larger chamber, one cubic meter, was used. A measured amount of methyl iodide was introduced and samples of air removed for analysis as described above. Inhalation of 1 milligram per liter produced death after repeated daily exposures totaling from 11 to 43 hours. (Reading)

That is still kind of an acute exposure. At .5 milligrams per liter all animals appeared normal after a total of 125 hours and 20 exposures spread over 30 days. Gained weight equally in total. (Reading)

DR. FROINES: We should take a break, a ten-minute break before we start our next phase.

(Break taken.)

DR. BLANC: We are going to start. So we are going to go back, taking one step back, and we are going to just say something about metabolism.

Dr. LIM: The reason metabolism was left, we were concerned about how long the talk would be and all the toxins stuff. But Dr. Blanc would like at least for me to describe the pharmacokinetics study. In this study the rats were given C-14 and there were two concentrations. The 25 is for male and 24 ppm is for female and two doses. And then 233 for the male and 250 for the female. And it showed no gender differences overall. The data showed that 100 percent absorption and that the label was found in all these tissues listed here and Tables 1 and 2 in the document.

In terms of metabolism, the two possible pathways, conjugation was glutathione, mediated by glutathione S transferase, resulting in iodide reduction and there is also oxidation by side 3, 4, 15 is already in the carbon dioxide that is measured in the exhaled air.

The elimination is primarily by expired air. 50 percent and 30 percent urine and very little of it in the feces. In this study they also did oral administrations, as I recall. So this is quick summary of the study.

And I think Dr. Blanc would like to make comments.

DR. BLANC: The reason I want to get in discussion is because I really think if this is all the scientific record has, it's another vital and sort of fatal deficiency in the database. It's hard to go forward with this. I think Figure 1 as shown on Page 24 -- and I know you don't have a slide for this, but those who have a report. This is just not acceptable. This is just not an acceptable metabolism pathway figure. Even on the rat side, it's not. Certainly on the human side. And so this has to be addressed. And some of the clinical papers, even on human experience would better inform this. They certainly have theoretical metabolic pathways that are far more detailed than what you present here.

Dr. LIM: I understand that. This slide was not meant to show all the pathways. Just want to present a summary in the document. It is misleading to list that whole list of metabolites under urine. That is not all of it.

DR. BLANC: I would like something that resembles a normal metabolic pathway.

Dr. LIM: I will revise that.

DR. BLANC: I mean, one of the questions I had that I think the paper that has the rat exhaled

air carbon dioxide percentage as a big proportion going out as carbon dioxide. As you summarized the table, that is Sved [phonetic] 2003. Dr. Sved, this was, again, something that was data for the registration, not published in the open peer review literature; is that correct?

Dr. LIM: Yes. Those are two submitted studies. The first one was male and second female.

DR. BLANC: I would like to see data from the open literature -- just since you have seen it and I can't access it, how did they know it was carbon dioxide?

Dr. LIM: Label, C-14 label.

DR. BLANC: How did they know it was carbon dioxide? They know it was carbon coming out in the air.

DR. LIM: I can't remember the detail.

DR. BLANC: I want to be sure it wasn't carbon monoxide. I think you are aware that the two iodinated forms of congener - whatever the word is - is metabolized as methylene chloride is. I wouldn't suspect that the one iodide is metabolized from carbon monoxide, but I would like to be doubly sure that they knew what they were measuring.

DR. MELNICK: As in a similar vein, I'd

want to know if methanol formaldehyde were.

DR. HATTIS: As a modeler, it is almost impossible to make much in the way of inferences from total C-14 disposition data without knowing the chemical species at various times. So the most valuable type of data usually is measurement to compare compounds over time. So it would be -- it might be helpful to describe, now that you have had the PBPK Model, describe for the reader how that model is calibrated for the rats or otherwise. That is the significant part that tells us, okay, what is the internal loss rate for the methyl iodide versus the iodide itself. If it is disappearing quickly, that you have one kind of interest. But disappearing relatively slowly, then you have a possibility of this neurotoxicity or other consequences from the methyl iodide itself.

One clue to that is, in fact, the generations of the reactive cysteine. If you have cysteine, that essentially -- and you have a rate constant between cysteine and methyl iodide, then you can infer the area under the curve, the integrated area under the curve of the methyl iodide, is apparent methyl iodide in the blood.

DR. MELNICK: My point, also. I want to be

clear about it didn't go from methyl iodide, poof, to carbon dioxide. There were intermediates, which might be of importance to understand.

DR. HATTIS: Right.

Dr. LIM: We will revise that figure to show more of the pathway. Then look into the carbon dioxide, carbon monoxide.

DR. FROINES: There is a lot of glutathione in lung lining fluid. It would interesting to know about that.

DR. HATTIS: Yeah. Even more in the liver. The lung gets 100 percent of the cardiac output. The liver gets 5 percent. It's usually convention for PBPK model to put all the metabolism. That is not really right, but it's of interest to know exactly how quickly the methyl iodide is disappearing from the circulation.

Dr. LIM: Move onto subchronic. For subchronic exposure, inhalation toxicity, the two endpoints were identified. One for systemic effect based on liver weight and body weight changes in rats. And the other endpoint is reproductive and developmental effects also seen in rats. And the data for the study is shown in the next slide.

This is the same 13 week subchronic

1 inhalation toxicity in which now we are looking at
2 the decrease in the mean body weight changes. Here
3 we have week zero to one and zero to 13. So you
4 start to -- this one is significant decrease here,
5 but you don't know see it at 21 ppm, and the
6 decrease is 70 ppm. And another endpoint of note
7 was change with the relative liver weight over the
8 final body weight ratio, in which is increased at
9 the 70 ppm. And we think that this increase is due
10 to the reduction in the body weight because no
11 change in absolute liver weight. The decrease in
12 the body weight could be related to the decrease in
13 the food consumption of this group.
14 So we set NOEL at 21 ppm for this sort of
15 general systemic impact.
16 DR. BLANC: Table 11 modified.
17 DR. SLOTKIN: Why would you set the 21 as a
18 NOEL if there were, in fact, significant effects at
19 five?
20 Dr. LIM: Because we look at the next dose.
21 Then this was not statistic.
22 DR. SLOTKIN: There is no difference
23 between 79 percent and 84 percent. It's not just
24 whether they are different from controls. Whether
25 the different from each other. Obviously part of a

continuum and you have a little bit of noise in there, but it is fairly clear to me that you've got decrease in food consumption at five. You've got a significant effect on weight. Again, I am curious as to how you can have a no effect level of 21 when there are effects at five.

DR. LIM: We looked at the overall data and the question is whether we should base our NOEL on this particular endpoint that shows the decrease, this zero to one week, and overall seeing the change until the 72 ppm when we looked at the overall.

DR. FROINES: I think statistically it is a mistake. It is as though you are taking individual points and making decisions based on those individual points, rather than looking at the trend of all the data and the trend is exactly what Ted is saying. Trend is that there is something going on there. Whereas, if you just picked up, picked out 36 and compare to 34, you can't do that. That is not -- that is not a valid way of looking at it.

DR. HATTIS: Again, it would be a better general way to do the benchmark type.

DR. FROINES: Should. Absolutely.

DR. LOECHLER: Do you have any sense of what tissue is decreasing? Is this just weight

throughout the animal, or is there some obvious thing that is different?

DR. LIM: In terms of liver weight?

DR. LOECHLER: I am thinking overall weight. It looks like week zero to one they're ten grams lighter. After 13 weeks they're also ten grams lighter. If you take the number seriously, it is as if they have lost something. You know, they're just overall smaller. Or is there less muscle mass or any sort of analysis of specifically what they have lost?

Dr. LIM: In this kind of study what happens is that at the end of the study the organs are taken out, and the absolute weight is determined unless there is any gross histology. The gross observations are in the case. Then they record that. But I don't think that we -- that this study gives results about the particular tissue.

The other endpoint that we want to assess is subchronic exposure is reproductive and developmental effects. And for that endpoint we looked into two generation reproductive toxicity study. And this particular study it was done with rats exposed to methyl iodide: 0, 5, 20 or 50 ppm, six hours per day. For the parental generation they

were exposed during premating for ten weeks, during mating to gestation day 20. And then they were also exposed to gestation day five to 21. And this generation results in the pups --

DR. SLOTKIN: What is the rationale for leaving the hole in the administration paradigm?

Dr. LIM: It is because it is an inhalation study, and you don't want to take the moms away from the babies right after they are born. The mom's will be in the inhalation chamber for six hours, and you take them where you could. Confound the result for the pups.

DR. SLOTKIN: You don't think that that would happen at lactation day five? There is enormous literature about maternal separation effects on development, metabolism and the like.

Dr. LIM: This hole is patched.

DR. SLOTKIN: I have two concerns about the data that are acquired in this way. One is that the hole that is being left is the major hole for the developmental -- whole series of brain nuclei, and it is hole in which, for example, the entire mechanism of hepatic control of gluconeogenesis is being programmed. It is also the period of sexual differentiation of the brain. And, therefore, that

hole leaves, as I said, a gaping hole in developmental studies. On the other hand, the fact that the pups are separated repeatedly during lactation the dam introduces a set of confounds that essentially will produce enormous noise in the results, making it much less likely that you pick up significant effect of the methyl iodide exposure because of maternal separation.

Dr. LIM: During the lactation, day five to 29, the pups get the milk from the moms. They are exposed to --

DR. SLOTKIN: They are not separated from the dam during the exposure? I would think they are.

DR. LIM: They are, but then they come back.

DR. SLOTKIN: Maternal separation repeatedly for six hours. There is a literature of hundreds, if not thousands of papers, about how that screws up stress responses, endocrine status, metabolism, behavior and the like. So it is analogous to taking someone, hitting them on the head with a two-by-four real hard and comparing them to a control that works. But if you take two individuals who whacked one of them once with the

two-by-four and the other one twice, there is probably less of a difference between them.

What has been done in these studies to the control group, which also has the separation, you have produced this enormous confound of variability that makes your ability to pick up difference caused by additional treatment of methyl iodide much less likely and much less sensitive. I think what that means is we have to look at the data, thinking that these kinds of results are going to be skewed towards a beta error.

Dr. LIM: In that case that was the study design. The same thing happened with the second generation which have from pups to their postnatal day 28 to gestation day 20. This is when they were mated. And then the rats get pregnant and then they give birth and then the end. There is lactation day five to 21 exposure and this generation produces the F-2 pup.

So when we look at pup results and the pups were exposed during in utero, during gestation as well as postnatally with the milk. For this particular study they were productive NOELs was 20 ppm for reduced live litter size for both generations. We are more interested in the

developmental NOEL and lower LOEL of 5 ppm resulting in reduced mean pup body weight as well as delayed development. And this is the NOEL that will be used to assess subchronic exposure.

Here is data. The yellow is the NOEL. And the 20 and 50 ppm up here. Here is the F-2 pup. Body weight in grams for day 14 and 21. And it is very clear at 20 and 50 we have the decrease in the body weight, and some changes at 5 ppm was significant. Females at day 14. And then the developmental landmark that are used they were done on the male pup and the female pup. And the F-2 pups were not assessed. We have only data for F-1 pups for the males. We have usual separation. And the way to gauge delayed development is how many days it take for that to occur. It takes longer. And also another measurement is the body weight at which time that occurred.

So in this case when the male, there is -- it takes a little bit longer and the body weight is less. More importantly, more interesting, female pup for the vaginal patency, which is the day for that to occur is significantly -- takes longer. Showing the late development at 20 ppm and 50 ppm, and that the body weight. This goes with the

delayed development, that they are higher body weight at that time. So the NOEL is set at five ppm.

DR. HAMMOND: I would like to comment. First, I understand that for a lot of these studies you are using -- you didn't do the experiment. You are trying to make use of the experiments that others have done. A lot of the experimental problems we have cited we need to note them, but understand you didn't make those decisions. But the decisions you do have to make are how to interpret the data that you do have, as here. And it looks to me as if in almost every row, as you go across, whatever effects you are seeing, it may be attained statistical significance at 20 ppm, but we actually see the beginning that trends at 5 ppm. And it happens in every single lot. Every line. Whatever going across the way started to go up when you hit 5 ppm.

DR. HATTIS: Moreover, you have the same kind of tendencies you saw in the rabbit developmental toxicity observations in utero. Again, every female being a bit more sensitive than the males. I bet if you make a plot, looks it might be more interpretable as it continues response than

as before.

DR. HAMMOND: I guess my point is we don't have to say this every time it comes up. But this is once again an example where, if are just by statistic significance one-on-one, maybe it doesn't attain that level. But if there is a trend analysis, then there is clearly in every single one of them you are seeing the trend. I guess it is part of the same trend. Its not a sudden departure from the trend when we get to 20 ppm; it's already started moving.

I think it is important we are trying to define the level. This is, again our benchmark dose. It is a way of looking at trends as opposed to statistical significance.

DR. HATTIS: It is important to notice that lots of these types of conclusions follow from imposing a traditional toxicological view of data, and there is another way of looking at the data. I think it is more indicated by the information that you have in this case.

DR. SLOTKIN: I think also given the limitations of the study design and knowing that the design has increased the chance of a beta error and considering the information about growth

impairment and the like, that one might also want to regard these kinds of data one failed. In which case some of those things that are not significant may become.

DR. HATTIS: The other thing I noticed in analyzing the rabbit data parallel to this. There is a slight disconnect between the doses as stated in milligrams per kilogram day and those dated as ppm. So just as a technical point, it is possible that there is a difference between the nominal concentrations that the authors intended to use and the actual concentrations. So if you have analytical data on what actually was in the exposure percent, you'd probably want to use that in a dose response analysis rather than minor technical.

DR. FROINES: I think that we have a problem that I think we need to acknowledge; and that is that this issue has come up today at least maybe five times. It is almost as though we have an etiological issue going on. That is that we are not looking at trend and we are not looking at benchmark. We are trying to pick out NOELs in a very traditional toxicologic context. So I think that this panel is unanimous in asking you to go back and look at this issue from this different

perspective. Because I think that this committee is concerned about, precisely about, the trends that we're seeing and that we're seeing the problem repeatedly. So it becomes an issue that between now and the next time, when we get together and the third meeting, that this is an issue that really needs to be -- I said everything I was going to say.

The point is that I think that we have a really quite fundamental issue that represents something of a disagreement. And, again, it is not your data. It is your interpretation of the data. I would ask you from the point of view of entire committee to look at this issue that we would, I think, simplistically called the benchmark issue or LOEL/NOEL issue. Because I think we're getting --somebody speaks to this issue each time, and it may not be the same person, but it comes up repeatedly. I don't mean that as a criticism at all. I mean it as a friendly gesture.

Dr. LIM: We are fully aware of some these data need to be analyzed with by BMR. One of the issues we would like to here from the panel is what level of BMR we should be using. I think that is very complicated --

DR. HATTIS: That makes it more explicitly

a policy call, rather than your side is -- this is the point at which there is no effect. It's something you have to discuss with your people who know the effect you're modeling and with your management to make appropriate value-related choice of where to set BM marker.

DR. LIM: I don't think the management comes in in terms of this kind of policy. By asking for recommendation from the panel knowing the database.

DR. BLANC: Well, just to clarify. We are talking about the subject. What you are essentially saying is that the percent lower limit based on presumed normal distribution and whether you've got the confidence level or you interval or you go out farther.

DR. HATTIS: No. The issue of what percentage of pup weights do you want to guard against. And I called that as a matter of policy. But it is to some extent it draws on how seriously consider different degrees of change of this endpoint as a predictor of potential health problems. So people have tried to do this on the basis of a certain number of standard deviations of a normal population. That is one way of setting an

overall policy. That sort of treats all different kind of endpoints the same. And I am not sure that that is right. But I don't have a magic formula to recommend to you.

But maybe as a round number candidate for consideration a 1 percent change in body weight is something of that sort is not out of question as a BMR. Who knows? Other people are going to have.

Ron, you perhaps have faced this issue.

DR. MELNICK: I would base it on modeling the data and using the excess risk in relationship to the experimental data, such that if all of the data, for example, are 30 percent, 40 percent, 50 percent male, you go down 10 percent. What you have is a trend that is down less than 5 percent. Then you want to go slightly lower than 5 percent.

DR. HATTIS: Slightly lower.

DR. MELNICK: Something lower than the experimental data.

DR. HATTIS: That is another way of approaching it. That is not a bad idea. But it is still the reason I have reservations about it, is that it depends too much on the vagaries of what the experimenters have chosen to do with their experimental doses.

DR. FROINES: Dale, the trouble, the reason why I like what Ron's saying is that we can't choose those experimental conditions. And so what he really is saying that is we need no make some sort of public health decision about the numbers that we think is relevant. And I would argue that that is exactly what we should do, and not get into the experimental design, which I think we all know there may be problem with the experimental design. And that is another issue which we haven't spent a lot of time on.

DR. HATTIS: If somebody from a community that is concerned about health says, "Oh, you shouldn't have done 1 percent, you should have done .1 point percent, I don't have a strong argument.

DR. MELNICK: What you're saying is how much confidence you have in that estimate when you selected it to be 1 percent or 10 percent or one-tenth percent. It's within the range of experimental data. We are saying with these data here, in the range of 2 percent we are quite confident that that is a pretty good representation of the data. Therefore, that --

DR. HATTIS: You want do some number of standard errors, then.

DR. MELNICK: A point of departure which is what --

DR. HATTIS: The issue is you consider what your standard error is and what seems to be a level that you could reasonably detect off.

DR. FROINES: What I'm saying is I want to go one step further just as a way of thinking about it. I want -- I think that DPR should acknowledge that this problem exists and that you folks need to -- you may come to 4 percent, 2 percent, 1 percent, one-tenth percent, one-thousandth percent, but there needs to be some acknowledgement that that is an issue rather than simply saying our number is two parts per million, which we all recognize very -- everybody at this table recognizes this is not an appropriate way of approaching it, scientifically speaking.

DR. BLANC: Just pragmatically, John, presume that they do these calculations and revise the document to reflect them, then what I think I hear you saying is that in the description method there should be a brief discussion that says we have elected to do this kind of analysis because there is a fundamental problem with trying to identify no effect levels, low effect levels, based on pairwise

comparisons of very small strata of data in experiments that we did not design.

If fact, Dale, wouldn't there be such language from the new document that you have discussed?

DR. HATTIS: You know it better than I. You wrote it.

DR. FROINES: I don't remember that.

DR. HATTIS: I don't remember that, but there is older -- basically, in the justification for the benchmark dose procedure itself there is language of that sort. But it still begs the question about why you think that biological significance, what you think about the significance of various amount of changes of different parameters.

One of the justifications that you can use is by noticing that the normal, the unexposed population has a certain variation. Statisticians have defined some number standard deviations of that population as an indication of how seriously nature takes that parameter because it exerts energy to control it within wider or narrower limits.

DR. FROINES: I would say two things, one thing. Two things, maybe. One of which is what Paul just said, if I were DPR, I would take that

section of the transcript and take it out exactly as he said and stick it in my document. I think it was so articulate that it really does address the problem. And then I thought, well, we don't need more than what Paul said. But, actually, what you just said is equally articulate. And I think these two thoughts are where we might argue as good starting points and you guys have to decide the number in the end, not us.

DR. BLANC: In this very specific case, ironically we are discussing now based on the comments on the experimental design of the separation issue. One would expect in your zero exposure group to have potentially more error or more variability so you may have to have some other approach to deciding what percentage is a departure.

DR. HATTIS: We haven't solved this BMR definition problem for you.

DR. FROINES: It's in their hands. You will keep trying to answer their questions.

DR. BLANC: I do think, also, as a very simplistic comparative value, if you want to come up with comparative values, I would take everything today, except for one instance which you said no effect level and I would calculate what would happen

treating that as low effect level and dividing by ten or by a hundred, depending on what the endpoint is, and see the traditional approach yield.

We have often found, if you come to very similar values by using different approach, they tend to reinforce. Because I think at the minimum, we have to treat these in each of the instances what you called a no effect level as being a low effect level, if you took the traditional safety factor approach what you end up with.

DR. FROINES: Can somebody tell me what time it is? Quarter of four. You have how many slides left.

Dr. LIM: Fifty slides.

DR. FROINES: This is slides to go, 50?

Dr. LIM: Yes.

DR. HATTIS: We have been as helpful as we are going to be.

DR. FROINES: I would propose, people, if people are willing, that we go till 6:00. But that means that at 5:00 or thereabouts, this panel have to talk amongst itself about what kind of work we are going to do over the next couple months.

DR. HATTIS: I have to leave at five.

DR. FROINES: I don't think it would take

--

DR. HAMMOND: He has to leave at five.

DR. FROINES: I think we can discuss -- I think we know pretty well what each person's in this room expertise is. So my sense, that we can do that pretty fast.

DR. SLOTKIN: Or first thing tomorrow. Just come a little early. That way it's not pending at the end.

DR. FROINES: Let's meet at 8:00. Okay with you?

DR. MCKONE: Yes.

DR. BLANC: Is the building open?

MS. VERDER-CARLOS: Open at 7:30.

DR. FROINES: You're leaving at five. We should be going as far as we can. I'm very worried about not having every member of the panel here, but we will have to see where we are at 5:00.

DR. MCKONE: I can go to 5:15.

Dr. LIM: I am going to chronic inhalation toxicity. This is -- we have only one inhalation tox study. In this study the rats were exposed to methyl iodide. The concentrations on the slide. And the key endpoint is with the inhalation, the salivary gland and the NOEL at 5 ppm. The data is

shown on the bottom here, where there are four out of 49 at 5 ppm. And female is three out of 55. and that is positive trend. Significant elevated incident for 20 and 60 ppm.

DR. BLANC: Yeah, I'd say. Universal squamous meta plasia. Let's not beat a dead horse. This one you have to absolutely do the same kind of benchmark. This is -- it this one isn't obvious to you why this a problem --

DR. HAMMOND: How about a sign, no NOEL, Benchmark dose?

DR. BLANC: No LOEL. No NOEL.

DR. FROINES: We are being respectful. The sign is how would you feel?

DR. HAMMOND: What I really mean, actually, with I really mean is I'm trying to say, I'm just giving us a hard time. I think maybe -- I respect them enough to think they got the point. And maybe we just say at this point will carry over to many other things.

DR. FROINES: Kathie, I apologize to you because I didn't really mean -- what a really meant to say got to find a way to keep Dale Hattis from solving the problem. They have to work on it.

DR. BLANC: From the panel, a biological

comment on exposure, which induce's almost 100 percent squamous meta plasia. Does that give us any biological --

Dr. LIM: It is known that iodide is concentrated in the salivary gland.

DR. BLANC: A mechanistic dose. It gives us a potency sense or who are our cancer people.

DR. LOECHLER: I don't have a comment on this.

DR. HATTIS: If is meta plasia, they are deliberately choosing a noncancer word.

DR. MELNICK: That raises to the issue in terms of histopathology. Since all we are seeing are numbers, we have no idea whether this is reviewed by one pathologist or a pathology review assessment that is done. What is the quality of the his pathology? We are assuming everything is fine. Don't like to assume. But pathologists differ in their diagnoses, and we are not capturing any of that by looking at summary data.

DR. BLANC: Is there something peculiar about rat salivary hyperplasia? I am asking. I don't know. The question is there something where no pathologist will ever call it cancer in a rat salivary gland no matter how hypoplastic it is?

DR. FROINES: Can we make that a question that one of us will address over the ensuing period?

DR. MELNICK: On a later lesion when we have hyperthyroid plasia, hyperthyroid adenoma there is some difference of opinion.

DR. FROINES: You know, you just won yourself at least a part-time job.

DR. MELNICK: As what?

DR. FROINES: By showing you had some level of knowledge where others were saying I don't know anything.

DR. LIM: Moving on to oncogenicity. Another big issue. This is the weight of evidence. The evidence is no data for human and the data we rely on in terms of cancer is laboratory animals, with thyroids tumors in male rats and in male mice. The astrocytoma in male rats and cervical uteran fibroma in female mice.

DR. MELNICK: Is this your category chronic or lifetime?

Dr. LIM: Lifetime.

DR. MELNICK: An 18-month male study is not a lifetime study. Even a two-year study is not lifestudy.

Dr. LIM: For a rat?

DR. MELNICK: Equivalent to a 60-year-old. It is not a lifetime study.

DR. HATTIS: Of course, it starts as an equivalent to teenage years.

DR. MELNICK: These are not early exposure, so it is not lifetime. Two-year study or 18-month study, wouldn't call it a lifetime study.

DR. FROINES: I did a chronic and bioassy on arsenic, and we stopped it at 18 months. I would say I have felt bad about that ever since because I felt we did not go anywhere near long enough to really see what we hoped to see in the various cancers. And so I reinforce the point they have based on my own laboratory experience.

DR. MELNICK: Did you begin in utero because that is where some of the arsenic carcinogenicity --

DR. FROINES: Don't embarrass me, please.

DR. LIM: This is a study design issue and we are limited to what was actually conducted.

This table shows the data. The rats exposed by inhalation. And what I have here is the male and female, the three-dose groups plus the control. The first part is the thyroid follicular cell tumor with adenoma and carcinoma with the incidence indicated.

We have the much higher incidence in the male versus the female. That is consistent with the greater thyroid effects in the male, including increase in the thyroid organ weight and some hormone changes.

The other tumor endpoint looked at was astrocytoma with benign and malignant and a combined. Again, the greater incidence in the male versus those in the female.

Later on we will talk about using the NOEL as far as a policy factor to assess cancer. And this highlights that the 20 ppm as the NOEL for the thyroid tumor with the incidence of 4 of 49 for the 20 ppm and the control is 4 of 45 and 60 as 12 out of 42.

DR. LOECHLER: That is NOEL under the assumption that the MOA involves perturbation of thyroid hormone?

Dr. LIM: Yes. I will go into that a couple slides after this.

The next slide is mouse study which the mice were exposed to methyl iodide that was micro encapsulated and in the diet. This was an oral exposure. Again, we are seeing the thyroid tumors with high incidence in the male and very low in the female. And then what was interesting was in the

female is the fibroma that was surrounding the cervix and rear end. And in the combined you see a positive trend, and this is the one of the endpoints that went through the pathology special review and all that. And their conclusion was that this was not treatment related, but we think this is something that we should add to our weight of evidence in terms of the oncogenicity of methyl iodide.

DR. HAMMOND: May I ask a question? I have seen this several times. I just keep wondering what does it mean when you have asterisks next to your control reports?

DR. LIM: That is a trend. That means it is a positive trend.

DR. HAMMOND: It refers to the whole line?

DR. LIM: All the way across.

DR. LOECHLER: Could you repeat what you said about what the pathologist said? There was a word in your sentence that I didn't quite catch.

DR. LIM: This particular data that went a special pathology review that tries to decide whether this was treatment related or not. I think the collusion was that it is probably not, but whereas we think that it shows some kind of a

control growth. So we add that to our weight of evidence.

DR. LOECHLER: Why did they think it wasn't treatment related?

DR. LIM: I don't remember all the details of analysis, but it is in my document.

DR. BLANC: Just a logic question. If the cervical and uterine fibroma is contributing to your weight of evidence in terms of oncogenicity, why doesn't the squamous meta plasia of the salivary gland contribute to your weight of evidence?

DR. LIM: We use that endpoint for chronic toxicity as a noncancer endpoint. So we already are using for that. I could see that you could add that as preneoplastic kind of effect added to it.

DR. BLANC: It comes back to Tom's earlier points this morning. Let's take a step back.

Our first question is: Is this a carcinogen in laboratory animals? When you get to it, it's a complete slam dunk; it is a mutagen. That is beyond question. We are asking the question: Is this a carcinogen in laboratory animals? And can we go beyond the issue of thyroid follicular tumor alone. Which I think you were very appropriate in saying, "We are not going to assume that because of iodide

perturbation and the other - this is a methylating agent." It goes preferentially to the thyroid. One can imagine a scenario where the thyroid gland gets methylated more than other glands that has nothing to do with iodide perturbation.

This is certainly an area in the document where the issue, leaving aside do I have a number to use for my benchmark and what is the NOEL. First lets decide if it is a carcinogen. And if it is, then I think it is quite appropriate to think about all of -- the lack of threshold issues that we generally start to think about with a carcinogen. If that is question on the table, then, yes, I would say that the squamous meta plasia salivary gland and other organ where, as you pointed out, the iodide is preferentially being taken up and, therefore, there is more of a chance of methylation of critical structures. It is exactly the organ you think you would you see meta plasia in. Isn't it? And that you can't argue is because of iodide perturbation. Because an acute dose -- where actually a lot of iodide, they get it from meta plasia of the salivary glands?

Dr. LIM: On Page 149 of my document where I talk about structure of activity relationship, on

Line 26 I list the language in which the animals were exposed to potassium iodide. They saw squamous cell carcinoma in the salivary gland. I see your point where I need to add that to my weight.

DR. FROINES: Just to add a very minor point to this. There is the two studies that you didn't quote. One is the Druckery [phonetic] study and the other is Poi@rEa study. And, as you know, the Poi@rEa study found lung tumors in strain A mice. And I forget the detail on the Druckery study. But we need to look at the whole database and not just select from it ones that are for analysis.

Dr. LIM: We didn't. Those studies are described in the document. There is some concern about the design of the experiment, so I didn't cite, carry forward to the discussion. Certainly could add it back in.

DR. FROINES: I would argue that we need -- there is certain attitudinal issues. I think we have to be careful about this notion there are concerns about studies. Because there are always concerns about studies and that enables you to make, draw negative conclusions. And that is not necessarily the approach that would lead to the most

greater protection that we would like to see. I think that, yeah, I can tell you about 25 studies of mine that have problems with them. But we got to careful to not draw conclusions that lock us into a corner, I think. And so that is all I have to say.

DR. BLANC: Have you had a chance to look at the ACGIH commentary on why they label this carcinogen, likely carcinogen in humans? Pretty strong language. Usually their documents have supporting discussions. So I think I would recommend highly. I haven't seen it. I don't have that whole set. That is the American Conference of Governmental Industrial Hygienists.

DR. FROINES: I think you can look this up. I couldn't find it yesterday. But I read that the German Mac Committee said that methyl iodide is unmistakably an animal carcinogen. And so that adds some weight, because the German Mac Committee is a responsible group of scientists.

DR. BLANC: They probably said unmishtaken [phonetic].

DR. LIM: At same time at Page 12 of my document, NTP in 2005 delisted methyl iodide as a carcinogen. And then the IARC also revised their classification as to nonclassified as to the

carcinogenicity to humans, but in California it remains to be listed as a carcinogen.

DR. FROINES: I understand all that. I chaired the committee on carcinogen denitrification for NTP, so I have had some experience with that. And certainly Ron's spend a whole career on this. The NTP decision was based on IARC changing point of view. So the two don't reinforce each other. I think that is important, too. The two are actually linked.

Now I haven't talked to Vince Cogliano recently, but we can actually talk to him and see where IARC is on methyl iodide. They may not be looking at it.

DR. MELNICK: They are on the hundred known carcinogens.

DR. FROINES: But you are right, IARC did make a decision that it's a class three. That is relevant evidence that we need to take into consideration.

DR. MELNICK: Could I ask something on this study? It is 18 months, not two years in your slide. But more important, did you look at the chemistry related to the dose feed, because, obviously, methyl iodide was micro encapsulated

because it's a volatile chemical. In a micro encapsulated form you need to be sure that they analyzed the feed afterwards. Because mice nest in their feeders and as a consequence, you can dissolve some of the gel capsules. A lot are gelatin capsules. They are made to break down once they are ingested. And if that has happened, the dose that you think was being administered was maybe significantly lower. You need -- if you look at the chemistry and you can verify, that is fine. If it hasn't, it needs to be done. That is why I'm looking to see the study report to see what was the chemistry on this particular chemical.

DR. LOECHLER: So I had a question. I noticed that you haven't highlighted the female thyroid hyperplasia, which also looks to be statistically significant. And perhaps the first step toward complete neoplasia. Would you consider that also to be further evidence, corroborative evidence, of progress towards cancer with methyl iodide?

Dr. LIM: I'm still looking at that data suspiciously. I can't figure out why there would be a gender difference. I went to great length in the discussion about that. So I'm not saying it is

negative, but it does strike me odd.

DR. MELNICK: To answer your question. I believe there is a continuum hyperplasia adenoma, carcinogen. Yes, that would be highly significant.

DR. LOECHLER: Both male and females have elevated hyperplasia. And so that should probably also be included as an indicator. Also, just wondered in this particular table I assume -- no, it is not in this table. Must be the previous table.

DR. LIM: I just checked. Hyperplasia incidence in females are lower than those in the male. They are elevated incidence, yes.

DR. LOECHLER: In one of tables, Table 27, I want to make sure I understand. Slide 20, I assume this is just a little mistake. Under thyroid follicular tumor, zero dose. There are no adenoma, one carcinoma and no adenoma plus carcinoma. That should be one?

DR. REED: Yes.

Dr. LIM: This should be one; zero plus one is one.

DR. FROINES: We obviously have a time problem. Can I suggest that there actually isn't significant debate about whether or not methyl iodide could cause cancer. EPA agrees with it and

DPR agrees with it. But the issue is really not so much whether or not it is a carcinogenic agent, but what I would call the mechanism - others call MOA - and also the approach to given the mechanism, given the approach, to the issue of multi-stage modeling or threshold modeling. In other words, there are a number of issues that are not controversial than the actual designation of the material as a carcinogen.

Dr. BLANC: That is actually why I was emphasizing multiple sites and coming back to the question about -- I guess I could have been more clear and said that the question is: Is it a carcinogen beyond the thyroid? Because I think that is where the difference is between your view and the EPA. Because the minute -- and I think you're right in making the argument. The minute you limit yourself to the thyroid, then you get into the data and, okay, it is the thyroid because it is perturbation and iodide, and, therefore, its an effect which is very narrow, which has a threshold and, therefore, you shouldn't use modeling that would assume absence of a threshold. And you would have to get in that threshold substantive.

I thought you were quite correct saying it could be for thyroid. It fits that. But there are

equally other plausible mechanisms.

DR. FROINES: So let's go on.

Dr. LIM: Which is exactly the next slide. Where we say the thyroid tumor is a non-genotoxic mechanism. With perturbation of that thyroid function we need to consider the possibility of a genotoxic level action. The other tumors we don't have the data, so it is going to be assumed that is a possible genotoxic mode of action.

DR. BLANC: What I don't understand in your argument, why doesn't the overwhelming evidence that this is a mutagen and genotoxic in other systems, not come into the oncogenicity weight of evidence? Why isn't that relevant?

You have this sort of thing where you have them separated out as if they are unrelated issues. Is it a muted gene or not?

DR. LIM: Because the way you treated in terms of quantitative assessment is that it was non-genotoxic. That is the NOEL and the genotoxic that gets to use the non-threshold, so it sort of goes into next.

DR. LOECHLER: So as I understand it in the report, you treat it both ways, included both in the report?

DR. LIM: In the end we said that we need to look at risk based on this mode of action.

DR. BLANC: When you said for other tumors possible genotoxic default. That would be like all the stuff that you have there genotoxic mode of action for thyroid is equally true. It is not just that it is a default for the other tumors; you know this thing is a potent mutagen.

DR. LIM: Right.

DR. BLANC: So the presumption, it is not even a default.

DR. LOECHLER: Let me try saying this a different way. You have two different approaches that you take, assuming two different MOAs. You're going through an exercise. And you look in the end as to which one shows you greater concern. That is worst outcome in terms of public health when you say, "Well, that is the one that we need to pay attention to when we issue our final assessment" And the one that gives you a higher value, we can ignore because it's not really relevant when we have one that is a greater concern. When you go through that exercise, then this non-genotoxic MOA, while very interesting, disappears from the final analysis or the final assessment.

Dr. LIM: Depending on incidence. You could have the opposite effect in which we have greater concern if your risk was based on the NOEL versus the potency factor. We are covering both grounds, and say we are taking the one that says this is showing in greater risk, and we are going to go with that.

DR. FROINES: I want to make sort of a generic argument that Ron may speak to as well. In the early 1990s IARC added to their way of looking at chemicals to include mechanism of action into their consideration. So mechanism of action became a criteria that was very important. That, for example, led to ethylene oxide going from a B-1 to an A. And we could give other examples of how chemical status change depending upon how IARC viewed mechanism of action.

And I want to make an argument here that in a sense doesn't disagree with the Panel, but I want to be very clear. I think muted genicity is, in fact, a very clear and specific mechanism of action. It is not just a bunch if AIMs test that we did in the 1970s. It is not simplistic. Muted genicity and a strong evidence for muted genicity, things like 06 methylguanine and so on and so forth that we have

a list a mile long here. That to me represents a mechanism of action; and that to me argues in favor of looking at methyl iodide from the standpoint of its carcinogenicity. If I then throw in the fact that it's got a very weak carbon iodide bond and it's a very strong alkaline agent, what we are talking about -- what I think we are talking about is not MOA, whatever that hell that is, we are talking about a mechanistic decision which, I think, we need to understand in the sophistication of our modern science.

Is that fair?

DR. LOECHLER: I would like to make another comment. Something I would love to get into, but in the interest of time I won't. This has to do with this hypothesis that thyroid hormone perturbation is involved in the thyroid tumor formation. That has to do with the levels of the thyroid hormones that are reported, which I will just say have in many cases show very small perturbations. And the only one that shows large perturbations is TSH where there are these huge standard deviations. You commented on this on Page 56, where, for example, the TSH level in animals what carcinomas range from 2.27 to 36.86.

And I just don't understand, first off, how the range could be so huge; and, secondly, given that it is so huge, how that could understandably relate to the mechanism of carcinogenesis given the fact that these things are supposed to be correlative, at least, and you don't have any correlation between a high level of TSH or whether there is a tumor out or not.

I don't think we need to discuss this now. I'm just going to note it and we will discuss it at some future point. I would love to get this data to look at because I think it's unusual.

DR. LIM: I think the problem is that TSH was only measured at 52 weeks and 104 weeks. We're taking a tiny snippet of what is happening with TSH. Makes it very difficult to interpret as to what is going on.

DR. LOECHLER: Several groups have made a point of using those data to support this particular hypothesis. So I think it is critical for us as we think about this particular hypothesis to look at that data very critically and decide whether it is supportive of the point of view of MOA as it's being purported to be.

DR. LIM: I totally agree.

DR. MELNICK: On the mechanistic issue, you've broken it into two boxes, a genotoxic and a non-genotoxic. What about the concept of merging the boxes because the non-genotoxic is based on the hypotheses that you increased TSH and you are getting increased cell turnover and increased cell mutation. All you're doing in the presence of a mutagen, which doesn't require all of that.

So can you derive an approach that could look at both events happening, since we note that the methyl iodide is reaching the thyroid based on the C-14 data. And it was even in higher concentrations than in other organs. Why not use that as a third approach?

DR. LIM: Quantitatively, I am not sure. Because right now the standard way of doing using a NOEL is to have a threshold. So you're saying something in between so, mathematic -- eventually this is all going to come back to the equation of exposure times potency factor or HEC over the human levels. It eventually comes down to a mathematic equation. So I am not sure how you could merge the two and to do that. Concept-wise, yes, I understand but --

DR. HATTIS: Let me ask a related question.

Has anyone done a bioassy on inorganic iodide? Has anybody shown that iodide itself in excess is an inducer of thyroid tumors? Because in order to support that, that would be evidence that methyl bromide could have done that by way of releasing iodide.

DR. LOECHLER: There is a study. And as I understand it, there are no thyroid tumors from tests in iodide perturbations in thyroid, but you do get the squamous cell carcinomas.

DR. LIM: On Page 149 I describe the study where the iodinated glycerol causes thyroid cell carcinoma, but that was only in a low dose. This is various effects. I don't think there is a really good study connecting that axis iodide in thyroid tumor.

DR. HATTIS: But is there a negative bioassay that could allow you to set a limit on how carcinogenic iodide itself could be? In which case you could perhaps use that as negative evidence.

DR. LIM: I have to think about that.

DR. FROINES: On Page 149 of their document, Dale, it does appear that there is some evidence in F-344 rats given potassium iodide for squamous cell carcinoma. And that is not a good

one.

I don't know what you do with this data on iodinated glycerol.

DR. HATTIS: I don't either.

DR. LOECHLER: There was an argument being made that structurally methyl iodide and iodinated glycerol are similar in structure and, therefore, without going through the details they ought to behave similarly. And I just think that they are structurally similar and the kind of arguments that are derived from the premise that they are structurally similar is flawed, or it's weak.

DR. FROINES: What page is the potassium data on?

Dr. LIM: 149.

DR. HATTIS: For the -- look at the implied -- what is the dose of iodide that was tested in squamous cell carcinoma experiment? If that didn't have thyroid tumors, that gives you some, at least something you can use. Although the presence of squamous cell tumors --

DR. MELNICK: I think there was a paper on that.

DR. HATTIS: A thousand ppm in the diet.

DR. FROINES: We are looking.

DR. LIM: Potassium iodide in the water, in the drink water study. On Page 149, Line 21.

DR. FROINES: Thousand parts per million.

DR. HATTIS: That sounds like a lot to me.

DR. FROINES: I think it is.

DR. HATTIS: If that is not giving you thyroid tumors, it's possible you should draw it.

DR. MELNICK: There are rats. No tumors in the rats. Carcinoma in the salivary gland.

DR. FROINES: Where is that?

DR. MELNICK: Reading the abstract.

DR. FROINES: Salivary glands, squamous cell cancer and not --

DR. MELNICK: No tumors observed in the thyroid.

DR. LOECHLER: It's not arguing the mechanism that is being used.

DR. HATTIS: I think methyl iodide is not likely to be -- I would like to get the calculation of the dose that they get. It sounds like quite a big larger dose than iodide for the thyroid.

DR. MELNICK: They could go to two stage study. They had a medium effect with the iodide. They didn't get tumors alone.

DR. LOECHLER: I have to look back in the

EPA document. I actually think that the level of iodide could be very higher than from the methyl iodide treatments. May very well be higher than this level here. We are just going to have to go back. That is something I have dig through.

UNIDENTIFIED PANEL MEMBER: The level of iodide is quite huge when you give methyl iodide.

Dr. LIM: Should I move on?

This slide summarizes all the genotoxicity studies. So the positive studies, in the interest of time I won't go through them.

We found studies that category of gene mutation, structural chromosomal aberration, DNA alkyation. Some negative studies. Overall, we look at database and weighted on the positive study to indicate that methyl iodide is a toxic compound.

And so this slide shows the two approaches that I have been talking or three. Certainly genotoxic mechanism that we use a threshold method for NOEL at 20 ppm.

DR. FROINES: There are two negative studies, FIFRA studies or academic?

Dr. LIM: The two, the gene mutation of chromosome damage, they were conducted under FIFRA guidelines.

DR. BLANC: But the EPA rejected the salmonella study because they didn't demonstrate that they prevented offgassing, but the Department of Pesticide Regulation found it acceptable that. That confused me.

Dr. LIM: I need to go back to the study. I can't explain what that means.

DR. BLANC: That was not part of the review process; it came to you that way.

Dr. LIM: Came that way. We can certainly clarify that.

DR. BLANC: I would clarify that.

DR. LIM: Over all we believe that the database shows methyl iodide is genotoxic.

DR. BLANC: It initially came through as strongly in your test as in your oral presentation. I think you kept throwing in the words like "probably might be," "could be."

DR. FROINES: We have added a number of studies on mutagenicity and so we will make available to you the list of mutagenicity studies and DNA added studies and hemoglobin additive and a what have you, since there is a very strong list. Just make sure that we are all on the same page. 'Cause I think Ed has some. We have some and then

Kathie Collins from Berkeley had the guanine study.

DR. BLANC: Is there actually a table in which you listed in one place all of the mutagenicity studies in tabular form?

Dr. LIM: Yes.

DR. BLANC: That is table number.

Dr. LIM: Thirty, Page 76.

DR. BLANC: That is good. I am not sure for the purpose of that table, why the FIFRA guidelines study should be broken out. But I do think that in the table it should say that there was no increase mutagenicity, but potential off gassing means that there was no exposure, means that critical, the fatal flaw in that study isn't mentioned. You see the very first thing as negative study. Casual reader might think that the FIFRA guidelines study makes it is a more definitive study when it is a far weaker study.

I don't see any reason to separate it out and to the separate categories because it is FIFRA. But I think you should make clear that it is uninterpretable study and then you can add -- I wouldn't have this differentiation between published study and the FIFRA study. I would comment somewhere in the little box that it was not peer

reviewed. As well as adding the extra studies that they are going to give you.

Dr. LIM: So back to the threshold and non-threshold. To determine the potency factor we use benchmark dose, multi-stage cancer model from USEPA and incidence ratio factor for rat. Reduce into three sustaining factors, convert that number to human equivalent number. 1.6 times 10 to the minus 2 per milligram per kilogram per day.

And that concludes the equivalent NOEL and endpoint presentation. The next part, it will be Dr. Reed's part talking about the human equivalent concentration or acute exposure when you take a NOEL of the ending level of my animal studies, we have to account for interspecies extrapolation. In this case we are looking at pharmacokinetic difference in exposure using PBPK modeling.

DR. BLANC: At what point did you plan on talking about the section that you have on human cases experience?

Dr. LIM: I don't have that in my presentation for human case studies.

DR. BLANC: I think before you go to human equivalent cross species comparison, it is worth saying what the human literature tells us. I want

to commend you again for having included that literature, despite nay saying by the EPA. We don't consider such literature. I do think, however, that because there is such a rarity of human case exposure data and because it is so relevant to the issues, I think you should include cases that you have left out. And I think these are not going to be so easy for you to retrieve from the literature or summarize the paper that summarizes them. So there is a very nice tabular summary of other cases in one of the papers you cite already.

Dr. LIM: The whole paper of all the cases.

DR. BLANC: And there is another, more recent, paper on skin exposure that you don't include at all. That needs to be included. And then I would like to see a tabular presentation which includes things that are consistent with seeing them in humans exposure - what do human exposures tell us is that this is a substance which consistently has as its target organ the central nervous system; that there is a delay effect that there appears to be preferential toxicity to the cerebellum and to the cranial nerves with a consistent clinical presentation that includes certain findings and neuro psychiatric series of

manifestations, all of which are delayed and persistent.

I also think that because the human exposure section per force has not that many examples it can talk about, I think there needs to be some comment on the neurotoxicity of methyl bromide and how that might or might not be consistent with methyl iodide, from what you see from it. Just as a parallel.

The reason I think all of this is so important, I think great that you started to go down that path, because as we get to where the critical things are, that are looking in our database, and why it may not be public health protective to make some of the assumptions made because we simply don't have good data that would help us identify the dose response for the endpoint. That is most important in adult humans, anyway.

DR. HATTIS: Just doing a literature search I found this is 1986 review article that says iodide excess could produce thyroid toxicity, but not cancer.

DR. LIM: I can review the ATS review. They have quite a lot of literature.

DR. LOECHLER: I went through the calculation talking about potassium iodide. At 20

parts per million methyl iodide you end up with iodide ion levels of 200 parts per million in the animal. And the high dose in the potassium iodide carcinogen study was a thousand. So the level of iodide ion in the potassium iodide treatment cancer study, which gave them cancer, is lower -- is higher than the level of iodide you get from methyl iodide.

DR. HATTIS: That seems to support this thesis, then. Although it certainly is harmful to the thyroid, it doesn't seem to be associated carcinogenicity as such.

DR. FROINES: I want to follow up with what Paul said. Because, quite frankly, I think that the human case studies represent very important data and information. And without wanting to overstate it, I think they are absolutely examples of devastating toxicity and the nature of that toxicity in terms of the central nervous system is particularly important and especially in terms of the long-term effect and the lack of repair that appears to occur. In addition to that I think that, as we think about those case studies and what their implications are, I think we cannot avoid thinking about what the implications of those are for exposure to children. Because if we have developing central nervous system

among children and potential for the kinds of effects that we see in those case reports, we really do have, I think, a safety factor and certainty factor issue when it comes to addressing the issue of children, based on the human studies, which, as I said and which I think we all agree, are really quite devastating in their outcome. Whether it be dermatologic or central nervous system.

It is 4:40 now. Should we make a shot of getting started on.

DR. SLOTKIN: I think we should use every minute we got. We are going to run out of time.

DR. REED: This is what I am going to be talking about. The acute human equivalent concentrations.

DR. FROINES: They can't hear back there.

DR. REED: So what I'm going to be talking about is how we derive the acute human equivalent concentration using PBPK Model. Also talk about the uncertainty factor application. As Dr. Froines mentioned, that has everything to do with the uncertain factor of application two. I am going to give a very, very general model overview.

Our modeler, Dr. Sweeney, is in the audience, so if you have any model questions, Dr. Froines, it

is up to you if you want to address that now or later.

DR. FROINES: I was just going to say one thing, which is we plan to have the committee meet at 5:00 to talk about -- oh, perhaps Dale and Tom can talk.

Dale, maybe the two of you can get together and chat about modeling tomorrow.

DR. REED: Can shorten the process if you deal with the model issues.

DR. HATTIS: Yeah.

DR. REED: So I'm going to give a very general overview. Mainly just to indicate that we are using the model to account for interspecies coming from genetic differences. Meaning that we apply certain factors, the pharmacodynamic and also inner individual and uncertainty factor state.

So the HECs are derived by matching human dose metrics to the animals and the NOELs and apparently now the NOELS will be changed, most likely. So that would be revised.

So about the use of PBPK model. We think what is important are the mode of action that would impact on the selection of dose metrics and also the model's specific issues in terms of how to apply

model to the endpoint of interest. And then the overall HEC dose metrics.

We would be presenting two acute HEC. One is for 24 hours for the general public. That includes for children and so forth. The other one is -- I couldn't put in, quote-unquote, the eight hour for workers under occupation settings because we believe that workers would go home, still be exposed to methyl iodide for the 16 hours. And so we derive equivalent, it's going to be different from deriving or determining the NOEL because NOEL you just pretty much use it for calculating the margin or exposure. But a lot of times people use HEC to back calculate for reference concentration. So it is important to keep in mind there is another 16 hours of exposure.

We develop our HEC. And the last thing I want to talk about is the application of uncertainty factors in risk assessments.

Any questions?

Model overview. The model is developed by the Sapphire Group, and it is reviewed by the National Center for Computational Toxicology in 2007. And it was used by USEPA, also, to establish their HECs. There is one model but two applications. One we call the rabbit model, being applied to the rabbit

fetal death endpoint. And the rat model. And the nasal is port of entry and also the rat brain for the neurotoxicity. The rabbit model is different in that there is no nose uptake; so there is only lung uptake. Again, if you identify any model issues, you can talk about it, come back and brief the panel that way.

The model description and parameters were extensively published in May 2009 inhalation toxicology issue. So what I am going to be talking about is mostly about endpoints, specific model issues.

Our showed a process in deriving our HEC is really going with subprior group in an iterated manner. And so they would be running model, and then I would review the model parameters and outcome, and I would decide that we want to change certain parameters. So subprior groups save us a lot of time by running these models and allowing us to do the analysis that way.

The question is how you know that the model is -- model run is conducted correctly. We really appreciate that the NCCT from USEPA who previous reviewed the model in 2007, now in May 2009 they repeat the runs for us to make sure that outcome is

wholesome. So in my presentation I would also be presenting USEPA's HEC for comparison. Some of them is significant, and I will point them out to you so, hopefully, facilitate your review.

DR. BLANC: This is basically an EPA comment when they kept rerunning things, saying we got exactly its same number, or we are going to run and say it was different.

DR. REED: The outcome is so different because we use different parameters, different dose measures. You are going to see.

DR. BLANC: In their response to your document, they reran a bunch of stuff. Is that partly what this is?

DR. REED: The May 1, yes.

DR. MELNICK: Without going into much of the modeling information, tell me what kind of dose metrics you obtained from the model.

DR. REED: Basically, a model has -- you can ask anything you want in that sense. But, I think, basically the model is focusing on serum iodide, serum methyl iodide. And in the fetal compartment, in maternal compartment, of course, you can do the area of the curve, of concentration, that kind of thing. I am going to show you the sort of

eight combinations of possibilities out of this. I am also going to mention that, of course, you can look at, say, thyroid concentration, fetal thyroid, but those were non critically evaluated in the sense that the model outcome might not be as reliable.

Does that make sense?

So the more focus is on the serum concentration of iodide, methyl iodide, from the model.

DR. MELNICK: So you don't have -- I noticed some partition coefficients that are also provided. Are you provided tissues, methyl iodide concentrations as well for the thyroid methyl iodide?

DR. REED: I don't -- I'm sure it is a parameter in the model. So you can pull it out, but I haven't pulled that one out. I was only impressed with the thyroid iodine, not methyl iodide.

DR. MELNICK: Why not?.

DR. REED: Mostly because To address the mode of action that's been proposed by the chemical company --

DR. MELNICK: You have two mode of actions?

DR. REED: Right. That I haven't pulled out.

DR. MELNICK: You have thyroid 14 uptake data that you can look at?

DR. REED: Right. At the end -- I totally agree with that.

At the end we have decided on the maternal serum iodide dose metrics. And so if you want the -- I also have HEC based on maternal methyl iodide dose metrics. You are going to see.

DR. HATTIS: Systemic in the blood? You can always do the thyroid.

DR. REED: Yeah. As I say, the thyroid outcome is less good. It has some funny, in my view -- I am going to show some funny numbers. I think Dr. Sweeney would not feel like we should be focusing on that because it looks a little bit strange. More focus on the serum levels of methyl iodide and iodine.

This is the diagram drawing of the model. This is a rabbit model. It has a fetal compartment in metabolism and everything else. Same as in maternal.

This is the inhalation intake in each of the lungs and so forth.

DR. MELNICK: Does your rat have a hepatic organ; rat or rabbit have hepatic organ? I don't

see one.

DR. REED: I don't know.

DR. MELNICK: I don't see hepatic orifice.

DR. REED: I don't know if it's going to hepatic section.

DR. MELNICK: It is 20 percent.

DR. REED: Are you making notes?

DR. HATTIS: It is often having the dual blood flow to the liver. Sometimes modelers don't do that type. Mea culpa.

DR. REED: My sense of personal philosophy, my sense that is way of approaching modeling.

DR. HATTIS: I do.

DR. MELNICK: How does it get out of the venus blood of the fetus?

DR. REED: I didn't hear your question.

DR. MELNICK: How dose the chemical iodide, whatever it is.

DR. REED: There is a line.

DR. MELNICK: There is no line out of fetus blood.

DR. HATTIS: It does. I am sure it does.

DR. SLOTKIN: The line across the top is supposed to be an arrow.

DR. MELNICK: That's an in, not an out.

That gets from the placenta. How does it get out of --

DR. REED: This is in, the in. I think the bottom.

DR. HATTIS: I trust that there is an arrow that goes back.

DR. FROINES: Can we move on, please?

DR. REED: You make notes, Dale, to clarify this, please. We can move on. Just hope we don't get bogged down by the model.

DR. FROINES: That is what I am trying to avoid, because there is clear potential for bogging down.

DR. REED: I am going to show you two model graphs. This one is the rabbit model, and it shows maternal and fetal serum iodide level, and this is maternal, the magenta one. The points are the data points, and lines are the simulated lines. And my comment is only that you notice that on the first day the fit is much better as you go along. Day two, three, four. There is only four days data. And so just keep that in mind. We are trying to model HEC. We are saying model only one day because there is really not that much information for use. This is good enough. And you should just --

DR. SLOTKIN: It also looks like it breaks down underestimating fetal exposure with repeating exposures. In another table you showed that the concentration of methyl iodide in the brain exceeds that of the serum. This means that the model is underestimating the fetal brain exposure by a fairly large amount because that is a log scale.

DR. REED: Essentially, at the end we feel like the dose metric should be of the maternal not the fetal. Fetal seem to have more issues. But you are going to follow through what our -- how we form our opinion.

DR. MELNICK: Do you have other data exposure concentrations?

DR. REED: That is a very good point. The only data we have data on are 20 and 25 ppm methyl iodide. What these model is inhalation. We don't know what is the 2 ppm, where this basis for.

DR. HATTIS: There is no way of checking even for the rat?

DR. REED: Right. Rat or rabbit.

DR. HATTIS: How well is the model units?

DR. REED: This is a nose over here at 25 ppm, at 100 ppm. And you see that the 25 ppm is pretty decent. A hundred ppm is deviating; 25 ppm

is closer to what we are looking for. So we felt like we could proceed.

This is rat serum concentration, 25 and then a hundred ppm.

The rat nose have model, two versions, the ethmoid and the other regions.

So first endpoint. First, rabbit fetal death.

DR. HATTIS: Can I just interject how exactly -- lots of these data were fit to different data. Some of the enzyme parameters were taken from in vitro measurements and some --

DR. REED: Yes.

DR. HATTIS: But was there a single set of in vitro data that were used to adjust some of the parameters?

I guess that is a question for Dr. Sweeney.

DR. REED: Write it down so you can clarify that. That is great. There is. I cannot.

DR. HATTIS: But still there is calculation.

DR. REED: There is. I think there is one or two sets in vitro.

DR. HATTIS: Some of the metabolism parameters were adjusted to X day or Y data set. I

haven't comprehended the paper well enough to --

DR. REED: In the rat model, also make a lot of adjustment or heavy adjustment on some of the in vitro data.

DR. HATTIS: What I understand is there is triangulation or parallelogram procedures, rat in vivo, rat in vitro and human in vitro information goes into estimating a human in vivo.

DR. REED: In this case we don't have human.

The first endpoint, rabbit fetal death. We started out of mode of action. There was four mode of action proposed. The first one was proposed by Arysta and used by USEPA, both. That they consider that rabbit fetal death came from fetal thyroid perturbation from excess iodide. So if you look at that, if you have some sufficient weight of evidence, strength of evidence for the mode of action, you would probably choose the fetal serum iodine as dose metrics. So the impact of mode of action on those metrics selection is something like that. But if you don't think it's fetal death perturbation from excess iodide, then you might not want to use the fetal dose metrics for your HEC.

The second one is glutathione depletion is a

marker of fetal stress. There is lot of data indicating glutathione depletion. We are going to go through some of it.

And the third one is direct alkylation and oxidative stress. We don't talk much about that. There is not enough or not actual -- actually any data that we could use to say if you had direct alkylation than rabbit fetal would die because of some key events. There is no key event in between that we could evaluate.

The fourth one was interesting one because we sort of poke around in the literature and I discovered some rabbit cholesterol profile during pregnancy. So I will show that. There is no further information for us to evaluate the mode of action for fetal death, we are saying.

So what is available in terms of the maternal versus fetal data? In mostly, only actually concentrating on this window of vulnerability which is gestation 23 to 26, there is no dose response data. As we mentioned before, it is only at high dose; and there is also not a whole lot of prenatal interspecies comparison. And interspecies is important thing because rabbit fetuses accumulate excess iodide. So the ratio between rabbit iodide

in rabbit fetuses versus maternal is greater than one. And some human data we showed the evidence is not greater than one.

So we are going to go through that. I want you to focus on the implication of mode of action so on the yellow outing is what we have decided -- at the end we decide to use maternal iodide on the curve. So the first one, first mode of action, remember, it is very specific to fetal thyroid perturbation and excess iodide. We talk a lot about the difference between methyl iodide and iodine. We are going to see some data. There is some available data on thyroid, colon profile, histopath, steroid iodide. There is some studies with iodide and there is some comparisons that you can make between rats and rabbits. I just want you to focus so that you don't get overwhelmed by the amount of data, especially in the next two slides I am going to show you.

The key question on this perturbation thyroid mode of action, what causes it. Is it the fetal or maternal thyroid being perturbed or both in terms of chemical form, and we talked some much about it. Now whether it's methyl iodide or iodine or both. The temporal is that I think - hopefully your

impressed as I am - that you see fetal death right after the second day of exposure. So within 30 hours they died. That is pretty impressive. So you are going to see the longer term data, and you're going to see some shorter term data for acute endpoint, where actually focusing on mode of action for acute fetal death.

So this, as said, the next slide is very complicated, and they are taken from the two tables that I have in there and nothing was taken out. Just so that you get action when you go home you see the same table is being there. First of all, TSH. We talk about TSH before between as indication of thyroid perturbation, which is maternal TSH. Fetal no. During the gestation day 23 to 24.

Serum iodide increase. But if you look at serum iodide before exposure and again in control and the MEI dose, methyl iodide dose, group. Actually, the maternal serum iodide increased in greater force, 350fold, compared to the increasing of fetal serum 264 or so. So that is kind of impressive.

In terms of fetal death at bottom. Immediately after second or fourth exposure, you are seeing death already.

DR. SLOTKIN: I'm sorry, I didn't understand your interpretation of maternal iodide versus fetal. Fetal serum is winding up with a higher concentration. When you talk about fold increases, it looks like you can't really measure the serum iodide. That should be reflecting a denominator effect. If it is iodide acting as a toxicant what matters is the absolute concentration, not the fold increase over base level.

DR. REED: That is the question, whether the fold or the absolute. 'Cause later on I will make argument about in humans whether the level or the fold, which I really don't have any answer, but interesting observation. I would like to hear your opinion about it. That is good.

DR. BLANC: John, I think we decided we wanted to have our whole panel as we went forward. I think we should break now. That is 5:00.

DR. FROINES: I think that, given the fact that your PBPK person is one of the reps and it wouldn't matter much. You actually count. So I think what we are going to do is have to continue tomorrow at 8:00.

DR. SLOTKIN: 8:30 for everyone else? Is the schedule for everyone else?

DR. HATTIS: To conclude the PBPK, do you have a comment on Figure 5 of the paper which in my mind has different numbers.

DR. REED: Look at it tonight.

DR. FROINES: Can we leave materials here?

MS. VERDER-CARLOS: Yes.

DR. HATTIS: Basically observed and expected plasma iodide, a concentration of mass of iodide.

DR. FROINES: Thank you, folks, DPR. It's been a long day, but it's, I think, been a very profitable one.

(Day of Review Panel adjourned 5:10 p.m.)

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REPORTER'S CERTIFICATE

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COUNTY OF SACRAMENTO)

I, ESTHER F. SCHWARTZ, certify that I was the official Court Reporter for the proceedings named herein, and that as such reporter, I reported in verbatim shorthand writing those proceedings;

That I thereafter caused my shorthand writing to be reduced to printed format, and the pages numbered 3 through 251 herein constitute a complete, true and correct record of the proceedings.

IN WITNESS WHEREOF, I have subscribed this certificate at Sacramento, California, on this 12th day of October, 2009.

ESTHER F. SCHWARTZ
CSR NO. 1564